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The Relationship Between Reticulated Platelets, Intestinal Alkaline Phosphatase, and Necrotizing Enterocolitis

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Abstract

Background—Necrotizing enterocolitis (NEC) affects up to 10% of extremely-low-birthweight infants, with a 30% mortality rate. Currently, no biomarker reliably facilitates early diagnosis/prevention. Since thrombocytopenia and bowel ischemia are consistent findings in advanced NEC, we prospectively investigated the impact of two potential biomarkers: reticulated platelets (RP) and intestinal alkaline phosphatase (iAP).

Methods—Infants born ≥ 32 weeks and/or ≥ 1500 g were prospectively enrolled from 2009–2012. Starting within 72 hours of birth, 5 weekly whole blood specimens were collected to measure RP and serum iAP. Additional specimens were obtained at NEC onset (Bell stage II or III) and 24 hours later. Dichotomous cut-points for both biomarkers sought to maximize sensitivity. The Mann-Whitney U test highlighted differences in median biomarker levels between NEC and non-NEC infants. Chi-square or Fisher's exact test highlighted categorical differences. The Kaplan-Meier method and Logrank test estimated the probability of developing NEC. The Cox proportional hazards model estimated hazard ratios.

Results—Of 177 infants, 8.5% developed NEC. Of these, 40% required surgery, 20% expired before discharge, 93% had “low” RP ($\leq 2.3\%$), and 60% had high iAP (>0 U/L). Infants with “low” RP were significantly more likely to develop NEC [HR=11.0 (1.4–83); $p=0.02$], while those with “high” iAP showed a similar trend [HR=5.2 (0.7–42); $p=0.12$]. Median iAP levels were significantly higher at week 4 ($p=0.02$), preceding the average time to NEC onset by one week (35.7 ± 17.3 days).

Conclusion—Decreased RP serves as a sensitive marker for NEC onset, thereby enabling early preventative strategies. iAP overexpression may signal NEC development.

Keywords

Premature; extremely-low-birthweight; biomarker; necrotizing enterocolitis

Introduction

Necrotizing enterocolitis (NEC) is a severe inflammatory disorder of the intestine that primarily affects preterm infants, with >90% of those affected having been fed.¹ Despite extensive research, the etiology of the disease remains elusive. NEC affects up to 10% of very low birthweight infants (<1500 grams at birth) with a mortality of up to 30%; it typically, presents around 3 weeks of age (later in extremely premature infants with delayed initiation of feeding).^{2,3} NEC most commonly presents with abdominal distention with or without abdominal wall discoloration, abdominal tenderness, bloody stools, increased/bilious residuals, apnea, lethargy, metabolic acidosis, and thrombocytopenia.⁴ Bell and colleagues devised a classification that differentiates suspected NEC (stage I) from proven NEC (stages II) and advanced NEC (stage III).⁵ Bell stages II and III NEC are characterized by both clinical and radiographic findings (Table 1).^{5,6} The consistent finding of thrombocytopenia in infants with NEC is presumed to be a result of consumption.

Many infants with proven NEC will respond to cessation of feedings, abdominal decompression via nasogastric tube, and initiation of broad-spectrum antibiotics (commonly Ampicillin, Gentamicin, and Metronidazole).⁴ However, up to 50% of infants with severe NEC will require surgical intervention for bowel perforation, nonviable bowel, bowel obstruction (from strictures), or abdominal compartment syndrome.⁷ Despite tremendous improvement in the care of extremely premature infants over the past few decades the morbidity and mortality caused by NEC remains at 10–30% and the total cost of care is estimated to be as much as \$500 million to \$1 billion annually in the United States alone.^{3,8}

While the pathophysiology of NEC remains unclear, inflammation, ischemia, immature mucosal immunity, and endothelial injury are thought to play a role.^{2,9} In preterm infants, NEC may be fulminant with rapid progression to multi-system organ failure, disseminated intravascular coagulation (DIC), severe metabolic acidosis and death within hours of presentation; often, early signs/symptoms of NEC are nonspecific and may be similar to those of sepsis.^{1,7} In the immediate period following NEC, infants may suffer from bowel perforation, bowel necrosis, peritonitis, and/or sepsis.¹ NEC is characterized not only by bowel necrosis, but also by systemic inflammatory responses, prompting the search for biomarkers from the inflammatory cascade. Among the biomarkers that are being currently studied are: acute-phase reactants, cytokines, chemokines, and cell surface antigens.¹⁰ Due to the multi-factorial nature of NEC, many biomarkers have been sought in order to allow for early diagnosis or prevention, but none have been found to specifically identify NEC.

Reticulated platelets represent newly produced platelets and are expected to be prevalent during periods of thrombocytopenia.¹¹ Intestinal alkaline phosphatase (iAP) is a brush border enzyme in the intestinal mucosa with unclear activity levels in preterm infants. Intestinal alkaline phosphatase is a controversial biomarker that in some studies have shown an association with elevated levels and bowel ischemia; yet, in other studies a protective role is suggested.^{9, 12} Given the consistent findings of thrombocytopenia and bowel ischemia with advanced NEC, these two biomarkers were prospectively studied to ascertain the role each plays in the development of NEC.

Methods

Loyola University Medical Center is a perinatal referral center with a fifty-bed level III NICU that admits both inborn and outborn infants. After obtaining IRB approval and parental consent, infants born at ≥ 32 weeks and/or ≥ 1500 g were prospectively enrolled. Enrollment extended from May 2009 through July 2012. An initial whole blood specimen (0.5ml) was drawn within 72 hours of birth and then repeated weekly for the next 4 weeks, for a total of 5 specimens per patient. If the infant developed NEC (as defined by Bell Stage II or III), a specimen was drawn at the onset of NEC and again 24 hours later.⁶ For those infants who developed NEC before the collection of the 5 specimens, no more samples were taken after the second NEC specimen.

Each blood specimen was analyzed for both reticulated platelets and intestinal alkaline phosphatase (iAP). Percentage of reticulated platelets were determined by flow cytometry. Serum iAP levels were determined by gel electrophoresis. Data were also collected regarding maternal blood group, infant blood group, gestational age, birthweight, date of birth, date of discharge or death, transfusion history, complete blood count data at the time of sample specimen (if available), and feeding history for each infant enrolled in the study.

Dichotomous cut-points for both biomarkers were sought to maximize sensitivity. Low reticulated platelets were defined as $\leq 2.3\%$ and high iAP was defined as >0 . The Mann-Whitney U test was used to highlight differences in median biomarker levels between NEC and non-NEC infants. The chi-square or Fisher's exact test highlighted differences categorical differences. The Kaplan-Meier method and Logrank test were used to censor infants who did not develop NEC by the time of discharge to generate curves that estimate the probability of developing NEC. The Cox proportional hazards model was used to estimate hazard ratios.

Results

A total of 177 infants were enrolled in the study, 15 (8.5%) of which developed NEC (Table 2). Of those infants who developed NEC, 14 (93%) had "low" reticulated platelets and 9 (60%) had "high" iAP in at least one sample collected before the onset of NEC. Using the set cutpoints for reticulated platelets and iAP, Kaplan-Meier plots (Figure 1) and hazard ratios were calculated for the probability of developing NEC. They showed that infants with "low" reticulated platelets are significantly more likely to develop NEC [HR=11.0 (1.4–83); $p=0.02$]. Infants with "high" iAP show a similar trend towards developing NEC [HR=5.2 (0.7–42); $p=0.12$]. Those infants with "low" reticulated platelets or "high" iAP also had significantly higher gestational ages and birth weights (Tables 3 & 4), thereby bolstering their predictive impact within a conventionally less vulnerable neonatal population. While the percentage of reticulated platelets at admission was lower in infants with "high" iAP (see Table 4), reticulated platelets did not translate into a predictive biomarker within this subgroup (data not shown). The relationship of other, related biomarkers to NEC onset – including: platelet count and absolute RP count – were also investigated, but none were related to NEC onset in our study.

Weekly comparisons of median reticulated platelets and iAP levels over all infants were performed. By week 4, infants who would go on to develop NEC demonstrated significantly higher levels of iAP over their non-NEC counterparts (MW $p = .02$; Table 2). A similar trend with low reticulated platelets was noted at week 2 in those who developed NEC (MW $p = .11$; Table 2).

Discussion

NEC is the most common surgical emergency in preterm infants in the neonatal intensive care unit.¹³ NEC occurs in 1–3/1,000 live births with 90% of NEC cases occurring in the most premature and smallest infants.^{4,10} With advances in neonatal care, these very low birthweight infants are surviving in greater numbers; thus, NEC has become a serious threat to the survival of these fragile infants. Unfortunately, treatment for NEC has not resulted in improved survival and there are no current methods available to predict which infants will develop NEC. Mortality for NEC is 10%–30% with extremely low birth weight infants and those with the lowest gestational age having the highest mortality.³ Approaches to improve outcomes with NEC include prevention, early risk stratification, early detection and improved treatment modalities. Thus, our use of reticulated platelets and iAP as possible biomarkers may enable early identification of those infants at high risk for developing NEC.

Reticulated platelets are newly synthesized platelets that have a higher content of ribonucleic acid than platelets that have been circulating for several days.¹¹ As newly produced platelets, these reticulated platelets are considered to be more active.¹¹ Normal reticulated platelet count values are not well-defined. A study by Peterec et al showed that infants born at ≥ 30 weeks had similar values to adults ($\sim 4\%$), whereas infants born at < 30 weeks had twice as many reticulated platelets ($\sim 8\%$).¹⁴ However, Joseph et al noted no differences between term and preterm infants with a reticulated platelet count of $< 1\%$ in both groups.¹⁵ A third study performed by Saxonhouse et al found that term infants have lower reticulated platelet counts (2.7%) compared to preterm infants (3.3–5.5%).¹⁶ Thus, by using a value of 2.3% as a cutoff for defining a low reticulated platelet count, based on current studies, this cut-off likely is a fairly accurate representation of those preterm infants who fall below the norm.

The role of reticulated platelets in the pathogenesis of NEC has not been previously studied. While thrombocytopenia in general is a frequent occurrence in the NICU, when severe and associated with NEC, it has been considered a marker of disease severity signifying underlying bowel gangrene and higher risk of short bowel syndrome in the future.¹⁷ While unclear if severe thrombocytopenia is a reflection of disease severity and the infant's inadequate response to the disease or if it may lead to NEC, it is an important area of study as platelets are an important part of the inflammatory response. In adult studies reticulated platelets have been noted to increase prior to the onset of thrombocytopenia (such as that seen in pre-eclampsia in pregnant women).¹⁸ However, Kayahan et al found that in inflammatory bowel disease (specifically ulcerative colitis), the reticulated platelets were actually reduced in patients (regardless of if the disease was active or inactive).¹¹

Sola et al have showed that thrombocytopenic neonates who had a hyporegenerative bone marrow also had lower thrombopoietin levels compared to adults, thus suggesting that neonatal thrombocytopenia is prolonged due to inadequate production of thrombopoietin.¹⁹ Our study showed preterm infants who had low reticulated platelet counts were significantly more likely to develop NEC than their counterparts. This increased likelihood may be a result of a combination of a suppressed bone marrow and may contribute to a decreased ability to generate an appropriate inflammatory response to yet unidentified stressors. Our study findings are interestingly similar to those of the Kayahn study of ulcerative colitis (both NEC and ulcerative colitis being characterized in part by inflammation and necrosis) in that reticulated platelets are unexpectedly low in these patients who would normally be expected to have markedly elevated reticulated platelet counts.¹¹ Thus, low reticulated platelet counts may serve not only as a biomarker to enable early identification of infants at risk for NEC, but serves an area to be further studied as part of the possible pathophysiology of NEC.

Although identified a brush border enzyme of the intestinal mucosa, the role of iAP in preterm infants and NEC is not clear. Expression of the intestinal fraction of alkaline phosphatase seems to vary based on the infant's gestational age at birth with fetal iAP (versus adult iAP) being predominantly expressed in those infants born at <35 weeks.¹² In addition, expression of iAP also appears to be related to one's blood type (due to secretor status), with Group O and B individuals having much higher levels than those that are Group A or AB.²⁰ McLachlan et al suggest that iAP may be associated with bowel necrosis as increased levels of iAP were found in those infants with bowel necrosis compared to controls.¹² However, Whitehouse et al suggest that iAP may actually have a protective role in NEC by potentially attenuating the inflammatory cascade.⁹ Due to the unclear role of iAP in NEC and the preterm infant, we chose to look at iAP as a biomarker with the assumption that it would be elevated in the serum of those infants with NEC due to breaks in the mucosal barrier allowing entry into the bloodstream, similar to those finding of McLachlan et al.¹² Our study showed a trend towards those infants with high iAP levels being more likely to develop NEC. Unfortunately, due to the small number of infants in our study and the even smaller number of infants with NEC, we were unable to determine what role secretor status (based on blood type) might have played in the results of our iAP levels.

As NEC affects up to 10% of very low birthweight infants, an already vulnerable population, it is important to discover reliable tests to detect those infants in this subpopulation who are most at risk of developing NEC in order to work towards prevention. Currently, no one test exists that can predict NEC; however, our study suggests that the findings of low reticulated platelets and a high iAP (especially if elevated at week 4 of life) may be useful in identifying those preterm infants at risk of NEC.

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Figure 1. Kaplan-Meier Plot of iAP and RP versus NEC Development

The probability of developing NEC over time is higher in neonates with "high" iAP, and trend approaches significance (Logrank $P = .08$). However, the probability of developing NEC over time is significantly higher in neonates with low RP (Logrank $P = .0038$). These trends are confirmed by their corresponding hazard ratios.

Table 1

Modified Bell Staging Criteria for Necrotizing Enterocolitis

Stage	Clinical Signs	Radiologic Signs
Stage I	Apnea, bradycardia, temperature instability	Normal gas pattern or mild ileus
Stage IIa	Same as I plus grossly bloody stools and abdominal distention	Ileus and pneumatosis intestinalis
Stage IIb	Same as IIa plus abdominal tenderness, mild metabolic acidosis and mild thrombocytopenia	Same as IIa plus portal venous gas $\pm$ ascites
Stage IIIa	Same as IIb plus hypotension, bradycardia, acidosis, coagulopathy, marked abdominal tenderness, abdominal wall erythema/induration	Same as IIb plus definite ascites
Stage IIIb	Same as IIIa plus shock	Same as IIb plus pneumoperitoneum

Modified from Walsh, Kliegman, and Fanaroff.⁵

Table 2

NEC versus non-NEC infants

All	NEC Infants (N=15)	Non-NEC Infants (N = 162)	P-value
Gestational Age (weeks)	26.5 ± 0.7 (24.0–32.0)	27.5 ± 0.2 (22.6–32.5)	.14 (MW)
Birth Weight (g)	903 ± 109 (430–1760)	1050 ± 32 (250–2190)	.15 (MW)
Maternal Rh	Rh+(14), Rh-(1)	Rh+(165), Rh-(22)	.55 (ψ^2)
Maternal Blood Type	A(6), B(3), AB(0), O(6)	A(58), B(20), AB(7), O(74)	.70 (ψ^2)
Infant Rh	Rh+(110), Rh-(4)	Rh+(171), Rh-(18)	.06 (ψ^2)
Infant Blood Type	A(7), B(1), AB(1), O(6)	A(55), B(23), AB(7), O(77)	.67 (ψ^2)
Days to NEC	35.7 ± 4.5 (8–69)	NA	NA
iAP(U/L)	NEC Infants	Non-NEC Infants	P-value
At Admission	23.3 ± 4.2 (15–28; N=3)	20.7 ± 3.3 (0–74; N=61)	.53 (MW)
Week 1	16.3 ± 12.3 (0–52; N=4)	15.2 ± 2.6 (0–77; N=74)	.87 (MW)
Week 2	17.7 ± 8.7(0–59; N=7)	16.7 ± 2.7 (0–82; N=78)	.79 (MW)
Week 3	14.8 ± 7.3 (0–41; N=5)	11.1 ± 2.1 (0–66; N=71)	.22 (MW)
Week 4	34.1 ± 11.1 (0–76; N=8)	13.0 ± 2.6 (0–83; N=71)	.02 (MW)
Reticulate Platelets (%)	NEC Infants	Non-NEC Infants	P-value
At Admission	3.2 ± 0.9 (0.7–12; N = 14)	5.3 ± 0.4 (0–25; N=149)	.15 (MW)
Week 1	3.1 ± 0.7(0.6–8.5; N=15)	4.4 ± 0.3 (0.3–21; N = 149)	.35 (MW)
Week 2	3.4 ± 1.2 (0.4–18; N = 14)	4.3 ± 0.3 (0–18; N=148)	.11 (MW)
Week 3	4.9 ± 1.5 (0.5–19; N=12)	3.6 ± 0.2 (0.4–13; N = 140)	.63 (MW)
Week 4	4.4 ± 1.8 (0.6–21; N=11)	4.3 ± 0.3 (0.3–22; N = 138)	.62 (MW)
Platelets (k/uL)	NEC Infants	Non-NEC Infants	P-value
At Admission	227 ± 26 (109–444; N = 15)	210 ± 6 (31–506; N=162)	.97 (MW)
Week 1	207 ± 32 (57–408; N=9)	198 ± 12 (52–509; N=82)	.50 (MW)
Week 2	261 ± 51 (122–514; N=8)	216 ± 16 (14–627; N=67)	.32 (MW)
Week 3	175 ± 34 (70–274; N=7)	236 ± 17 (67–540; N=50)	.28 (MW)
Week 4	288 ± 70 (63–581; N=B)	286 ± 27 (53–755; N=39)	.92 (MW)

Data: Average ± Standard Error (Minimum-Maximum)MW = Mann-Whitney; ψ^2 = Chi-square or Fisher's Exact P

Table 3

Infants with low versus high reticulated platelets (RP)

	Low RP(2.3%)	High RP(>2.3%)	P-value
Gestational Age (weeks)	27.9 ± 0.3 (23.0–32.5; N=103)	26.9 ± 0.3 (22.6–32.2; N=74)	.01 (MW)
Birth Weight (g)	1107 ± 41 (440–2170; N=103)	939 ± 45 (250–2190; N=74)	.01 (MW)
Maternal Rh	Rh+(87), Rn-(14)	Rh+(66), Rh-(7)	.49 (ψ^2)
Maternal Blood Type	A(40), B(12), AB(3), O(46)	A(24), B(11), AB(4), O(34)	.68 (ψ^2)
Infant Rh	Rh+(88), Rh-(15)	Rh+(70), Rh-(4)	.08 (ψ^2)
Infant Blood Type	A(39), B(14), AB(6), O(44)	A(23), B(10), AB(2), O(39)	.49 (ψ^2)
NEC/No NEC	14/89	1/73	.005 (ψ^2)
iAP (U/L)			
At Admission	23.0 ± 4.2 (0–73; N=39)	17.3 ± 4.7 (0–74; N=25)	.41 (MW)
Week 1	15.5 ± 3.3 (0–76; N=47)	14.8 ± 4.0 (0–77; N=31)	.84 (MW)
Week 2	19.0 ± 3.6(0–82; N=51)	13.4 ± 3.6 (0–66; N =34)	.50 (MW)
Week 3	11.2 ± 2.5 (0–66; N=48)	11.7 ± 3.6 (0–59; N=28)	.69 (MW)
Week 4	15.4 ± 3.6 (0–80; N=47}	14.8 ± 3.9 (0–83; N=32)	.87 (MW)
Platelets (k/uL)			
At Admission	209 ± 8 (31–506; N= 103)	214 ± 8 (78–359; N=74)	.97 (MW)
Week 1	207 ± 32 (57–08; N=9)	198 ± 12 (52–509; N=82)	.50 (MW)
Week 2	261 ± 51 (122–514; N=8)	216 ± 16 (14–627; N=67)	.32 (MW)
Week 3	175 ± 34 (70–274; N=7)	236 ± 17 (67–540; N=50)	.28 (MW)
Week 4	258 ± 70 (63–581; N=B)	286 ± 27 (53–755; N=39)	.92 (MW)

MW = Mann-Whitney; ψ^2 = Chi-square or Fisher's Exact P

Table 4

Infants with low versus high intestinal alkaline phosphatase (iAP)

	High iAP (iAP >0)	Low iAP (0)	P-value
Gestational Age (weeks)	27.9 ± 0.3 (23.0–32.5; N=92)	26.1 ± 0.3 (23.1–31.0; N=41)	.001 (MW)
Birth Weight (g)	1138 ± 47 (480–2190; N=92)	805 ± 47 (250–1530; N=41)	<.001 (MW)
Maternal Rh	Rh+(87), Rh-(14)	Rh+(66), Rh-(7)	.49 (ψ^2)
Maternal Blood Type	A(40),B(12), AB(3), O(46)	A(24), B(11), AB(4), O(34)	.68 (ψ^2)
Infant Rh	Rh+(88), Rh-(15)	Rh+(70), Rh-(4)	.08 (ψ^2)
Infant Blood Type	A(39), B(14),AB(6), O(44)	A(23), B(10), AB(2), O(39)	.49 (ψ^2)
NEC/No NEC	9/84	1/41	.17(ψ^2)
RP%			
At Admission	4.3 = 0.5 (0–25; N=88)	6.4 = 0.9 (0.5–18; N=35)	.01 (MW)
Week 1	4.0 ± 0.4 (0.5–21; N=90)	4.9 ± 0.8 (0.7–17; N=34)	.42 (MW)
Week 2	3.8 ± 0.4 (0.6–18; N=87)	3.5 ± 0.5 (0.2–10; N=37)	.60 (MW)
Week 3	3.6 ± 0.4 (0.4–19; N=82)	3.5 ± 0.5 (0.7–11; N=35)	.83 (MW)
Week 4	4.0 ± 0.4 (0.3–21; N=77)	3.7 ± 0.5 (0.8–11; N=32)	.69 (MW)
Platelets (k/uL)			
At Admission	214 ± 7 (72–444; N=92)	207 ± 14 (31–506; N=41)	.52 (MW)
Week 1	205 ± 15 (56–509; N=48)	178 ± 19 (52–385; N=24)	.36 (MW)
Week 2	208 ± 23 (14–482; N=29)	235 ± 28 (78–627; N=25)	.57 (MW)
Week 3	207 ± 21 (67–486; N=27)	225 ± 27 (97–394; N=27)	.53 (MW)

MW = Mann-Whitney; ψ^2 = Chi-square or Fisher's Exact P