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Blood group AB is associated with poor outcomes in infants with necrotizing enterocolitis

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) is a neonatal disease associated with necrosis and perforation of the bowel. We investigated the association between blood group and NEC outcomes and the potential contribution of fetal-maternal blood group incompatibility.
Methods: Retrospective study including all preterm-born infants with NEC (≥ Bell's stage IIa) admitted to our NICU between January 2008 and October 2019. We analyzed the association between infants' blood groups and fetal-maternal blood group incompatibility with Bell stage severity, need for surgery, and mortality due to NEC.
Results: We included 237 NEC patients. In univariable analyses both AB blood group and fetal-maternal blood group incompatibility increased infants' risk of severe outcomes, with odds ratios (OR) ranging from 6.57 to 12.06 and 1.97 to 2.38, respectively. When adjusted for gestational age only AB blood group remained significant with OR 7.47 (95% confidence interval, 1.95–28.53, $P=0.003$), 12.37 (2.63–58.20, $P=0.001$), and 8.16 (2.28–29.14, $P=0.001$) for NEC Bell's stage III, need for surgery, and NEC related mortality, respectively. Blood group incompatibility adjusted for gestational age was not related to worse outcomes with OR 1.84 (0.87–3.89, $P=0.11$, 2.08 (0.98–4.41, $P=0.06$) 1.52 (0.68–3.42, $P=0.31$), for NEC Bell's stage III, need for surgery, and NEC related mortality, respectively.
Conclusion: Our data confirm an association between blood group AB and worse outcomes in NEC infants, but this is not based on fetal-maternal blood group incompatibility.

1. Introduction

Necrotizing enterocolitis (NEC) is characterized by an acute inflammation of the bowel that may progress rapidly to frank necrosis and intestinal perforation. It represents the most common intestinal emergency in preterm infants [1]. Its origin is multifactorial and as yet little understood. Immaturity of the bowel and the immune system, intestinal ischemia, and bacterial colonization are some of the factors involved [2]. Despite optimal conservative treatment, approximately 25% to 50% of the infants with NEC still require surgical intervention and the mortality rate remains 30% [3,4].

Identification of factors associated with poor outcomes may give insight into the pathophysiology of NEC and could potentially lead to novel therapeutic strategies. Prognostication is also important to identify those infants at highest risk of poor outcome. In this paper we elucidate the possible contribution of blood group to NEC poor outcome and pathophysiology.

In 2012, Thomson and colleagues suggested an association between blood group and the clinical course of NEC patients [5]. NEC patients with blood group AB might have particularly unstable clinical courses seeing that their mortality rate was higher than that of other blood groups [5]. Although only limited amounts of maternal iso-agglutinins are transferred to the fetus, fetal-maternal blood group incompatibility was suggested by the authors as a possible contributing factor. This makes sense because preterm infants express blood group antigens A and B not only on red blood cells, but also throughout their small and large intestine [6]. Our primary aim was to confirm the association between blood group and NEC severity as defined according to Bell's staging criteria, need for surgery, and mortality due to NEC. Second, we aimed to

Abbreviations: Necrotizing enterocolitis, (NEC); gestational age, (GA); odds ratio, (OR); Rhesus, (Rh); iso-agglutinins, (Ig); interquartile range, (IQR); red blood cell, (RBC).

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elucidate the possible role of fetal-maternal blood group incompatibility by assessing any relationship between the aforementioned clinical parameters and fetal-maternal blood group incompatibility.

2. Methods

In this retrospective study we included all preterm-born infants with a gestational age of < 37 weeks who had been diagnosed with NEC (Bell's stage ≥ IIa) and who had been admitted to our NICU between January 2008 and October 2019. We excluded term-born infants with NEC because NEC pathogenesis in this group of children might be different [7]. The patient data we collected included information on sex, gestational age (GA), birth weight, postmenstrual age at NEC diagnosis, ABO and Rhesus (Rh) blood groups of both the infants and the mothers, and number of red blood cell (RBC) transfusions administered to patients. We compared the blood group distribution within our cohort and that of their mothers with the general Dutch population.

We characterized NEC severity in three different ways: the Bell's stage, need for surgery, and mortality due to NEC. We judge need for surgery as laparotomy indication (upon prolonged fixed bowel loops or bowel perforation or when conventional treatment stopped working) and included cases with redirection of care. We defined mortality due to NEC as death as a result of NEC or palliative treatment in case further treatment was no longer considered to be in the infant's best interest.

Fetal-maternal blood group incompatibility was defined as the mismatch between the mothers' blood groups and that of their children and the ability to produce immunoglobin (IgG) antibodies that could bind to fetal intestinal antigens. We also collected data on red blood cell transfusions, but we did not consider those in our analysis despite of providing its median number . The reason being that in our NICU transfusions are performed using leukocyte depleted blood group compatible red blood cells after cross-matching with both neonatal and maternal serum. Thus limiting any risk of transfusion reactions.

2.1. Statistics

All statistics were performed using IBM SPSS Statistics Version 23.0 (Armonk, NY, USA:IBM Corp.), with a P value of < 0.05 considered statistically significant. We assessed continuous data (demographic) distributions using the Shapiro-Wilk test and presented the data as medians (IQRs). We compared demographic data (age at diagnosis, birth weight, and gestational age) among different blood groups using the Kruskal–Wallis test. We tested differences of blood group distribution frequencies between our population (both neonates and mothers) and the Dutch population using one-way chi-square tests.

We determined odds ratios between the infants' blood groups and fetal-maternal blood group incompatibility and the outcome variables (Bell's stage III, need for surgery, and NEC-mortality) using logistic regression analyses. After univariable regression analyses, using dummies for blood groups with blood group O as reference, we ran a multivariable model. In this model we combined blood groups and fetal-maternal blood group incompatibility. We corrected analyses for potential confounders. Confounders were included if they were significantly related to the outcome variable using the Mann Whitney U test, after checking for collinearity.

3. Results

3.1. Study population

Following our inclusion criteria, we could include 237 cases out of the 261 NEC infants who had been admitted to our NICU during the study period (see Fig. 1). The study population consisted of 151 boys and 86 girls with a median GA of 28 (26–31) weeks and median birth weight of 1105 (825–1510) grams. The median age at diagnosis NEC was 11 (8–21) days, which corresponded to 31 (29–33) weeks post-menstrual age. Birth weight, gestational age, and NEC incidence were not significantly different among infants with various blood groups (Table 1). The distribution of blood groups in the NEC population, based on the ABO blood group system, was significantly different from the distribution of blood groups in the general population, with a higher incidence of types B (12% vs 9%) and AB (8% vs 3%) and a lower incidence of blood types O (44% vs 47%) and A (36% vs 41%), $P = 0.01$ (Table 1). The Rhesus blood group distribution was similar to the distribution in the general Dutch population.

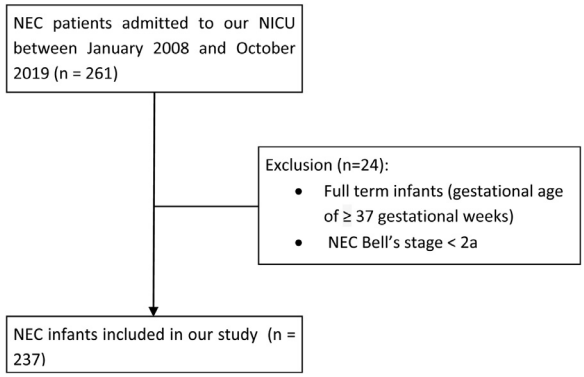

Fig. 1. Flowchart of selection of infants.

We were able to retrieve the maternal blood groups in 177 (75%) cases. Blood type O tended to occur less frequently (39% vs 47%), and more types B (14% vs 9%) and AB (6% vs 3%) tended to occur more frequently when compared to the Dutch population (Table 2). GA, birth weight, and postmenstrual age at NEC diagnosis were related to Bell's stage III (P-values, < 0.001, 0.001, and <0.001, respectively), need for surgery (P values, < 0.001, 0.002, and <0.001, respectively), and NEC mortality (P values, <0.001, <0.001, <0.001, respectively). These three potential confounders correlated significantly with each other. The P values of all correlations were < 0.001, leaving GA as the confounder with the strongest relation to outcome.

The number of RBC transfusions per blood group population was not different ($P = 0.48$), nor Rhesus group distribution in our and in the Dutch population ($P = 0.8$) (Table 1). The presence of the Rhesus antigen did not differ between infants with or without NEC Bell's stage III ($P = 0.78$), nor between infants with or without need for surgery ($P = 0.8$), nor between infants who did or did not die from NEC ($P = 0.50$) (Table 4).

3.2. Blood group and bell stage

Blood group AB was associated with a higher incidence of infants with NEC Bell's stage III. In the AB group, Bell's stage III was present in 84% of the cases as opposed to 42% to 50% in the other blood groups (Tables 1 and 3).

When corrected for GA, in both the univariable and multivariable analyses, blood group AB increased the odds of developing Bell's stage III (Table 4). The odds ratio (OR) was 7.27 (95% CI, 2.00–28.50, $P = 0.003$) but fetal-maternal blood group incompatibility did not OR 1.84 (95% CI, 0.87–3.89), $P = 0.1$. When combining the data, in a multivariable model, blood group and fetal-maternal blood group incompatibility, AB blood group patients still had higher chance to develop Bell's stage III, when compared to

Table 1
The demographic characteristics of the study population and comparison of median gestational age, birth weight, age at NEC diagnosis, red blood cells transfusion and expected blood group prevalence among each study group (total cohort, blood groups O, A, B and AB).

	Study Cohort ($N=237$)	O($n=104$, 44%)	A($n=86$, 36%)	B($n=28$, 12%)	AB($n=19$, 8%)	P value
Sex						
Boys	151 (64%)	69 (66%)	54 (63%)	19 (68%)	9 (48%)	
Girls	86 (36%)	35 (33%)	32 (37%)	9 (32%)	10 (52%)	
Bell's stage						
IIa	82 (34%)	40 (39%)	31 (36%)	11 (40%)	0 (0%)	
IIb	44 (19%)	20 (19%)	18 (21%)	3 (11%)	3 (16%)	
IIIa	40 (17%)	17 (16%)	11 (13%)	5 (18%)	7 (37%)	
IIIb	71 (30%)	27 (26%)	26 (30%)	9 (32%)	9 (47%)	
Median gestational age in weeks (IQR)	28 (26–31)	29 (27–32)	28 (26–31)	28 (26–29)	27 (25–31)	0.30§
Median Birth Weight in grams (IQR)	1105 (825–1510)	1157 (839–1543)	1120 (890–1514)	960 (806–1250)	1075 (770–1500)	0.24§
Median postmenstrual age at diagnosis in weeks (IQR)	31 (29–33)	31 (29–34)	30 (29–34)	30 (28–33)	27 (29–33)	0.16§
Median no. of RBC transfusions (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	3 (2–6)	3 (1–4)	0.48§
Patients transfused with RBC's 48 h before NEC diagnosis	38 (16%)	18 (17%)	17 (20%)	2 (7%)	1 (5%)	0.23°
Expected blood group prevalence according to the distribution in the Dutch population		47%	41%	9%	3%	<0.001*
Rhesus#						0.6*
+	196 (83%	83 (80%)	71 (83%)	25 (89%)	17 (89%)	
–	41 (17%)	21 (20%)	15 (17%)	3 (11%)	2 (11%)	

§ Using Kruskal-Wallis Test; * comparison of expected prevalence versus actual prevalence in the Dutch population, using one-way chi-square test, $P < 0.001$ for neonatal ($N=237$), and $P=0.010$ for maternal ($n=177$) blood group distribution
# expected frequency of Rhesus + in the Dutch population is 84;° using chi-square test; IQR, interquartile range. RBC's, red blood cells.

Table 2
Fetal-maternal blood group incompatibility which may theoretically result in antagonism among the various neonatal blood groups ($n=177$).

		Blood group distribution			
		Neonatal blood group			
		O (n78, 44%)	A ($n=60$, 34%)	B ($n=24$, 14%)	AB ($n=15$, 8%)
Maternal blood group ($n=177$)	O ($n=70$, 39%)	47 (67%)	18 (26%)	5 (7%)	0 (0%)
	A ($n=72$, 41%)	27 (37%)	36 (50%)	2 (3%)	7 (10%)
	B ($n=25$, 14%)	4 (16%)	1 (4%)	13 (52%)	7 (28%)
	AB ($n=10$, 6%)	0 (0%)	5 (50%)	4 (40%)	1 (10%)
Fetal-maternal blood group incompatibility with potential antagonism ($n=40$)		0 (0%)	19 (32%)	7 (29%)	14 (93%)

Potential neonatal-maternal blood group antagonism in italic type.

Table 3
Prevalence of NEC outcomes in each infant's blood group.

	Bell's stage III($n=111$, 47%)	Need for surgery*($n=114$, 48%)	NEC mortality rate($n=56$, 24%)
O ($n=104$, 44%)	44 (42%)	43 (41%)	18 (17%)
A ($n=86$, 36%)	37 (43%)	40 (47%)	18 (21%)
B ($n=28$, 12%)	14 (50%)	14 (50%)	9 (32%)
AB ($n=19$, 8%)	16 (84%)	17 (90%)	11 (58%)
Blood group incompatibility ($n=40$, 23%)	25 (23%)	26 (23%)	15 (27%)

* Included infants with redirection of care before surgery.

other blood group patients, OR 7.02 (95% CI, 1.12–43.93), $P=0.04$ (Table 4).

3.3. Blood group and need for surgery

Surgery was indicated in 114 patients (48%). In 18 infants, however, surgery was not deemed to be in the children's best interest any longer and they were given comfort care. These infants remained in the surgical group for comparison, nevertheless. The percentage of infants requiring surgery was significantly higher in the AB group, viz. 90% (Table 3).

After correcting for GA, infants with blood group AB were at significantly higher odds of requiring surgery. The OR was 12.37 (95% CI, 2.08–58.620), $P=0.001$. Again, fetal-maternal blood group incompatibility failed to reach statistical significance OR 2.08 (95% CI, 0.98–4.41), $P=0.06$ and blood group AB odds ratio remained significant when including both fetal-maternal blood group incompatibility and blood group, OR 7.02 (95% CI, 1.12–43.93), $P=0.04$ (Table 4).

3.4. Blood group and mortality

Overall, mortality due to NEC was 23.6%. Once again, following the severity of NEC and need for surgery, the mortality rate was associated with the infants' blood groups. Among patients with blood type AB, 58% died from NEC (Table 3).

In univariable and multivariable analysis models (corrected for GA) the odds of dying from NEC were significantly higher in infants with blood group AB. The OR was 8.16 (95% CI, 2.28–29.14), $P=0.001$. Fetal-maternal blood group incompatibility did not increase de risk of mortality due to NEC: OR = 1.52 (95% CI, 0.68–3.42), $P=0.3$. Multivarable analysis with blood group and

Table 4
Odds ratios of blood group (ABO and Rh) and blood group incompatibility for NEC outcomes (Bell's stage III, need for surgery, and NEC mortality). The first column provides the univariable analyses, the second model separate analyses regarding blood group and fetal-maternal blood group incompatibility adjusted for gestational age; the third column the multivariable model entering blood group and fetal-maternal blood group incompatibility, adjusted for gestational age.

		Univariable			Univariable (adjusted for GA)			Multivariable Model (entering both blood group ABO amd Incomp, adjusted for GA)		
Bell's stage III		OR (95% CI)	P value	R^2	OR (95% CI)	P value	R^2	OR (95% CI)	P value	R^2
	O	(ref)			ref			ref		
	A	1.03 (0.58–1.84)	0.92	0.07	0.94 (0.52–1.71)	0.84	0.15	0.80 (0.37–1.73)	0.57	0.16
	B	1.36 (0.59–3.15)	0.47	0.03	1.12 (0.47–2.64)	0.81	0.11	1.26 (0.47–3.37)	0.65	
	AB	7.27 (2.00–26.50)	0.003	0.000	7.47 (1.95–28.5)	0.003		7.02 (1.12–43.93)	0.040	
	Incomp	2.14 (1.04–4.41)	0.039		1.84 (0.87–3.89)	0.11		1.10 (0.42–2.87)	0.84	
	Rh +	0.91 (0.46–1.79)	0.78							
Need for surgery		OR (95% CI)	P value		OR (95% CI)	P value	R^2	OR (95% CI)	P value	R^2
	O	ref			ref			ref		
	A	1.23 (0.69–2.2)	0.48	0.09	1.15 (0.64–2.08)	0.64	0.15	0.96 (0.45–2.06)	0.91	0.15
	B	1.42 (0.61–3.28)	0.41	0.04	1.19 (0.50–2.80)	0.69	0.11	1.30 (0.49–3.49)	0.59	
	AB	12.06 (2.65–54.93)	0.001	0.000	12.37 (2.63–58.20)	0.001		6.77 (1.10–41.83)	0.040	
	Incomp	2.38 (1.15–4.96)	0.020		2.08 (0.98–4.41)	0.057		1.21 (0.47–3.13)	0.69	
	Rh +	1.09 (0.56–2.14)	0.80							
NEC mortality		OR (95% CI)	P value		OR (95% CI)	P value	R^2	OR (95% CI)	P value	R^2
	O	ref			ref			ref		
	A	1.27 (0.61–2.62)	0.53	0.09	1.08 (0.49–2.38)	0.85	0.32	1.22 (0.48–3.11)	0.68	0.26
	B	2.26 (0.88–5.80)	0.09	0.03	1.85 (0.67–5.11)	0.24	0.20	2.40 (0.79–7.30)	0.12	
	AB	6.57 (2.32–18.64)	<0.001	0.003	8.16 (2.28–29.14)	0.001		8.47 (1.56–46.07)	0.013	
	Incomp	1.97 (0.93–4.18)	0.078		1.52 (0.68–3.42)	0.30		0.68 (0.23–2.03)	0.49	
	Rh +	1.34 (0.58–3.09)	0.50							

R^2 = Nagelkerke's R-squared. Incomp = fetal-maternal blood group incompatibility with potential antagonism. Statistically significant results are presented in bold type.

fetal-maternal blood group incompatibility showed an increased chance for mortality due to NEC for AB patients, when compared to other blood group patients, OR 8.47 (95% CI, 1.56–46.07), $P = 0.013$, (Table 4).

3.5. Fetal-maternal blood group incompatibility

The distribution of fetal-maternal blood group incompatibility per neonatal blood group is depicted in Table 2. It was not associated with any of the outcomes when corrected for GA and it hardly affected the ORs found for blood group AB (Table 4).

4. Discussion

In this retrospective analysis we confirmed that NEC severity is associated with ABO blood groups. We found that patients with blood group AB had the worst prognosis. Indeed, in comparison to patients with other blood groups, these infants had a 6 to 12-fold higher risk of Bell's stage III, indication for surgery, and death due to NEC. Other infant characteristics, such as gestational age and birth weight, were similar among blood groups and did not explain this finding.

The first research group to suggest that blood groups might have an influence on mortality as a result of NEC was Thomson and colleagues [5]. They found that both maternal and neonatal blood groups were associated with the infants' risk of dying from NEC. In their study, the distribution of the study blood groups was similar to that of the general population. The present series confirms the association between blood group AB and a more severe course of disease, but it also suggests that the percentage of patients with blood group AB is higher in children with NEC.

Thomson and colleagues suggested that fetal-maternal agglutination reactions might be involved in their results. These reactions develop when maternal isoagglutinins (Ig) cross the placenta and recognize fetal intestine blood group determinants [6]. Potentially, this could lead to intestinal inflammation starting up a cascade leading to severe NEC.

As fetal-maternal blood group antagonism is exceedingly rare and not always tested, we used fetal-maternal blood group incompatibility in our study, defined as an incompatible blood group between mother and neonate with potential maternal IgG crossing the placenta. We found no relation between fetal-maternal blood group incompatibility and worse NEC outcome when adjusted for GA. If fetal-maternal antagonism were involved, a higher incidence would be expected in infants with blood group A, who have mothers with blood group B, or in infants with blood group B, who have mothers with blood group A. This was not the case. Because infants with blood group AB express both antigens A and B, these infants have a two-fold chance of experiencing fetal-maternal blood group incompatibility in comparison to infants with other blood groups. Multivariable logistic regression analyses enable us to disentangle blood groups from blood group incompatibility. In fact, most outcomes regarding the severity of NEC display an odds ratio below 1 in case of blood group incompatibility, in comparison to blood group O, for which fetal-maternal ABO blood group incompatibility cannot occur. Our data make a strong case for fetal-maternal blood group incompatibility not being a factor that relates to the poorer outcomes of infants with NEC who have blood group AB.

Thomson and colleagues also suggested that hemolytic reactions as a result of red blood cell transfusions could possibly lead to a worse outcome. Red blood cell transfusions are considered a risk factor for NEC, although this has not yet been fully elucidated [8]. However, like Thomson and colleagues reported, it is highly unlikely that this is the result of agglutinin reactions, seeing that administering blood group O is the standard transfusion practice at some NICUs. Moreover, at our NICU blood transfusions are cross-matched with both neonatal and maternal blood before administration, excluding hemolytic reactions as a causative agent of the detrimental outcomes observed.

We know that maternal IgG antibodies are transferred mainly from the third trimester onward and rarely cause hemolytic disease [9]. Therefore, we were not surprised to find that fetal-maternal blood group incompatibility did not explain the relation between blood group AB and worse NEC outcomes. Seeing that our cohort of infants was born largely before the third trimester commenced, transfer of maternal IgG was unlikely. Blood group antigens A and B, however, are not only expressed on red blood cells, but also throughout the small and large intestine [6]. This means

that transferred maternal IgG anti-A and anti-B can also bind to antigens in the intestines, even in small amounts, and thus initiate a local inflammatory response. Blood group incompatibility could thus have caused the higher odds for severe NEC, but our findings reject this hypothesis. At this point in time, we can only speculate about other underlying mechanisms, which should be a topic of investigation given its vital clinical importance.

All in all, the above arguments support that the results we obtained in this study are unrelated with fetal-maternal blood group incompatibility. In fact, even if fetal-maternal blood group incompatibility without GA age adjustment seemed to be related to NEC outcome, we find this untrustworthy. GA age is a well-known confounder of NEC outcome (which was also confirmed by our statistical analysis) and thus needs to be accounted for in the study of factors that contribute to NEC outcome. Conversely, AB blood group remained associated with NEC severity even when adjusted for GA. In order to elucidate the relationship between these two variables, despite expecting collinearity, we did run a model with both variables. The comparison of the multivariable analysis of blood group with and without fetal-maternal blood group antagonism showed that the ORs for fetal maternal blood group incompatibility decreased, whereas remained more or less unchanged and considerably high for blood group AB. Moreover, of the 40 infants with fetal maternal blood group incompatibility only 14 had blood type AB. We would have expected higher ORs for the fetal maternal blood group incompatibility if the remaining 26 infants, with incompatibility, would also have had more severe outcomes. So we believe these data indicate that it is indeed blood group AB, and not fetal maternal blood group incompatibility, that is responsible for our findings.

In our cohort, the ABO blood group distribution differed from the Dutch population. There was a higher incidence of blood groups B and AB, in comparison to the normal population. This distribution of blood groups was also found in the mothers, which is not surprising seeing that infants' blood groups depend on that of their mothers for 50%. It could be that mothers with blood group B or AB are more prone to deliver preterm. However, due to ethnicity and other characteristics that were not taken into account during our analysis, it is impossible to speculate about the relation between blood group (mother and/or infant) and preterm birth/NEC severity.

4.1. Strengths and limitations of this study

The major strengths of our study are the relatively large and uniform sample size of NEC infants, the relatively large number of maternal blood groups retrieved, and the possibility to compare the distribution of blood groups with that of the general population in the Netherlands. Nevertheless, we also recognize some limitations, such as its being a retrospective single center study, that we did not measure irregular antibodies of the IgG class anti-A or anti-B in the infants' serum and that the AB blood group patients cohort is relatively small. These limitations may weaken our results reproducibility in the general population. Furthermore, we have limited our outcomes number in order to avoid small numbers in each outcome. This means that we did not consider severity of various surgical requirements, for example just fixing small perforation, versus removal of large segments of the intestines. Finally, we did not have data on the association between long-term outcomes beyond mortality and blood group.

Conclusion

There is a strong association between blood group AB and outcomes in preterm infants with NEC. In comparison to infants with other blood groups, patients with blood group AB have a significantly worse outcome in terms of Bell's stages, their need for surgery, and mortality. This does not seem based on fetal-maternal blood group incompatibility. We speculate that an unknown factor links severity of NEC to blood groups, which may explain why blood group AB renders infants with NEC more vulnerable to worse outcomes. This should be the subject of further studies.

Nonetheless, this study should create awareness among physicians towards NEC AB patients being at higher risk of worse outcomes.

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