Human Milk Use in the Preoperative Period Is Associated with a Lower Risk for Necrotizing Enterocolitis in Neonates with Complex Congenital Heart Disease

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Objective To evaluate the hypothesis that feeding volumes exceeding 100 mL/kg/d and exposure to cow's milk formula preoperatively increase the risk for preoperative necrotizing enterocolitis (NEC) in infants with complex congenital heart disease.

Study design All infants, of any gestational age, with an isolated cardiac lesion at high risk for NEC (ductal-dependent lesions, transposition of the great arteries, truncus arteriosus, and aorto-pulmonary window) admitted to Texas Children's Hospital from 2010 to 2016 were included. NEC was defined based on the modified Bell criteria. Feeding regimen information and relevant covariates were collected. Logistic regression was used to evaluate the association of feeding regimen and other potential risk factors with NEC.

Results In this single-center, retrospective cohort of 546 infants, 3.3% developed Bell stage I-III NEC preoperatively. An exclusive unfortified human milk diet was associated with a significantly lower risk of preoperative NEC (OR 0.17, 95% CI 0.04-0.84, $P = .03$) in a multivariable regression model controlling for cardiac lesion, race, feeding volume, birth weight small for gestational age, inotrope use presurgery/pre-NEC, and prematurity. Feeding volumes exceeding 100 mL/kg/d were associated with a significantly greater risk of preoperative NEC (OR 3.05, 95% CI 1.19-7.90, $P = .02$).

Conclusions The findings suggest that an unfortified exclusive human milk diet may reduce the risk of preoperative NEC in infants with complex congenital heart disease. *(J Pediatr 2019;215:11-6)*.

Necrotizing enterocolitis (NEC) is a complex illness with high morbidity and mortality.[1-4] Most cases of NEC occur in infants who are premature or have very low or extremely low birth weights; however, an estimated 10% of cases occur in infants born full term.[5-7] Congenital heart disease (CHD) is a major risk factor for NEC and may account for as much as 33% of the cases seen in infants born at term.[5,8] Depending on the study population, 1.5%-11% of infants with CHD develop NEC in the neonatal period.[1-4,9-11] Among infants with CHD, it is theorized that those with ductal-dependent (dd) cardiac lesions may have the greatest risk of developing NEC. This is a result of diastolic steal from a patent ductus arteriosus leading to mucosal damage from decreased intestinal perfusion, predisposing the infant to NEC.[12]

Infants with dd cardiac lesions often have feeds held or severely limited during the preoperative period due to concern for NEC,[13] despite a lack of evidence for this practice. Although the incidence of preoperative NEC is largely unknown, a systematic review of infants with CHD reported that, of those who developed NEC in a cohort of 6683 patients, 48% of cases occurred before cardiac surgery.[14] Feeding infants during the preoperative period may be beneficial by improving overall fluid status and stability in the postoperative period[15] and may improve overall growth and nutrition. Prolonged periods of fasting result in intestinal villus atrophy as well as derangement of the intestinal microbiota,[13,16] which may increase the risk for NEC postoperatively and have a long-term impact on growth. As such, there is increasing recognition of the need to develop standardized feeding protocols that optimize nutrition and minimize the risk for NEC during the preoperative period.[15,17-19]

In this retrospective cohort study of infants with complex CHD, we evaluated multiple potential feeding risk factors for NEC in the preoperative period. We

BiV	Biventricular
CHD	Congenital heart disease
dd	Ductal-dependent
HMD	Human milk diet
NEC	Necrotizing enterocolitis
PBF	Pulmonary blood flow
SBF	Systemic blood flow
SV	Single-ventricle without ductal-dependent pulmonary or systemic blood flow

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hypothesized that exposure to cow's milk formula during the preoperative period and feeding volumes exceeding 100 mL/kg/d would increase the risk for NEC in this population.

Methods

This was a retrospective cohort study of infants with complex CHD admitted to Texas Children's Hospital from January 1, 2010, to January 1, 2016. Infants of all gestational ages were enrolled into the study if they had 1 of the following cardiac physiologies: biventricular lesion (BiV) with dd pulmonary perfusion (PBF), BiV dd with systemic perfusion (SBF), single-ventricle (SV) lesion with dd-PBF, SV dd-SBF, single-ventricle without ductal-dependent pulmonary or systemic perfusion (SV), d-transposition of the great arteries, truncus arteriosus, aortopulmonary window, severe Ebstein anomaly requiring prostaglandin, or tetralogy of Fallot absent pulmonary valve.

Infants were excluded if they were admitted at >72 hours of age or had heterotaxy, omphalocele, gastroschisis, bowel atresia, Hirschsprung disease, imperforate anus, diaphragmatic hernia, or hypoxic ischemic encephalopathy. Infants with cardiac anomalies that did not require intervention were excluded. There were no restrictions on the type of intervention needed, including transcatheter procedures. Infants were identified for possible inclusion in the study via pharmacologic records or echocardiogram results. The hospital's pharmacologic database was used to identify patients admitted during the time frame of interest who received prostaglandin E_1. Further, infants with the aforementioned congenital heart lesions were identified from the hospital's echocardiogram database. These 2 lists were combined, duplications were removed, and each resulting medical record was reviewed for possible inclusion.

For the infants who met inclusion criteria, the data were collected retrospectively starting from admission until the first cardiac surgery, first episode of NEC, or discharge, whichever came first. The following data were collected for every enrolled infant: race; sex; gestational age; birth weight; cardiac lesion; days to first surgery; need for respiratory support, antibiotics, and inotropes; date feeds were initiated; type of feeds provided; largest volume of feeds (mL/kg/d) provided; and the feeding route that was used (oral vs nasogastric).

Cardiac lesions were categorized based on physiology. Each infant's echocardiogram results were reviewed along with surgical records. Infants were defined to have SV or BiV disease and determined to have dd PBF or SBF based on the initial echocardiogram. Infants with d-transposition of the great arteries, truncus arteriosus, and aortopulmonary window were defined as separate categories, as they have slightly different physiologies than those of the other groups.

Preoperatively, these infants were either admitted to the Cardiovascular Intensive Care Unit or the level 4 Neonatal Intensive Care Unit at Texas Children's Hospital. At the time of this study, there were no institutional guidelines addressing the feeding of these infants. Feeds were started preoperatively if an infant was deemed stable by the care team. Each provider, in conjunction with a multidisciplinary team (consisting of cardiologists, neonatologists, and neonatal dietitians) could make decisions about the timing of feeding initiation, feeding type, feeding initiation volume, feeding advancement rate, and the feeding route. Typically, infants with complex CHD were fed preoperatively in our hospital if they were hemodynamically stable and not requiring respiratory support, regardless of the use of a prostaglandin infusion. In infants born at term, feedings were usually initiated with mother's own milk. If mother's own milk was not available, unfortified formula or donor human milk was offered depending on family and physician preference. Feeds were started at a trophic volume of 20 mL/kg/d and advanced by 20 mL/kg/d with a total fluid restriction of 120-140 mL/kg/d, although there were no institutional guidelines at the time of this study. The maximum enteral feeding volume was also at the discretion of the provider. Feeds in infants born at term were not fortified until feeding volumes exceeded 100 mL/kg/d and the infant failed to achieve appropriate weight gain.

A case of NEC was defined based on the modified Bell criteria (**Figure 1**; available at www.jpeds.com).[19] Each case of NEC was reviewed by 2 neonatologists and a radiologist to determine staging (Bell Ia-IIIb). Discrepancies were first addressed by mutual discussion with third-party involvement if necessary. In the case of a perforation, surgical and pathologic reports were used to differentiate between NEC and spontaneous perforation.

We limited the cohort to the last 6 years, as pasteurized donor human milk has only been available for use in infants of any gestational age at Texas Children's Hospital since 2009. In the remainder of this paper, human milk diet (HMD) will refer to feedings of either mother's own milk or donor human milk.

Statistical Analyses

Quantitative variables were summarized using the median and IQR separately for the preoperative NEC vs no-NEC groups. Maximum feeding volume and gestational age were compared for patients with and without NEC using the Wilcoxon rank sum test. Bivariate associations with NEC were examined by fitting logistic regression models separately for each hypothesized risk factor. A multivariable logistic regression model was built by including all risk factors found to be significantly associated with NEC ($P = .05$) and those that were considered to be clinically relevant covariables. SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) was used for all data analysis.

Results

We identified 878 infants for possible inclusion in the study, and 546 patients were enrolled (**Figure 2**; available at www.jpeds.com). The demographics of the final cohort are summarized in **Table I**. The cohort was predominately male, born at term, and white. Forty-four percent of the

Table I. Demographic characteristics

Characteristics	N = 546 (%)
Sex	
Male	319 (58.4)
Race	
African American	67 (12.3)
White	453 (83)
Asian	16 (2.9)
Native American/Pacific Islander	1 (0.2)
Unknown	9 (1.6)
Ethnicity	
Hispanic	197 (36.1)
Apgar scores, median	
1-min Apgar	8 (7-8)
5-min Apgar	9 (8-9)
Gestational age, wk 38.9 (37.4-39.3)	
Gestational age <37 wk	105 (19.2)
Birth weight, g	
<1000	0 (0)
1000-1500	7 (1.3)
1501-2000	29 (5.3)
>2000	510 (93.4)
Small for gestational age*	
<10%	76 (13.9)
Cardiac lesions	
SV dd-SBF	126 (23.0)
BiV dd-SBF	119 (21.8)
d-TGA	89 (16.3)
BiV dd-PBF	85 (15.6)
SV dd-PBF	61 (11.2)
SV	31 (5.7)
Truncus	28 (5.1)
Other†	7 (1.3)
NEC	
NEC presurgery	18 (3.3)
NEC stage	
I	8 (44.4)
II	6 (33.3)
III	4 (22.2)

d-TGA, d-transposition of the great arteries.
Data are presented as the number (%) or median (IQR).
*Based on the 2013 age-specific Fenton charts.
†A-P window, severe Ebstein requiring prostaglandins, absent pulmonary valve.

Table II. Preoperative feeding exposures

Risk factors	n (%)
Any feeds	363 (66.5)
Received >100 mL/kg/d	139 (38.3)
Exclusive unfortified HMD*	198 (54.5)
Received fortification*	63 (17.4)
Received any formula*	151 (41.6)
Feeds with UAC in place*	184 (50.7)

UAC, umbilical artery catheter.
*% of those patients receiving any feeds (N = 363).

cohort had left-sided obstructive cardiac lesions. During their first hospitalization, 3.3% of patients developed NEC before their first cardiac surgery. Patients who developed NEC in the preoperative period did so at a median age of 8.5 days, IQR 5-11; the median age at surgery was 16 days (IQR 13-34). The median age at which feeds were started was 3 days (IQR 2-5). NEC developed a median of 5 days (IQR 3-10.5) after starting feeds. Two infants with NEC received packed red blood cell transfusions preoperatively.

Approximately two-thirds of the cohort were fed before their first cardiac surgery or first episode of NEC (**Table II**). An exclusive unfortified HMD was received by 54.5% of infants in the study, and 25.5% attained a maximum feeding volume >100 mL/kg/d. In bivariate analyses, an exclusive HMD and white race were associated with a lower risk for NEC, whereas birth at <37 weeks of gestation, feeding volumes >100 mL/kg/d, and BiV dd-PBF cardiac lesions were associated with increased risk for NEC (**Table III**). A larger maximum volume of feeds during the preoperative period was associated with an increased risk for NEC (median 100 mL/kg/d [IQR 40-140] for the NEC group vs median 20 mL/kg/d [IQR 0-100] for the non-NEC group, $P = .04$).

In the multivariable regression model (**Table IV**), an exclusive unfortified HMD was associated with a significantly lower risk for NEC after we controlled for feeding volume, birth weight small for gestational age, race, inotropic support preoperatively/pre-NEC, prematurity (gestational age <37 weeks), and cardiac lesion. Infants with cardiac lesions characterized as BiV dd-PBF had an increased risk of NEC. Compared with infants with other types of dd lesions, patients with BiV dd-PBF were younger (37.5 weeks vs 38.2 weeks, P value = .01), waited longer for surgery (19 days vs 9.2 days, P value = .008), reached larger maximum feeding volumes (103.2 mL/kg/d vs 45.6 ml/kg/d, P value < .0001), and were less likely to be maintained on an exclusive unfortified HMD (31.9% vs 60.1%, P value < .001).

Additional analyses were conducted in infants who developed stage II or stage III NEC during the preoperative period. Bivariate associations are summarized in **Table V** (available at www.jpeds.com). No risk factor for stage II or III NEC remained statistically significant when included in a multivariable regression model that controlled for the covariates previously described. Evaluating the risk for NEC during the entire first hospital admission, including both the preoperative and postoperative periods, we found that infants with SV dd-SBF lesion were at the greatest risk (unadjusted OR 4.30, 95% CI 2.39-7.73, $P < .0001$).

Discussion

Our study evaluated the association between an exclusive HMD and preoperative NEC in a population of infants with complex CHD and found that an unfortified HMD was associated with a statistically significant reduction in the risk for preoperative NEC within this population after controlling for multiple covariables. We also found, contrary to past studies,[1-4,9-11] that infants with BiV dd-PBF physiology were at an increased risk of NEC in the preoperative period compared with those with other types of dd lesions. It is unlikely that infants with BiV dd-PBF lesions are truly at increased risk for NEC compared with infants with other types of dd lesions, but rather, this association may reflect current practices at Texas Children's Hospital. We are more willing to offer aggressive medical therapy for younger infants with this physiology. This creates a unique situation,

Table III. Bivariate associations with NEC in the preoperative period

Risk factors	Preoperative NEC (n = 18)	OR (95% CI)	*P* value
Female	10 (55.6)	0.56 (0.22-1.43)	.22
White	**12 (66.7)**	**0.36 (0.13-0.99)**	**.049**
<37 wk gestation	**7 (38.9)**	**2.79 (1.06-7.39)**	**.04**
PGE dose >0.0125	9 (50.0)	0.82 (0.31-2.20)	.68
SGA	4 (22.2)	1.79 (0.57-5.60)	.32
Nasal CPAP	2 (11.1)	1.48 (0.32-6.95)	.62
Mechanical ventilation	9 (50.0)	0.93 (0.28-3.10)	.91
Inotrope use	4 (22.2)	1.14 (0.37-3.52)	.83
Antibiotic use	12 (66.7)	2.40 (0.87-6.4)	.09
Culture-positive sepsis	1 (5.6)	1.74 (0.21-14.6)	.61
Any feeds	15 (83.3)	2.59 (0.74-9.05)	.14
Feeds >100 mL/kg/d	**9 (50.0)**	**3.05 (1.19-7.90)**	**.02**
Feeds while on PGE	9 (50.0)	1.46 (0.57-3.73)	.43
Feeds via NG tube	8 (44.4)	1.89 (0.67-5.34)	.23
Exclusively unfortified HMD	**2 (11.1)**	**0.12 (0.03-0.54)**	**.006**
Formula fed	10 (55.6)	2.94 (0.98-8.77)	.054
Fortified feeds	5 (27.8)	2.49 (0.82-7.56)	.11
Feeds with UAC	5 (27.8)	0.64 (0.22-1.84)	.41
Cardiac lesion			
SV	1 (5.6)	0.98 (0.13-7.59)	.98
SV dd-BPF	2 (11.1)	0.99 (0.22-4.43)	.99
SV dd-SBF	2 (11.1)	0.41 (0.09-1.80)	.24
BiV dd-PBF	**9 (50.0)**	**5.95 (2.29-15.46)**	**.0003**
BiV dd-SBF	1 (5.6)	0.2 (0.03-1.55)	.13
d-TGA	1 (5.6)	0.29 (0.04-2.24)	.24
Truncus arteriosus	1 (5.6)	1.09 (0.14-8.51)	.93
Tetralogy of Fallot with absent pulmonary valve	1 (5.6)	5.12 (0.58-44.89)	.14

CPAP, continuous positive airway pressure; *NG*, nasogastric; *PGE*, prostaglandin E1; *SGA*, small for gestational age.
Values in bold are statistically significant.

Table IV. Multivariable regression model for NEC in the preoperative period

Risk factors	OR (95% CI)	*P* value
Exclusive unfortified HMD	**0.17 (0.04-0.84)**	**.03**
Cardiac lesion: BiV dd-PBF	**3.27 (1.07-9.96)**	**.04**
Feeds >100 mL/kg/d	1.02 (0.32-3.28)	.97
SGA infant	1.20 (0.30-4.73)	.80
Prematurity, gestational age <37 wk	1.45 (0.43-4.90)	.55
White	0.37 (0.11-1.21)	.10
Inotropic support presurgery/pre-NEC	1.05 (0.26-4.26)	.95

Values in bold are statistically significant.

increasing their risk for NEC in the preoperative period, simply because they have a longer duration of exposure to risk factors during this period. Although statistical methodology may help control for confounders in a retrospective cohort study, these methods often do not completely control for all biases. We recognize this limitation and acknowledge that the results of this study may be biased by the large group of infants with BiV dd-PBF lesions.

We found that unfortified HMD was associated with a statistically significant reduction in the risk for preoperative NEC stage I-III. When infants with Bell stage I NEC were excluded from the analysis, the association with human milk was no longer statistically significant. However, we chose to include infants with stage I NEC for the primary outcome because, at our institution, any condition that warrants cessation of feeds and antibiotics could delay surgical repair and subsequently affect the clinical course of the infant. We note that 2 infants received packed red blood cell transfusions preoperatively, although based on the timing of the transfusions, it does not appear that the transfusions were related to the development of NEC.

It is noteworthy that when we considered the risk for NEC during the entire first hospital admission, including both the preoperative and postoperative periods, infants with SV dd-SBF lesion were at the greatest risk. Although the primary purpose of our study was to evaluate preoperative NEC, postoperative NEC in infants with CHD deserves further investigation. This is especially true for those at-risk infants with SV physiology, given the high overall mortality rate during the interstage periods. As a result, a number of studies have focused on postoperative gastrointestinal morbidity in this population.[17,20,21] Our results are consistent with this observation.

Although it has not been shown previously that an exclusive HMD is protective against NEC in infants with complex CHD, the use of exclusive human milk diets (mother's own milk, and/or pasteurized donor human milk) has been extensively studied in infants born premature, and there is mounting evidence to support a possible biological explanation for protective effects in infants with complex CHD. The consensus in infants born premature is that an exclusive HMD reduces the risk of medical NEC by 60% and surgical NEC by 90%.[6,22-25] In the infants born premature, there are a wide variety of initial insults that can result in mucosal damage in the intestines, including decreased blood flow secondary to a patent ductus arteriosus, medications, hypotension, inflammation due to milk components in the feeds themselves, or abnormal intestinal flora.[26-31] Current theory proposes that the initial response of the immune system in the immature gut is dysregulated, and once activated, triggers a cascade of events resulting in NEC. This dysregulated immune response leads to mucosal breakdown and ultimately bowel wall necrosis. Human milk appears to play an important role in lessening the dysregulated response and may have a protective impact on the infant's microbiota, although further studies of this are needed.[29-31] Although outside the scope of this paper, extensive research on the role of specific immune factors in the development of NEC is ongoing, with new receptors and modulators being discovered regularly.[26-31]

In infants born at term, the immune system typically is more developed, thereby decreasing the risk for NEC. However, in infants with CHD, ischemia from hypoperfusion may serve as the trigger for dysregulation of the immune system. Similar to the preterm population, the numerous immune protective factors in human milk may provide a protective mechanism against NEC in infants with CHD who are at risk for similar inflammatory insults.

The protective effects of human milk against NEC in this population appear to be multifactorial. There are many beneficial factors of human milk, including immunoglobulin A, lactoferrin, growth factors, and cytokines. In addition, the

use of human milk has been thought to impact the intestinal microbiota of infants born both preterm and term.[32] As a particularly vulnerable population, infants with CHD are subject to a number of inflammatory processes that could cause an alteration of the microbiota. These include hypoxia, infection, hospitalization, and exposure to antibiotics. Further, the absence of enteral feeding can lead to intestinal mucosal atrophy, causing a loss of important cell wall barriers. This can result in bacterial overgrowth and trigger an inflammatory response,[33] particularly in those infants who are already at risk for poor splanchnic perfusion. When these risk factors are combined, the risk of NEC may be compounded. We hypothesize that the unique components of human milk may dampen the inflammatory process and serve as a protective mechanism against NEC in this population. The association of lower volume feeds with a decreased risk of NEC also supports the concept of priming the gut with the protective factors of human milk. However, it is important to appreciate that the splanchnic perfusion is in a vulnerable state and could be burdened by high-volume feeding.

This study was a retrospective cohort study at a single pediatric center, and the associations described here may not be generalizable to all infants with similar lesions. The study was not powered to fully evaluate risk factors associated with stage II and stage III NEC in the preoperative period. As the symptoms of stage I NEC are notoriously nonspecific, there is an increased risk for bias in this data set. However, every attempt was made to faithfully identify cases of NEC. We strictly adhered to the modified Bell criteria for stage I NEC, and each case of NEC was reviewed by research staff and met specific predesignated criteria for inclusion. The fact that the study period was defined by the use of donor breast milk at our center may introduce selection bias. Although our findings suggest that an unfortified, exclusive human milk diet may reduce the risk for preoperative NEC in infants with complex CHD, this study should be primarily viewed as a hypothesis-generating study, and further prospective randomized controlled studies are needed. ■

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Data statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Rape: A Complex Management Problem in the Pediatric Emergency Room

Lipton GL, Roth EI. J Pediatr 1969;75:859-66

This 1969 article is one of the first to describe the range of presentations and complexities of the management of adolescent rape victims in the emergency department (ED). Rape is common, with 11.3% of female and 3.5% of male high school students reporting some form of sexual assault.[1] The article also highlights ways in which ED care of rape victims has advanced. In contrast to Lipton et al, the role of today's ED provider is not to diagnose "rape," but instead to provide appropriate medical and psychological care, as well as legal/law enforcement referrals.[1] Rape is very traumatic for a young person. Best practices require respect for an adolescent's privacy and confidentiality, including taking the history in a quiet, comfortable setting prior to the physical examination, interviewing the patient with and without parents present, and limiting the number of people to whom the patient must tell their story by referring for a single forensic interview.[2] The examination itself is very low yield in the diagnosis of rape, with the most common finding a normal physical.

We must also trust our adolescents. What Lipton et al did not appreciate was that adolescent rape victims may have unpredictable emotional responses and unstable testimony, neither of which indicates that they are not truthful. ED providers and staff must guard against subtle "blaming the victim." Prior consensual sexual experience (even with the alleged perpetrator), provocative dress, or appearing older than their age do not imply complicity.[2] Finally, rape is an area of marked racial and sex inequities in incidence and care, and as providers we must be aware of our own implicit biases. Adolescents of color and lesbian, gay, bisexual, transgender and intersex (LGBTI) adolescents are disproportionately vulnerable to sexual abuse because of discrimination and the historical sexualization of women of color.[2]

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Modified Bell's Staging for NEC			
Stage	**Systemic Signs**	**Gastrointestinal Findings**	**Radiologic Findings**
I a	Temperature instability, A&Bs, Lethargy	Elevated residuals, mild abdominal distention, emesis, guaiac-positive stool	Normal, mild ileus, mild dilation
I b	Same as I a	Above + Bright red blood from rectum	Same as I a
II a	Same as I a	Above + absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
II b	Above + Mild metabolic acidosis, mild thrombocytopenia	Above + definite abdominal tenderness with or without abdominal cellulitis or right lower quadrant mass	Above + portal venous gas with or without ascites
III a	Above + hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, neutropenia	Above + signs of generalize peritonitis, marked tenderness, abdominal distention	Above + definite ascites
III b	Same as III a	Same as III a	Above + pneumoperitoneum

Figure 1. Clinical criteria for diagnosis of NEC by modified Bell staging.

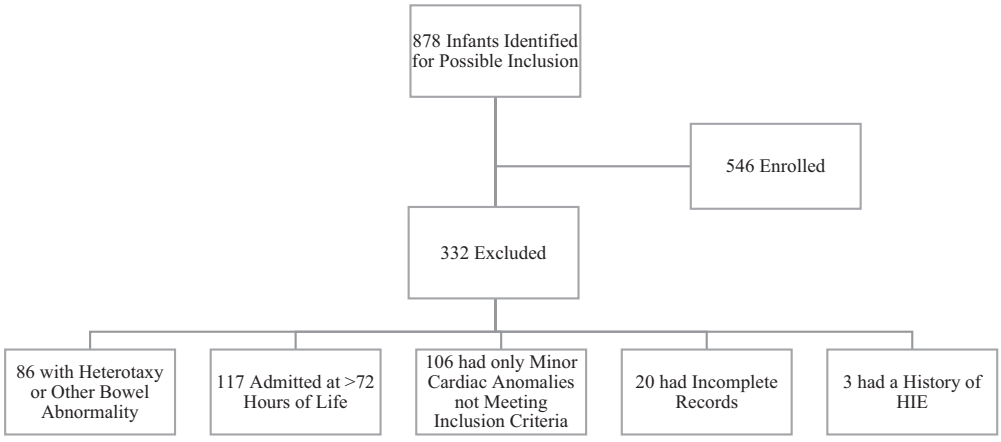

Figure 2. Flowchart of infants included in the study and reasons for exclusion.

Table V. Bivariate associations with stage II/III NEC in the preoperative period

Risk factors	OR (95% CI)	*P* value
White	0.28 (0.08-0.99)	.05
<37 wk gestation	6.62 (1.80-23.91)	.004
SGA	1.55 (0.32-7.43)	.59
Feeds >100 mL/kg/d	4.53 (1.26-16.31)	.02
Exclusively unfortified HMD*	0.23 (0.05-1.12)	.07
Received any fortified feeds†	3.99 (1.04-15.3)	.04
Patient with BiV dd-PBF	3.75 (1.03-13.56)	.04

*Unfortified human milk vs unfortified formula, fortified human milk, fortified formula.
†Unfortified human milk, unfortified formula vs fortified human milk, fortified formula.