HHS Public Access

Author manuscript

Am J Perinatol. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Am J Perinatol. 2015 June ; 32(7): 633–638. doi:10.1055/s-0034-1390349.

Necrotizing Enterocolitis in Infants with Ductal-Dependent Congenital Heart Disease

Kristian C. Becker[1], **Christoph P. Hornik**[1,2], **C. Michael Cotten**[2], **Reese H. Clark**[3], **Kevin D. Hill**[1,2], **P. Brian Smith**[1,2], and **Robert W. Lenfestey**[1]

[1]Duke Clinical Research Institute, Durham, North Carolina

[2]Duke University Medical Center, Durham, North Carolina

[3]Pediatrix-Obstetrix Center for Research and Education, Sunrise, Florida

Abstract

Objective—Infants with congenital heart disease (CHD) receiving prostaglandins (PGE) may be at increased risk for necrotizing enterocolitis (NEC). Enteral feeding may further increase risk of NEC in these patients. We evaluated the incidence of NEC and its association with enteral feeding in infants with ductal-dependent CHD.

Study Design—We examined a cohort of infants with CHD receiving PGE in neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2010. We used logistic regression to evaluate the association between NEC and enteral feeding, as well as other risk factors including antacid medications, inotropic and ventilator support, and anatomic characteristics, controlling for gestational age.

Results—We identified 6710 infants with ductal-dependent CHD receiving PGE for 17,158 infant days. NEC occurred in 21 of 6710 (0.3%) infants, of whom 12/21(57%) were <37 weeks gestational age. The incidence of NEC was 1.2/1000 infant days while on enteral feeds versus 0.4/1000 infant days while not on enteral feeds (p=0.27). Enteral feeding was not associated with a statistically significant increased odds of NEC on the day of diagnosis (odds ratio [OR] 2.08; 95% confidence interval [CI] 0.38, 11.7). Risk factors associated with a significant increased odds of NEC included a diagnosis of single-ventricle heart defect (OR 2.82; 95% CI 1.23, 6.49), although the overall risk in this population remained low (8/1631, 0.5%).

Conclusion—The incidence of NEC in our cohort of infants with ductal-dependent CHD on PGE therapy was low and did not increase with enteral feeding.

Keywords

single-ventricle anomaly; neonatal intensive care; prostaglandin E1; NPO

Address for correspondence: P. Brian Smith, MD, MPH, MHS, Duke Clinical Research Institute, Box 17969, Durham, NC, 27715; phone: 919-668-8951; fax: 919-668-7058; brian.smith@duke.edu.

Conflict of Interest

The remaining authors have no conflicts to declare.

Necrotizing enterocolitis (NEC) is a life-threatening, multifactorial disease process caused by gastrointestinal ischemia leading to excessive inflammation and ultimately necrosis of tissue.[1–3] Ductal-dependent congenital heart disease (CHD) may lower diastolic gut perfusion pressures and limit systemic oxygenated blood flow, directly contributing to gastrointestinal hypoperfusion and ischemia and increasing the risk of NEC.[3–7]

Enteral feeding also plays a role in the pathogenesis of NEC, possibly due to carbohydrate and lipid maldigestion resulting in bacterial overgrowth and mucosal injury.[8,9] The risks of enteral feeds in infants with CHD are less clear.[10,11] Some investigators have argued for rapid advancement of high–caloric-density feeds, while others propose more conservative approaches.[12,13] The role of enteral feeds in the pathogenesis of NEC may also be significantly altered by perioperative hemodynamic changes including low systemic saturation, low cardiac output, increased central venous pressure, and diastolic run-off, resulting in inadequate oxygen delivery to the intestines.[12] As a consequence, there is widespread variability in enteral feeding regimens in infants with CHD, particularly while receiving prostaglandin (PGE) therapy.[8,14,15]

We reviewed a large retrospective cohort of infants with ductal-dependent CHD to evaluate the association between enteral feeding, as well as other known risk factors, and NEC. We hypothesize that enteral feeds are not a risk factor for NEC in this patient population.

Methods

Study population

The study population consisted of a cohort of all infants both inborn and outborn discharged from 322 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group between 1997 and 2010 who were diagnosed with potentially ductal-dependent CHD and treated with PGE during their initial hospitalization. These inclusion criteria were chosen to eliminate infants treated with PGE without a cardiac diagnosis (possibly while awaiting cardiac evaluation) and infants with cardiac diagnoses that may potentially be ductal-dependent but were not severe enough to require patency of the ductus (e.g., tetralogy of Fallot). Days of hospitalization without PGE therapy were not included in the analysis. Data were obtained from an administrative database that prospectively captures information from daily progress notes generated by clinicians on all infants managed by the Pediatrix Medical Group.[16]

Definitions

The primary outcome of our study was a diagnosis of NEC while infants were exposed to PGE. Diagnosis of NEC was defined based on the documentation of NEC diagnosis by the treating neonatologist. We recorded all cases of medically or surgically treated NEC diagnosed on a day the infant was exposed to PGE. All cases of “suspected” or “presumed” NEC were excluded.

We defined ductal-dependent CHD as any of the following diagnoses: hypoplastic left heart syndrome (HLHS), hypoplastic right ventricle, tricuspid atresia, other single-ventricle defects, double-outlet right ventricle (DORV), Ebstein’s anomaly of the tricuspid valve,

tetralogy of Fallot, truncus arteriosus, transposition of the great vessels, atrioventricular canal defect, coarctation of the aorta, interrupted aortic arch, pulmonary atresia, and pulmonary stenosis. We excluded all infants who received PGE therapy diagnosed with normal cardiac anatomy or with heart defects other than the above diagnoses. We defined single-ventricle disease as diagnosis of HLHS, tricuspid atresia, hypoplastic right ventricle, atrioventricular canal defect, or other single-ventricle anatomy.

We defined inotropic support as the administration of dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, or vasopressin for each day. We defined antacid exposure as the administration of rantidine, famotidine, cimetidine, nizatidine, omeprazole, pantoprazole, or lansoprazole for each day. We defined mechanical ventilation as the need for conventional or high-frequency mechanical ventilation for each day. We defined supplemental oxygen administration as the highest fraction of supplemental oxygen (FiO_2) administered for each day. We defined nil per os (NPO) as the absence of enteral nutrition on a given day. We defined breast milk exposure as exposure to either maternal or donor breast milk on a given day. Infants who remained NPO for the duration of this study were defined as having never fed.

Statistical analysis

The unit of observation for this study was an infant day of exposure to PGE. Continuous variables are reported as medians and interquartile ranges, and categorical variables as counts and percentages. We compared infant-level continuous and categorical variables between infants with and without a diagnosis of NEC using Wilcoxon rank sum and Fisher's exact tests, respectively. We performed univariable logistic regression to examine the association between individual daily predictors and NEC diagnosis. Predictors evaluated by logistic regression included: NPO status, administration of inotropic therapy, administration of antacid therapy, use of mechanical ventilation, the highest daily FiO_2, single-ventricle anatomy, and a diagnosis of HLHS. We then performed multivariable logistic regression of each of the above models, controlling for gestational age (GA). We used the method of generalizing estimating equations to account for within-infant correlation for all models. We performed complete case analysis only and did not impute values of missing data. All analyses were performed using Stata 12 (College Station, TX), and a $p < 0.05$ was considered statistically significant.

Results

Patient demographics

We identified 17,019 infants with CHD and 7986 infants exposed to PGE. Of those, 6710 (39% and 84% of the original cohorts, respectively) had both a cardiac diagnosis consistent with ductal-dependent CHD and were treated with PGE and constituted our final cohort. The median GA and birth weight were 38 weeks (interquartile range: 37, 39) and 3045 g (2555, 3433) (Table 1), and total duration of PGE exposure was 17,158 infant days. The majority of infants had 2-ventricle CHD (5079/6710, 76%), and the most common CHD diagnosis was transposition of the great arteries (1271/6710, 19%) (Table 2).

NEC incidence and risk

Of the 6710 infants identified, 21 (0.3%) were diagnosed with NEC. The median postnatal age at NEC diagnosis was 16 days (10, 27). A greater proportion of infants <37 weeks gestation were diagnosed with NEC compared with infants ≥37 weeks gestation (12/21 [57%] vs. 1575/6689 [24%], p=0.001). Infants with NEC also had a lower median GA (33 weeks [31, 38] vs. 38 weeks [37, 39], p<0.001) and lower birth weight (2020 g [1310, 2861] vs. 3045 g [2558, 3435], p<0.001) (Table 1). The incidence of NEC in our cohort decreased with increasing GA: <28 weeks 3/83 (4%); 28–34 weeks 8/704 (2%); 35–36 weeks 1/800 (<1%); >36 weeks 9/5107 (<1%). Premature infants were diagnosed with NEC at a higher median postnatal age compared with term infants (22 [16, 36] vs. 10 [4, 11], p=0.01). Of the 21 cases of NEC, 13 were treated medically, and 8 required surgical intervention. Median postnatal age at the time of surgical intervention for NEC was 13 days (4, 31). Infants with NEC received PGE for a longer duration compared with infants without NEC (26 days [2, 66] vs. 1 day [1, 87], p<0.001), but PGE was started at a similar age in both groups (0 days [0, 2] vs. 0 [(0, 1], p=0.38). The most common CHD diagnosis in infants with NEC was HLHS (5/21, 24%), and 8/21 (38%) infants had a single-ventricle heart defect. The presence of any single-ventricle heart defect increased the odds of NEC after controlling for GA (odds ratio [OR] 2.82, 95% confidence interval 1.23, 6.49) (Table 3). The specific diagnosis of HLHS was also associated with increased odds of NEC after controlling for GA (OR 3.12 [1.16, 8.43]) (Table 3). Of the 21 infants with NEC, 10 (48%) died prior to hospital discharge. Of those infants, 7/10 (70%) were premature, and 4/10 (40%) had a single-ventricle heart defect. Only 1 infant with NEC was full-term and did not have a single-ventricle heart defect. Mortality was significantly higher in infants with NEC compared with those without: 10/21 (47%) vs. 440/6689 (7%), p<0.001. The median duration from NEC diagnosis to death was 4 days (1, 21).

Enteral feeding status

A large proportion of infants in our cohort were never enterally fed (2409/6710, 36%) while on PGE. The proportion of infants never fed was significantly smaller in the NEC group (3/21, 14%) compared with the non-NEC group (2406/6689, 36%, p<0.001). The median NPO time was not significantly different in infants with NEC compared with infants without NEC (1 day [0, 14] vs. 1.5 days [0, 5], p=0.35) but the median time to first enteral feed was longer in infants who developed NEC (5 [3, 7] vs. 2 [1, 4], p<0.001). The incidence of NEC with enteral feeding was 1.2/1000 infant days, and the incidence of NEC without enteral feeding was 0.4/1000 infant days (p=0.27). The incidence of NEC while fed breast milk was 1.1/1000 infants days, and the incidence of NEC when fed formula was 1.3/1000 infant days (p=0.62). Enteral feeding demonstrated a trend towards increased odds of NEC but was not statistically significant (Table 3).

Temporal relationship between enteral nutrition and NEC

The median delay between first day of enteral feeds and diagnosis of NEC was 13 days (5, 21). To evaluate whether NEC risk was delayed in relation to enteral feeding, we repeated our model, including enteral feeding on the day prior to NEC diagnosis. Again, we found increased but non-significant odds of NEC (OR 4.54 [0.98, 21.0]). Results were unchanged

when including any enteral feeds during 48 hours prior to NEC diagnosis (OR 4.54 [0.98, 21.0]).

NEC incidence in premature infants with CHD

When limiting our cohort to premature infants only (<37 weeks GA, n=1587), the proportion of NEC was similarly low (12/1587, 0.8%). Of the 12 premature infants with NEC, 3 had a single-ventricle heart defect, and 1 had HLHS. The incidence of NEC with enteral feeding was 1.7/1000 infant days for premature infants, and there was no diagnosis of NEC while infants were kept NPO. Median postnatal age at NEC diagnosis was older than in the overall cohort (22 days [16, 36]). Of the 12 premature infants with NEC, 7 (58%) died prior to hospital discharge.

Discussion

We present a large cohort of infants with ductal-dependent CHD treated with PGE and describe the association between NEC and enteral feedings. Overall, the proportion of infants with NEC was low (21/6710, 0.3%), and a majority of NEC cases was observed in infants born <37 weeks gestational age (12/21, 57%) and in infants with single-ventricle heart defects (8/21, 38%). In contrast, only 4 term infants with 2-ventricle CHD developed NEC while receiving PGE therapy. Furthermore, enteral feeding on the day of diagnosis was not associated with increased odds of NEC. Of the other risk factors examined, only the presence of a single-ventricle heart defect, particularly HLHS, was associated with NEC.

In infants with ductal-dependent CHD, systemic desaturation, decreased abdominal aortic blood flow, abdominal aortic “run-off” in diastole, and overall decreased cardiac output may contribute to mesenteric circulatory insufficiency, which may predispose an infant to the development of NEC.[12,17,18] Despite all of these theoretical risk factors, we report a relatively low NEC risk of 0.3% in infants with ductal-dependent CHD on PGE. This is almost 10-fold lower than the 3% reported in the only prior analysis of pre-operative NEC risk in infants with ductal-dependent CHD.[5,19] In contrast to our cohort, 28/67 (42%) of infants in this single-center study had single-ventricle CHD (28/67, 42%), which may have contributed to a higher incidence of NEC. Other analyses of CHD influence on NEC development have combined pre- and postoperative NEC risk.[12,20–23] In an analysis of the National Inpatient Sample and Kids’ Inpatient Databases, the incidence of NEC was 1.6%,[21] while other single-center reports have reported a much higher incidence.[12,20,22] Recent studies have suggested that the majority of NEC cases in infants with CHD occur in the post-operative phase, which might explain the substantially lower incidence of NEC that we report.[12]

Among infants diagnosed with NEC, we found a delay between day of first enteral feed and diagnosis of NEC. To evaluate whether NEC risk was delayed in relation to enteral feeding, we repeated our model, once including enteral feeding on the day prior to NEC diagnosis and once including enteral feeding within 48 hours prior to NEC diagnosis. Again, we found increased but non-significant odds of NEC. These findings are consistent with prior observations from single-center cohort studies where pre-operative enteral feeding has

generally been well tolerated.[5,15] Likewise, single-center analyses in the post-operative setting have not found an association between NEC risk and enteral feeding.[12,20]

Despite the reassuring findings from these studies, concerns about the safety of enteral feeding may still limit its use in some centers. In an international survey, 44% of infants were never enterally fed.[24] Survey responders listed concerns about directionality of ductal shunting, doses of PGE, and presence of umbilical arterial or venous catheters, among others. These same concerns may explain why a similar proportion of infants (36%) were never fed while on PGE in our cohort. It is worth noting that, while that the proportion of infants never fed was smaller in the NEC group (3/21, 14%) compared with the non-NEC group (2406/6689, 36%), the incidence of NEC in infants who fed was still only 18/4301 (0.4%) compared with 3/2409 (0.1%) in the never-fed group. This is consistent with prior reports in both the pre- and post-operative settings that have identified that absence of enteral feeding does not prevent NEC.[12,25]

Much of the concern related to enteral feeding in these patients is likely a consequence of the high morbidity and mortality associated with NEC. Indeed, in our population, mortality in infants with NEC was substantially higher (48%) than in the remainder of the patient cohort (6.7%). Importantly, 7 of the 10 deaths occurred in premature infants. Excluding the premature infants, mortality for infants with NEC (14%) was comparable to the 19–24% mortality reported in recent studies.[12,21] This mortality risk highlights that NEC is a serious comorbidity in infants with ductal-dependent CHD, and further study is needed to reduce mortality in affected patients.[18,26,27]

The strengths of our study include its large multi-center cohort of infants with diverse forms of ductal-dependent CHD and varying gestational ages. This allows us to evaluate risks of NEC across a wider range of baseline risk conferred by both gestational age and CHD. Our analysis at the infant-day level allows us to control for variable duration of PGE exposure in our database, as well as several surrogates of severity of illness such as inotropic medication, mechanical ventilation, and supplemental FiO_2 that vary on a daily basis. Our study is limited by the retrospective nature of the analysis and the fact that the data are derived from electronic documentation. The diagnosis of NEC was made by treating neonatologists as recorded in the database and did not include Bell staging. We did not have detailed information on cardiac diagnoses or physiologic states, including no information about prenatal diagnoses. To provide a better understanding of the cardiac anatomy and physiology of our population, we included only those infants with a subset of clearly defined potentially ductal-dependent CHD who were also treated with PGE. While our sample size was large overall, the incidence of NEC in this population of mainly term infants was low. We were therefore not able to perform more extensive analyses of NEC risk factors and only controlled for GA in the regression analysis. Although the incidence of NEC was greater in premature infants than in term infants with CHD, fewer numbers of premature infants with CHD precluded us from performing any further analyses on feeding and the development of NEC in this population. Sample size limitations such as these are a concern for any analysis of a rare condition and highlight the utility of registry data, such as the Pediatrix dataset, that include large numbers of hospitalized infants. Retrospectively, our sample size proved us with >80% power to detect a 0.5% difference in NEC incidence between infants of all GA

who fed vs. those who never fed. Similarly for full term infants, we had 80% power to detect a 0.6% difference, while the smaller sample of premature infants increased the detectable difference level to 1.7%. The sample size of premature infants did not provide sufficient power to detect statistically significant differences in the incidence of NEC between those who were fed vs. those who were never fed. Several important covariates, including the volume and osmolarity of enteral feeds, the rate of advancement of enteral feeds, and blood transfusions, were not captured in the database at the time of this analysis. Lastly, it is important to note that we focused our analysis on the pre-operative setting and thus cannot generalize these results to address the risk factors, specifically the risk of enteral feeding, among infants with CHD in the post-operative state.

In summary, in this study of mainly term infants receiving PGE for ductal-dependent CHD, we observed an overall low incidence of NEC. Enteral feeding was not associated with a statistically significant increase in the odds of NEC even after adjusting for GA. In the absence of a randomized controlled trial and given the benefits of enteral feedings, our study supports the practice of enteral feeding in an infant cohort of varying gestational ages with CHD requiring PGE. Future studies might include larger cohorts of premature infants with CHD in whom the incidence of NEC is higher.

Acknowledgments

C.P.H. receives support from support for research from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) (UL1TR001117). P.B.S. receives salary support for research from the NIH and the National Center for Advancing Translational Sciences (HHSN267200700051C, HHSN275201000003I, and UL1TR001117); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp).

References

1. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011; 364:255–264. [PubMed: 21247316]
2. Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet. 2006; 368:1271–1283. [PubMed: 17027734]
3. Sharma R, Tepas JJ 3rd. Microecology, intestinal epithelial barrier, and necrotizing enterocolitis. Pediatr Surg Int. 2010; 26:11–21. [PubMed: 19967379]
4. Lugo B, Ford HR, Grishin A. Molecular signaling in necrotizing enterocolitis: regulation of intestinal COX-2 expression. J Pediatr Surg. 2007; 42:1165–1171. [PubMed: 17618875]
5. Natarajan G, Anne SR, Aggarwal S. Outcomes of congenital heart disease in late preterm infants: double jeopardy? Acta Paediatr. 2011; 100:1104–1107. [PubMed: 21362036]
6. Ostlie DJ, Spilde TL, St Peter SD, et al. Necrotizing enterocolitis in full-term infants. J Pediatr Surg. 2003; 38:1039–1042. [PubMed: 12861534]
7. Stapleton GE, Eble BK, Dickerson HA, Andropoulos DB, Chang AC. Mesenteric oxygen desaturation in an infant with congenital heart disease and necrotizing enterocolitis. Tex Heart Inst J. 2007; 34:442–444. [PubMed: 18172526]
8. Berseth CL. Feeding strategies and necrotizing enterocolitis. Curr Opin Pediatr. 2005; 17:170–173. [PubMed: 15800406]
9. Buddington RK, Bering SB, Thymann T, Sangild PT. Aldohexose malabsorption in preterm pigs is directly related to the severity of necrotizing enterocolitis. Pediatr Res. 2008; 63:382–387. [PubMed: 18356743]
10. Sehgal A, Coombs P, Tan K, McNamara PJ. Spectral Doppler waveforms in systemic arteries and physiological significance of a patent ductus arteriosus. J Perinatol. 2011; 31:150–156. [PubMed: 20651695]

11. Torres A Jr. To (enterally) feed or not to feed (the infant with hypoplastic left heart syndrome) is no longer the question. Pediatr Crit Care Med. 2010; 11:431–432. [PubMed: 20453619]
12. Iannucci GJ, Oster ME, Mahle WT. Necrotising enterocolitis in infants with congenital heart disease: the role of enteral feeds. Cardiol Young. 2013; 23:553–559. [PubMed: 23025968]
13. Pillo-Blocka F, Adatia I, Sharieff W, McCrindle BW, Zlotkin S. Rapid advancement to more concentrated formula in infants after surgery for congenital heart disease reduces duration of hospital stay: a randomized clinical trial. J Pediatr. 2004; 145:761–766. [PubMed: 15580197]
14. Medoff-Cooper B, Irving SY. Innovative strategies for feeding and nutrition in infants with congenitally malformed hearts. Cardiol Young. 2009; 19 (Suppl 2):90–95. [PubMed: 19857355]
15. Willis L, Thureen P, Kaufman J, Wymore E, Skillman H, da Cruz E. Enteral feeding in prostaglandin-dependent neonates: is it a safe practice? J Pediatr. 2008; 153:867–869. [PubMed: 19014824]
16. Hornik CP, Fort P, Clark RH, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev. 2012; 88 (Suppl 2):S69–S74. [PubMed: 22633519]
17. Carlo WF, Kimball TR, Michelfelder EC, Border WL. Persistent diastolic flow reversal in abdominal aortic Doppler-flow profiles is associated with an increased risk of necrotizing enterocolitis in term infants with congenital heart disease. Pediatrics. 2007; 119:330–335. [PubMed: 17272623]
18. Giannone PJ, Luce WA, Nankervis CA, Hoffman TM, Wold LE. Necrotizing enterocolitis in neonates with congenital heart disease. Life Sci. 2008; 82(7–8):341–347. [PubMed: 18187159]
19. Natarajan G, Reddy Anne S, Aggarwal S. Enteral feeding of neonates with congenital heart disease. Neonatology. 2010; 98:330–336. [PubMed: 20453528]
20. McElhinney DB, Hedrick HL, Bush DM, et al. Necrotizing enterocolitis in neonates with congenital heart disease: risk factors and outcomes. Pediatrics. 2000; 106:1080–1087. [PubMed: 11061778]
21. Mukherjee D, Zhang Y, Chang DC, Vricella LA, Brenner JI, Abdullah F. Outcomes analysis of necrotizing enterocolitis within 11 958 neonates undergoing cardiac surgical procedures. Arch Surg. 2010; 145:389–392. [PubMed: 20404291]
22. Leung MP, Chau KT, Hui PW, et al. Necrotizing enterocolitis in neonates with symptomatic congenital heart disease. J Pediatr. 1988; 113:1044–1046. [PubMed: 3193310]
23. Pickard SS, Feinstein JA, Popat RA, Huang L, Dutta S. Short- and long-term outcomes of necrotizing enterocolitis in infants with congenital heart disease. Pediatrics. 2009; 123:e901–e906. [PubMed: 19403484]
24. Howley LW, Kaufman J, Wymore E, et al. Enteral feeding in neonates with prostaglandin-dependent congenital cardiac disease: international survey on current trends and variations in practice. Cardiol Young. 2012; 22:121–127. [PubMed: 21771388]
25. Iannucci GJ, Mahle WT, Clabby ML. Coarctation of the aorta in the setting of tetralogy of Fallot: an uncommon cause of myocardial dysfunction. Cardiol Young. 2012; 2:1–3.
26. Hasegawa T, Yoshioka Y, Sasaki T, et al. Necrotizing enterocolitis in a term infant with coarctation of the aorta complex. Pediatr Surg Int. 1997; 12:57–58. [PubMed: 9035212]
27. Bolisetty S, Lui K, Oei J, Wojtulewicz J. A regional study of underlying congenital diseases in term neonates with necrotizing enterocolitis. Acta Paediatr. 2000; 89:1226–1230. [PubMed: 11083380]

Table 1

Demographics

	NEC (N=21, 0.3%)	No NEC (N=6689, 99.7%)	p value
Birth weight (g)			<0.001
< 1000	2 (10%)	104 (2%)	
1000–1499	5 (24%)	237 (4%)	
1500–2499	6 (28%)	1159 (17%)	
2500–3499	7 (33%)	3724 (55%)	
≥ 3500	1 (5%)	1440 (22%)	
Gestational age (weeks)			<0.001
< 28	3 (14%)	80 (1%)	
28–34	8 (38%)	696 (11%)	
35–36	1 (5%)	799 (12%)	
> 36	9 (43%)	5098 (76%)	
Male	12 (57%)	3995 (60%)	0.83
Race/ethnicity			0.11
White	7 (35%)	3524 (55%)	
Black	4 (20%)	754 (12%)	
Hispanic	9 (45%)	1752 (28%)	
Other	0 (0%)	345 (6%)	
Inborn	11 (55%)	4498 (68%)	0.23
Never fed	3 (14%)	2406 (36%)	<0.001
Inotropes (days/patient)[a]	2 (0, 8)	0 (0, 29)	<0.001
NPO (days/patient)[a]	1.5 (0, 5)	1 (0, 14)	0.35
Prostaglandins (days/patient)[a]	26 (2, 66)	1 (1, 87)	<0.001

[a]Median and interquartile range.

Abbreviations: NEC, necrotizing enterocolitis; NPO, nil per os.

Table 2

Congenital heart defects in the study population

	NEC (N=21)	No NEC (N=6689)
Single-ventricle defects	**8 (38%)**	**1623 (24%)**
Hypoplastic left heart	5 (24%)	1106 (17%)
Tricuspid atresia	1 (5%)	194 (3%)
Hypoplastic right ventricle	0 (0%)	8 (<1%)
Other single ventricle	0 (0%)	115 (2%)
Non–single-ventricle defects	**13 (62%)**	**5161 (80%)**
Pulmonary stenosis	3 (14%)	451 (7%)
Coarctation of the aorta	2 (10%)	1071 (16%)
Tetralogy of Fallot	2 (10%)	602 (9%)
Interrupted aortic arch	2 (10%)	256 (4%)
Pulmonary atresia	1 (5%)	744 (11%)
Transposition of great arteries	1 (5%)	1270 (19%)
Truncus arteriosus	1 (5%)	79 (1%)
Aortic valve stenosis	0 (0%)	286 (4%)
Ebstein’s anomaly	0 (0%)	150 (2%)
Double outlet right ventricle	1 (5%)	257 (4%)

Abbreviation: NEC, necrotizing enterocolitis.

Table 3

Risk of necrotizing enterocolitis while on prostaglandin infusion, odds ratio (95% confidence interval)

	Unadjusted	Adjusted[a]
Enteral feeding	2.86 (0.57, 14.3)	2.08 (0.38, 11.7)
Inotropic support	1.79 (0.72, 4.46)	1.88 (0.75, 4.73)
Antacid medication	3.76 (1.15, 12.30)	2.65 (0.71, 9.81)
Mechanical ventilation	1.87 (0.82, 4.28)	1.61 (0.69, 3.78)
FiO_2		
21%	Reference	Reference
22–50%	1.64 (0.63, 4.25)	1.34 (0.49, 3.66)
>50%	1.61 (0.51, 5.04)	1.77 (0.55, 5.64)
Single-ventricle heart defect	2.40 (1.07, 5.38)	2.82 (1.23, 6.49)
Hypoplastic left heart syndrome	2.20 (0.86, 5.63)	3.12 (1.16, 8.43)

[a] Adjusted models control for gestational age.

Abbreviation: FiO_2, fraction of supplemental oxygen.