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Necrotizing Enterocolitis Associated with Congenital Heart Disease: a Different Entity?

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) predominantly occurs in preterm infants (PT-NEC). In term neonates, NEC occurs more frequently when a congenital heart disease is present (CHDNEC). Our aim was to evaluate differences and similarities in disease characteristics of PT-NEC versus CHD-NEC.
Methods: In this retrospective case–control study we identified all CHD infants who developed NEC Bell's stage ≥2 in our center from 2004 to 2014. We randomly selected (1:2 ratio) PT-NEC infants from the same period. Biochemical and clinical variables were retrieved from patient files.
Results: We found 18 CHD-NEC infants and selected 36 PT-NEC infants (gestational age 28.3 [25–35.6] weeks vs. 38.6 [31.7–40.7] weeks). Postnatal age at onset was significantly lower in CHD-NEC patients (4 [2–24] vs. 11 [4–41] days, $p < 0.001$). Lowest pH levels were lower (7.21 [7.01–7.47] vs. 7.27 [6.68–7.39], $p = 0.02$), and highest CRP levels were higher (112.5 mg/L [5.0–425.0] vs. 66.0 [5.2–189.0], $p = 0.05$) in PT-NEC vs. CHD-NEC. Anatomic localisation of the disease differed: the colon was significantly more often involved in CHD-NEC versus PT-NEC (86% vs. 33%, $p = 0.03$). Mortality caused by NEC was not different (22% vs. 11%, $p = 0.47$).
Conclusion: While outcome of NEC in both groups is similar, the predominant NEC localisation differed between CHD-NEC and PT-NEC patients. This suggests that both variants of the disease have a different underlying pathophysiological mechanism that predisposes different intestinal regions to develop NEC.
Type of Study: Retrospective Case–Control Study.
Level of evidence: Level III.

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Necrotising enterocolitis (NEC) is the most prevalent acute gastroenterological disease in the Neonatal Intensive Care Unit (NICU). Typical characteristics of the disease are intestinal inflammation, hypoxia/ischemia and necrosis [1,2]. NEC is a leading cause of neonatal morbidity and mortality [3].

Although NEC is primarily seen in preterm infants, with an approximate incidence of 7% in infants with a very low birth weight (VLBW; <1500 g) [4–6], it has also been reported in full-term infants [7]. Various studies identified clinical features associated with the development of NEC in full-term infants. Particularly congenital heart disease (CHD) is recognized as a risk factor [8–10]. In a population of infants with complex CHD, the risk of developing NEC is substantially higher than in the general population [11,12].

Splanchnic hypoperfusion and intestinal ischemia have been suggested to be key factors in the pathophysiology of NEC in infants with a CHD. The hypothesized pathophysiology involves reduced systemic perfusion, leading to insufficient mesenteric circulation and thereby causing intestinal ischemia [11,12]. Immaturity of the intestinal tract and immune system, and abnormal bacterial colonization in the bowel are (amongst others) nowadays recognized as additional key factors in the pathophysiology of NEC in preterm infants (PT-NEC) [1,2].

As yet, relatively little is known about the exact pathogenesis of NEC, neither in preterm infants nor in patients with a CHD. The question arises whether PT-NEC and CHD-NEC are different diseases with a different pathophysiology, while symptoms are quite similar [13]. The aim of this study was to evaluate the differences and similarities of the pathophysiological mechanisms underlying PT-NEC and CHD-NEC, by comparing clinical and biochemical characteristics of both diseases.

1. Materials and methods

This was a retrospective 1:2 ratio case–control study performed in the tertiary Neonatal Intensive Care Unit (NICU) of the University Medical Center Groningen. In the period from 2004 until 2014 we identified 147 NEC (Bell's stage ≥2) infants. Twenty-two of them had a congenital

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heart disease other than isolated patent ductus arteriosus. We excluded four CHD-patients because they were also born preterm with a VLBW (<1500 g), making it impossible to assign them to exclusively to one of the groups. The remaining 18 patients were considered as cases and included in the CHD-NEC group. As controls, we randomly selected 36 preterm NEC patients (GA <37 weeks) without CHD using SPSS to form the preterm NEC (PT-NEC) group, with equal proportions in the first (2004–2009) and second (2010–2014) half of the inclusion period to neutralize any possible bias by (minor) changes in management.

Of the CHD-NEC patients we documented their type of CHD, whether the CHD was surgically corrected and at which age (before or after NEC). Hemodynamic characterization of the CHD's was defined by the consultant pediatric cardiologist using echocardiographic characteristics of the CHD's. We analyzed various parameters to identify differences between both groups, including general patient characteristics that possibly could have contributed to developing NEC (gender, GA, birth weight, Apgar scores at 1 and 5 minutes and presence of patent ductus arteriosus before NEC onset) and disease-specific variables that indicate clinical severity of the disease. Disease-specific variables included clinical variables (e.g. age at onset, Bell's stage, need for inotropic medication, presence of bowel perforation), biochemical variables from clinical onset of NEC symptoms until clinical recovery or surgery if surgery took place (mean or median and most abnormal [highest or lowest] value of leukocyte count, thrombocyte count, Hb, CRP, lactate, glucose, pH, pO2, pCO2), intestinal location of NEC lesions (only in surgical NEC patients), and outcome variables (mortality, complications such as anastomotic leakage or post-NEC stenosis), all of which have been reported as important indicators of disease severity and prognosis [14–16].

The data were analyzed using SPSS statistics 20 (IBM Corp. Armonk, New York, N.Y., USA). First we used descriptive statistics to describe the population and parameters, using mean ± standard deviation for normally distributed data, or median [minimum-maximum] for non-normally distributed data. For comparison of categorical variables we used X^2 test or Fisher's exact test and for comparison of continuous variables we used student's t test or Mann–Whitney U test, as appropriate. $p < 0.05$ was considered statistically significant. Missing data were deleted pairwise. We performed an additional within- and between-group analysis of cases with and without presence of a persistent ductus arteriosus (PDA).

The Medical Ethical Committee of the UMCG waived the need for consent from patients to access their medical records. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

2. Results

2.1. CHD characteristics

The various types of congenital heart defects are presented in Table 1. More than half of the infants either had a transposition of the great arteries with or without a ventricular septal defect (N = 6; 33%), or an aortic coarctation or interruption combined with a ventricular septal defect (N = 4; 22%). Hemodynamic characterization of the CHD's in this series shows decreased lower body/intestinal perfusion (either by pulmonary steal or obstruction of systemic circulation) in all 18 infants (100%), combined with low saturated blood to the lower body in 13 (72.2%).

Two patients had undergone balloon atrial septostomy (BAS procedure) before they developed NEC to provide acceptable arterial oxygen saturation levels before definitive surgical correction of the CHD. All patients developed NEC prior to the surgical correction of their CHD. In eight patients the CHD was not surgically corrected at all, in six because the patient had passed away and in two because the CHD (in both cases a VSD) had become hemodynamically insignificant.

2.2. Patient characteristics

Patient characteristics are presented in Table 2. PT-NEC patients had a lower gestational age and birth weight compared to CHD-NEC (28.3 [25–35.6] weeks vs. 38.6 [31.7–40.7] weeks); 1135 [615–2280] g vs. 2895 [1545–3700] g). Patent ductus arteriosus occurred more often in the CHD-NEC group than the PT-NEC group (78% vs. 44%, p = 0.02), which in 12 out of 14 CHD-NEC patients was achieved by prostaglandin treatment. Patients in both groups were fed by human milk or formula equally often. Fortification of the feeding (either milk or formula) was used more often in PT-NEC compared to CHD-NEC (80.6% vs. 27.8%, p < 0.001). The CHD-NEC patients that received fortified feeding were all except one (borderline) premature. Requirement of inotropic support prior to and during NEC did not differ between PT-NEC and CHD-NEC infants (p = 0.47, p = 1.00).

2.3. Disease characteristics and outcome

Postnatal age at onset of NEC was higher in PT-NEC compared to CHD-NEC infants (11 [4–41] vs. 4 [2–24] days, p < 0.001). Absolute age at onset of NEC was significantly lower in PT-NEC compared to CHD-NEC infants (31.4 [26.1–37.0] vs. 39.4 [34.0–41.1] weeks, p < 0.001). There were no significant differences in Bell's stage between the two groups. The clinical parameters that were analyzed are presented in Table 3.

Mean hemoglobin levels were lower in PT-NEC compared to CHD-NEC (8.0 ± 0.8 vs. 8.5 ± 1.0, p = 0.047). Lowest pH levels were lower in PT-NEC than in CHD-NEC (7.21 [7.01–7.47] vs. 7.27 [6.68–7.39], p = 0.02). Median pH levels tended to be lower in PT-NEC than in CHD-NEC (7.33 [7.20–7.49] vs. 7.38 [7.27–7.42], p = 0.07). Highest CRP levels were higher in PT-NEC compared to CHD-NEC (112.5 mg/L [5.0–425.0] vs. 66.0 [5.2–189.0], p = 0.05). Median CRP levels also tended to be higher in PT-NEC than in CHD-NEC (43.3 mg/L [4.5–184.0] vs. 30.5 [0.7–117.7], p = 0.10). The other biochemical parameters were not different. All biochemical parameters are presented in Table 4.

Table 1
Characteristics of the congenital heart diseases.

CHD classification	PDA	DDSC	DDPC	A	B	N = 18
Transposition of the great arteries +/− VSD	+	-	-	+	+	6 (33%)
Left-sided obstructive heart disease CoAo/ Ao-interruption (n = 5) + VSD or DORV HLHS (n = 1)	+	+	-	+	+	6 (33%)
Tetralogy of Fallot	+	-	+	+	-	2 (11%)
TAPVR	+	-	-	+	+	1 (6%)
Isolated VSD	-	-	-	+	-	3 (17%)

PDA = patent ductus arteriosus; DDSC = duct dependent systemic circulation; DDPC = duct dependent pulmonary circulation; A = decreased perfusion of lower body due to pulmonary steal and/or obstruction systemic circulation; B = relative low oxygen saturated blood directed to lower body; VSD = ventricular septal defect; CoAo = aortic coarctation; DORV = double outlet right ventricle; HLHS = hypoplastic left heart syndrome; TAPVR = total abnormal pulmonary venous return. Data are presented as N (%).

Table 2
Demographic data.

	PT-NEC (N = 36)	CHD-NEC (N = 18)	p-Value
Gender (M)	20 (56%)	8 (44%)	p = 0.44
Gestational age (weeks)	28.3 [25–35.6]	38.6 [31.7–40.7]	p < 0.001
Birth weight (g)	1135 [615–2280]	2895 [1545–3700]	p < 0.001
Apgar score at:			
- 1 min	4.5 [0–9]	8.0 [2–9]	p = 0.01
- 5 min	7.0 [3–10]	8.0 [7–10]	p = 0.02
Patent Ductus Arteriosus	16 (44%)	14 (78%)*	p = 0.02
Feeding strategy			
- Human milk	6 (33.3%)	12 (33.3%)	p = 1.00
- Formula	7 (38.9%)	17 (47.2%)	p = 0.56
- Fortified (either milk or formula)	5 (27.8%)	29 (80.6%)	p < 0.001
- Unknown			
	5 (27.8%)	7 (19.4%)	p = 0.51
Inotropy pre-NEC**	8 (22%)	2 (11%)	p = 0.47
- Dopamine			p = 0.24
- Dobutamine			p = 0.11
- Norepinephrine	- 8 (22%)	- 1 (6%)	p = 1.00
- Milrinone	- 0 (0%)	- 2 (11%)	p = 0.33
	- 0 (0%)	- 0 (0%)	
	- 0 (0%)	- 1 (6%)	
Inotropy peri-NEC**	9 (25%)	5 (28%)	p = 1.00
- Dopamine			p = 1.00
- Dobutamine			p = 0.04
- Norepinephrine	- 8 (22%)	- 3 (17%)	p = 1.00
- Milrinone	- 1 (3%)	- 3 (17%)	p = 0.33
	- 1 (3%)	- 1 (6%)	
	- 0 (0%)	- 1 (6%)	

Data are presented as N (%) or median [range] accordingly.
* in 12 out of the 14 CHD-NEC patients with a PDA, the ductus was maintained patent by prostaglandin administration.
** the patients that required inotropic support received 1–2 inotropic agents.

Surgical intervention was deemed necessary in 18 (50%) of the PT-NEC cases and in seven (39%) of the CHD-NEC infants (p = 0.44). In 10 (56%) surgical PT-NEC patients small bowel resection was performed, compared to 2 (29%) CHD-NEC patients (p = 0.38). Colonic resection was performed in 7 surgical PT-NEC patients (39%) vs. 5 (71%) CHD-NEC patients (p = 0.20). One PT-NEC patient (5.6%) and no CHD-NEC patients were treated by primary peritoneal drainage (p = 1.00). Hence, we could not demonstrate significant differences in surgical approach between PT-NEC and CHD-NEC patients.

In Fig. 1A we present the location of the NEC lesions, categorized into focal (subdivided into small bowel, ileocecal or colon), multifocal and panintestinal. Focal-colonic lesions were more prevalent in the surgical CHD-NEC infants (five [71%] vs. two [11%], p = 0.001). In Fig. 1B we

Table 3
Clinical parameters.

	PT-NEC (N = 36)	CHD-NEC (N = 18)	p-Value
Postnatal age at onset (days)	11 [4–41]	4 [2–24]	p < 0.001
Absolute age at onset (weeks)	31.4 [26.1–37.0]	39.4 [34.0–41.1]	p < 0.001
Final Bell's stage			p = 0.15
○ 2A	17 (47%)	8 (44%)	
○ 2B	1 (2.8%)	3 (17%)	
○ 3A	3 (8.3%)	1 (5.6%)	
○ 3B	15 (42%)	6 (33%)	
Perforated bowel	16 (44%)	6 (33%)	p = 0.43
Surgery	18 (50%)	7 (39%)	p = 0.44
Complications			
- Overall*	10 (28%)	4 (22%)	p = 0.75
- Stenosis	5 (14%)	2 (11%)	p = 1.00
- Anastomotic leakage	2 (5.6%)	1 (5.6%)	p = 1.00
- Adhesions	1 (2.8%)	0 (0%)	p = 1.00
- Perforation (post-NEC)	2 (5.6%)	0 (0%)	p = 0.55
- Short bowel syndrome	1 (2.8%)	0 (0%)	p = 1.00
- Catheter sepsis	1 (2.8%)	0 (0%)	p = 1.00
- Wound dehiscence	2 (5.6%)	1 (5.6%)	p = 1.00
- Strangulation ileus	0 (0%)	1 (5.6%)	p = 0.33
Mortality			
- Overall	9 (25%)	7 (39%)	p = 0.29
- As consequence of NEC	8 (22%)	2 (11%)	p = 0.47
Blood transfusion during NICU admission	31 (89%)	14 (78%)	p = 0.42
Mechanical ventilation	29 (81%)	12 (67%)	p = 0.32

Data are presented as N (%) or median [range] accordingly.
* Overall represents the number of patients that experienced complications. Some patients experienced multiple complications, with a median of 0 [0–2] per patient in each group.

Table 4
Laboratory values.

	PT-NEC (N = 36)	CHD-NEC (N = 18)	p-Value
Leukocytes ($\times 10^9$/L)			
- Lowest	6.3 [2.3–17.7]	7.4 [1.2–20.3]	p = 0.83
- Median	12.0 [3.2–32.5]	11.5 [2.1–21.4]	p = 0.54
Thrombocytes ($\times 10^9$/L)			
- Lowest	93.0 [3.0–542.0]	131.0 [4.0–329.0]	p = 0.58
- Median	198.0 [5.0–576.0]	241.8 [52.0–678.0]	p = 0.18
Hemoglobin (mmol/L)			
- Lowest	6.5 ± 1.1	7.0 ± 1.1	p = 0.12
- Mean	8.0 ± 0.8	8.5 ± 1.0	p = 0.047
CRP (mg/L)			
- Highest	112.5 [5.0–425.0]	66.0 [5.2–189.0]	p = 0.05
- Median	43.3 [4.5–184.0]	30.5 [0.7–117.7]	p = 0.10
Lactate (mmol/L)			
- Highest	2.7 [1.1–13.0]	3.6 [1.3–22.6]	p = 0.56
- Median	1.9 [1.1–12.6]	2.3 [1.2–11.5]	p = 0.60
Glucose (mmol/L)			
- Lowest	4.0 [1.1–9.9]	4.2 [2.3–6.5]	p = 0.76
- Median	5.5 [4.1–19.0]	5.9 [2.9–10.7]	p = 0.98
pH			
- Lowest	7.21 [7.01–7.47]	7.27 [6.68–7.39]	p = 0.02
- Median	7.33 [7.20–7.49]	7.38 [7.27–7.42]	p = 0.07
pO2 (kPa)			
- Lowest	5.9 [3.9–9.8]	5.1 [2.5–8.3]	p = 0.32
- Median	7.8 [5.1–22.0]	6.6 [2.5–16.7]	p = 0.41
pCO2 (kPa)			
- Highest	7.6 [4.6–16.2]	6.5 [4.6–10.5]	p = 0.07
- Median	5.6 [3.8–7.6]	5.5 [4.3–7.0]	p = 0.73

Data are presented as mean ± S.D. (for normally distributed data) or median [range] (for not-normally distributed data) accordingly.
These data were collected from NEC onset until recovery or surgery took place.

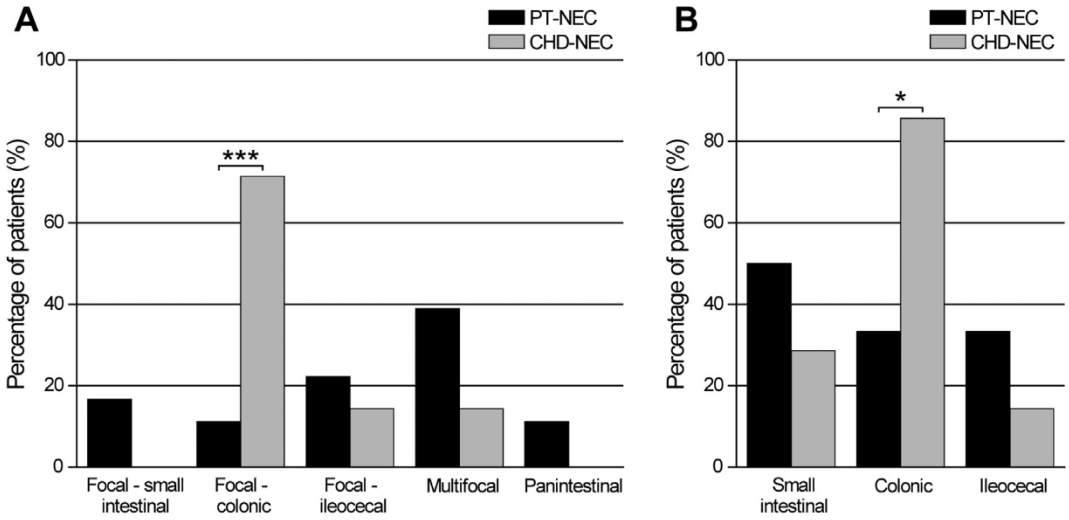

Fig. 1. (a) Location of NEC lesions in PT-NEC versus CHD-NEC patients, (b) total percentage of NEC patients with disease involvement (focal or multifocal) of the small intestine, colon and ileocecal region. *p = 0.03 ***p = 0.001.

present the combined percentage of infants with focal or multifocal NEC that showed involvement of each intestinal area (small bowel, ileocecal or colon). Again, when combining focal and multifocal disease, the colon was more often affected in the surgical CHD-NEC infants (six [86%] vs. six [33%], p = 0.03). In the focal-colonic group, all lesions were located in the ascending or transverse colon. The descending and sigmoid colon were only affected in case of multifocal and panintestinal lesions.

Mortality rates were not different between PT-NEC and CHD-NEC infants (four [22%] vs. four [11%], p = 0.47). Complication rates (intestinal as well as extra-intestinal) were also not different between both groups. Stenoses occurred in a comparable rate in both groups: in 2 (11%) CHD-NEC patients (1 treated surgically and 1 treated conservatively) and in 5 (14%) PT-NEC patients (2 treated surgically and 3 treated conservatively). Short bowel syndrome occurred in comparable rates in both groups: in 1 PT-NEC patient (2.8%) vs. 0 CHD-NEC patients.

2.4. Presence of a PDA

Comparison of CHD-NEC cases with (78%) and without (22%) a PDA showed no significant differences in clinical or biochemical parameters. Comparison PT-NEC cases with (44%) and without (66%) a PDA showed lower gestational age and birth weight when a PDA was present, a trend towards higher incidence of Bell's stage 3, significantly higher mortality rates, intubation rates, incidence of surgical NEC, prolonged hospitalization, higher CRP and pCO2 levels and lower pH and pO2 levels when a PDA was present.

3. Discussion

This study demonstrated that, during the course of NEC, the colon was considerably more often affected in infants with a CHD than in preterm infants. The most important indicators of short-term outcome and clinical disease progression (mortality, Bell's stage, surgical NEC and complication rates) were not significantly different. Some of the other variables including Hb, pH and CRP levels and duration of NICU stay were different between groups and either reflected gestational age-dependent differences or support the theory of different pathophysiological mechanisms.

The most striking difference between the groups was that CHD-NEC evidently more often involved the colon, instead of the small intestine or ileocecal region. Intestinal blood supply is provided by the superior and inferior mesenteric artery (SMA/IMA) and celiac artery. Intestinal regions along the most distal parts of these arteries ('watershed zones') are at risk for ischemic injury. Particularly the splenic flexure (watershed between SMA and IMA) and to a lesser extent the rectosigmoid junction (watershed between IMA and rectal arteries) are prone [17–19]. Previous clinical and experimental research confirmed susceptibility of the colon to ischemic injury in various situations, such as nonocclusive mesenteric ischemia, systemic sepsis and shock. Presumably increased susceptibility of the colon results from inferior collateral blood supply compared to other intestinal regions [20–24]. Our findings correspond to the hypothesis that ischemia is a key factor in the pathophysiology of CHD-NEC, in contrast to PT-NEC showing much less colonic involvement.

Intestinal hypoperfusion associated with CHD can be caused directly by decreased cardiac output, or by the *diving reflex*; redistribution of cardiac output to ensure perfusion of the brain and heart at the expense of other organs. This reflex has been associated with necrotizing enterocolitis [25]. However, a more plausible mechanism in the present study is the "steal" phenomenon: decreased tissue perfusion caused by diastolic backflow to areas of lower resistance. This is in line with previous studies reporting an increased risk of NEC in CHD's with persistent retrograde diastolic blood flow in the descending aorta by Doppler flow pattern analysis [26].

From a hemodynamic point of view there are two important mechanisms in our study that could predispose these patients to develop CHD-NEC. First, all of the CHDs our infants had caused decreased perfusion of the lower body, including the intestinal organs. This occurs either by a "pulmonary steal" phenomenon, as described previously, or by obstruction of systemic circulation. This may lead directly to intestinal ischemia and could therefore cause CHD-NEC. Furthermore, the majority of CHDs in our study also led to low saturated arterial blood directed towards the lower parts of the body, forming an additional risk factor for intestinal hypoxia.

Clinically PT-NEC and CHD-NEC had similar outcome in our study. Surgical NEC occurred equally often in both groups. Complication rates were comparable. Theoretically the risk of short bowel syndrome would be higher in PT-NEC patients compared to CHD-NEC, because it more often involves the small intestine. However our data do not confirm this theory. Mortality rates were not different in both groups. Our mortality rates in PT-NEC correspond to previous research. Our mortality rates in CHD-NEC are comparable to general mortality rates in infants with a CHD (~15%) [27]. Previous research showed better outcome in NEC associated with CHD compared to NEC without CHD [28]. While our findings suggest increased severity of disease in PT-NEC compared to CHD-NEC based on biochemical parameters, we did not find significant differences in outcome. Perhaps our study was underpowered to confirm these findings.

Biochemically we found higher CRP levels in PT-NEC versus CHD-NEC, indicating more excessive inflammatory reaction in PT-NEC patients. This also supports different pathophysiological mechanisms: a primary inflammatory disease with secondary necrosis (PT-NEC) versus a primary ischemic disease with secondary inflammation (CHD-NEC). We found lower Hb levels in PT-NEC versus CHD-NEC, which is likely caused by prematurity or by hypoxia-induced erythropoiesis in CHD-NEC. Also we found lower pH levels in PT-NEC compared to CHD-NEC, which might indicate worse clinical status in PT-NEC cases, or could be a result of different underlying pathophysiology. In PT-NEC metabolic acidosis is a well-described finding, caused by acids produced by bacterial fermentation. In case of ischemia, such as in CHD-NEC patients, acidosis is suggested to be more likely a lactic acidosis caused by anaerobic metabolism [29]. However, this remains relatively speculative, and our data do not show significantly different lactate levels between the two groups.

We observed higher incidence of PDA in our CHD-NEC group, however this was achieved by prostaglandin administration in the majority of cases. Since hemodynamic function of a PDA is fundamentally different in both groups we do not draw any conclusions to this higher incidence. To investigate possible influence of the presence of PDA on our findings we compared patients with and without PDA in both groups. In the CHD-NEC the presence of PDA (in 78%) is not associated with significant differences in clinical or biochemical parameters; however this is limited by the low number of PDA- CHD-NEC cases. In the PT-NEC group the presence of a PDA (in 44%) is associated with a trend towards more Bell stage 3, a higher mortality rate and a higher incidence of surgical NEC, just as a to a lower GA and birth weight. This indicates that PT-NEC patients with a PDA were more severely premature, as expected, and had a trend towards increased disease severity and worse outcome. Based on our data we cannot distinguish whether this was caused by presence of PDA or by more severe prematurity. We suggest the latter, but future research is necessary to address this question. Hence, the presence of a PDA does not seem to influence our results.

Although clinical symptoms and outcomes are quite similar, our study points out that CHD-NEC and PT-NEC are different diseases. One might therefore question whether prevention and treatment strategies should not differ. For instance probiotics might be less useful for prevention of CHD-NEC. One might also consider the routine use of Near Infrared Spectroscopy or Doppler ultrasound to regularly assess intestinal oxygenation and perfusion. We suggest that the general treatment principles of nonocclusive mesenteric ischemia could be appropriate in cases of CHD-NEC. These treatment principles imply intensive monitoring and maximal (hemodynamic) support on one hand, and on the other hand correction of the underlying cause including surgical correction of the CHD [30]. Future research is necessary to identify novel treatment strategies.

In our present study we studied NEC in patients with a CHD. However, CHD is one of many risk factors that predispose full-term neonates to NEC. A CHD is present in 9–15% of full-term NEC cases, but also various maternal/gestational factors (asphyxia, eclampsia or maternal diabetes), organic pathology (gastroschisis, Hirschsprung's disease) and other conditions (hypoglykemia, respiratory distress, sepsis) have been identified as risk factors [7–10,31]. While our findings suggest different underlying pathophysiology of CHD-NEC versus PT-NEC, its pathophysiology might be comparable to that of full-term NEC associated with other risk factors. For example, NEC in full-term infants with sepsis could be caused by similar mechanisms including intestinal ischemia caused by hypoperfusion. Hence, CHD-NEC might be considered part of a spectrum of full-term NEC, which as a group is a pathophysiologically different entity compared to PT-NEC. We recommend screening for underlying cause and targeted treatment in any case of full-term NEC.

A limitation of this study was the relatively small number of included patients, which was limited by the incidence of CHD-NEC in our center. For future research a multicenter approach could be pursued to reveal more clinical and biochemical differences between both groups of patients. Furthermore, we were only able to determine NEC location in surgical NEC patients due to the unavailability of a method to reliably determine the exact location of NEC lesions in non-surgical patients.

4. Conclusion

While PT-NEC and CHD-NEC share symptoms and outcomes, our study indicated that in CHD-NEC, the disease is much more often localized in the colon when compared to PT-NEC. This supports the hypothesis that CHD-NEC is mostly a disease of ischemic/hypoxic origin. Various clinical biochemical variables further support different pathophysiological mechanisms, which probably require different approaches particularly in prevention of NEC.

CRediT authorship contribution statement

J.M. Bubberman: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review and editing. **A. van Zoonen:** Data curation, Formal analysis, Writing - original draft, Writing - review and editing. **J.L.M. Bruggink:** Formal analysis, Writing - original draft, Writing - review and editing. **M. van der Heide:** Formal analysis, Writing - original draft, Writing - review and editing. **R.M.F. Berger:** Formal analysis, Writing - original draft, Writing - review and editing. **A.F. Bos:** Formal analysis, Writing - original draft, Writing - review and editing. **E.M.W. Kooi:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review and editing. **J.B.F. Hulscher:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review and editing.

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