Mother milk use in the perioperative period, is there an association with NEC? A retrospective cohort study.

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25-04-2023
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16 January – 7 April

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Abstract

Background

Patients with a congenital heart disease (CHD) are at high risk for developing necrotizing enterocolitis (NEC) due to the decreased perfusion to the intestines. To limit the risk of NEC, nutrition, and specific mother milk, is an important factor. Due to its many benefits for the neonate. Therefore, we investigated if there is any association between mother milk and the risk of developing NEC in patients with a CHD.

Method

A retrospective cohort study was performed of all newborns admitted to the Pediatric Intensive Care Unit (PICU) and the high care cardiology ward of the Wilhelmina Children's Hospital (WKZ) between 2017 and 2022 with a congenital heart disease (CHD) and who needed a heart surgery within the first 6 weeks of life. Nutritional information and relevant covariates were collected. Patients were divided in two cohorts based on the development of NEC. The cohorts were analyzed using different statistic tests.

Results

270 patients met the inclusion criteria, 36 developed NEC. The mean value (ml/kg/day) in patients with NEC was lower than in patients without NEC. There was a significant difference in feeding type between the patients with and without NEC in the period postnatal, and overall (p= 0.0352 respectively p= 0.0058). The periods post first surgery and post second surgery did not show any significant difference (p= 0.5991 respectively p= 0.0863). After pairwise comparing a significant difference was seen between only formula and a combination in the overall period (OR 2.69 95% CI 1.20-6.38, p=0.019). And a significance difference was seen between only formula and a combination in the postnatal period (OR 13.82 95% CI 2.31-146.4, p=0.00).

Conclusion

Patients with NEC are more likely to be formula fed. And patients with NEC have a lower mean value (ml/kg/day) intake compared to patients without NEC.
But due to the limitations of this retrospective cohort study no firm conclusion can be drawn about an association between type and/or amount of feeding between patients with and without NEC.

Abbreviations

NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
PICU: pediatric intensive care unit
CHD: congenital heart disease
WKZ: Wilhelmina kinder ziekenhuis
TGA: transposition of great arteries
VSD: ventricle septum defect
ASD: arterial septum defect

Introduction

Necrotizing enterocolitis (NEC) is a common disease seen at the neonatal intensive care unit (NICU). It causes high morbidity and mortality among those patients. The exact pathogenesis of NEC is not yet fully known, but we know that it's a multifactorial disease of the gastrointestinal tract.[1-4] It most commonly affects preterm infants, both small for gestational age and low birth weight, due to the immaturity of the gastrointestinal tract.[5,6]

Eventually, the different risk factors associated with NEC can lead to damaging of the gastrointestinal tract. These damages to the intestinal wall making it easier for bacteria to penetrate. In an advanced stage of NEC, perforation of the intestinal wall can occur.[5,6]

Perinatal and neonatal risk factors influence the development of NEC and are widely described in the literature.[5] Low gestational age, low birth weight, abnormal microbial colonization and hypoxia are perinatal factors that are often described.[5,7]
In addition, feeding type, pharmacological interventions, pediatric intensive care unit (PICU) admission and congenital heart disease (CHD) are important neonatal risk factors that may contribute to the development of NEC.[5,8]

Several congenital heart diseases are associated with an increased risk of NEC. Most likely due to the decreased blood flow to the intestines. This is caused by systolic cardiac dysfunction, outflow tract obstruction or low diastolic blood pressure. All those factors lead to decreased perfusion of the gastrointestinal tract.[4,8,9] Necrotizing enterocolitis is most seen in patients with ductal-dependent defects,[4,10] cyanotic CHD [4,11] and HLHS. [3,8,12,13]

NEC is staged with the Bell's Modified Staging Criteria, looking at systemic, abdominal and radiological signs. The lowest score that can be given is stage I (suspected NEC), which include temperature instability, lethargy, bradycardia, abdominal distension and emesis. But without any radiological symptoms. At stage II, radiological abnormalities are visible such as intestinal dilatation, pneumatosis intestinalis and ascites. At stage III, the patient is serious ill with the radiological features described above and sometimes even with a pneumoperitoneum.[14,15,16]

When an infant is diagnosed with stage I, supportive care is been given. From stage II, medical support is given. This include antibiotic treatment, nasogastric decompression and total parenteral nutrition. When the infant does not respond to the antibiotic treatment, surgical treatment is considered. From stage III, inotropic support is sometimes required.[17]

In addition to risk factors there are also protective factors for NEC. Over the years, the general benefits of mother milk for infants has been described. The WHO recommendation is that children should be breastfed for the first 6 months of life because of its many benefits.[18] The benefits of mother milk are e.g. optimal growth, it contributes to gastrointestinal function, protective against infections and it helps to build the immune response.[2] It may also reduce the risk of NEC. Research shows that infants have a lower risk of developing NEC if they are fed breast milk compared to formula[1,2]. These benefits are also described for the specific group of neonates with a CHD.[19,20]

Due to the complexity of NEC, standard feeding protocols have been developed to implement the best treatment. These protocols include duration of minimal enteral feeding, prioritizing breast milk and avoiding fortification until minimum volume has been achieved. Enteral feeding is advised to strengthen intestinal maturation.[13] It is also advised to start with small feeding volumes after birth.[13,21] In addition Cognata et al, shows that a lager maximum volume during the pre-operative period was associated with an increased risk for NEC.[19]

Unfortunately, not much research has yet been done on the effect of nutrition in neonates with a congenital heart disease on the development of NEC. Therefore, the primary objective of this study is to investigate whether mother milk in children with congenital heart diseases is associated with a lower risk on the development of necrotizing enterocolitis. In addition, the mean value (ml/kg/day) between the patients with and without NEC is examined, to see if there is any difference between them.

Methods

Study design

We performed a retrospective cohort study of all newborns admitted to the Pediatric Intensive Care Unit (PICU) and the high care cardiology ward of the Wilhelmina Children's Hospital (WKZ) between 2017 and 2022 with a congenital heart disease (CHD) and who needed a heart surgery within the first 6 weeks of life. It is part of the ongoing NECTAR study.

The Wilhelmina Children's Hospital is currently working with a nutritional protocol developed for the PICU. Last year, the implementation of this nutritional protocol started. Before that the nutritional policy was based on the clinical symptoms of the neonate including the tolerance of food.

Data collection

Inclusion

Eligible patients were identified by manual examination of the hospital admission books of the PICU and the high care cardiology ward, and the surgical database. Patients were included if they had a congenital heart disease requiring surgical intervention or therapeutic catheter intervention (e.g. balloon dilatation or stenotic valves) within 6 weeks of birth. Patients were also included if the intention was to perform surgery within 6 weeks of life but the procedure had to be postponed due to clinical instability (e.g. if a patient developed NEC). And finally, patients were included if, due to the severity of the congenital heart disease and/or additional (genetic) abnormalities, there was no intention to treat or comfort care was decided. Patients were excluded if the only surgery was patent ductus arteriosus closure, if the surgery was >6 weeks, if they didn't have any heart surgery, if the surgery was performed in another hospital, if the patient had also a severe gastro-intestinal abnormality, or that a decision for comfort care was made during the treatment process.

Data were retrospectively collected from hospital charts/patient files/electronic medical records including type of CHD, birth weight, gestational age. In addition, nutritional information was collected including value and type of feeds (mother milk, formula or combination).

For the type of food, the information from the MetaVision database was collected. This is an extensive database where, a.o. the fluid status per patient per minute is recorded. From this we gathered the value and type of feeding per hour. The value and type of feeding the patient received was manually entered into the electronic medical chart by nurses for each feeding moment. Because not every feeding moment the type of feeding was documented, this resulted in missing data. In case of missing data regarding the type of feeding, data was imputed as follows: if the type of feeding was documented only once in a certain period, it was assumed that the same type of feeding was given throughout that period. If no information was available before surgery, it was assumed that a patient had been given formula. If there was no information of type of feeding postoperatively, it was assumed that the same type of feeding was given as preoperatively.

It was chosen to collect the nutritional information from day 0 to day 10 postnatal, because by then most patients reach the maximum value intake. For the periods post first surgery and post second surgery the nutritional information from day 0 to day 7 was collected. Because after surgery there is a gradually increase of value intake over the days before reaching the same value as before surgery.

Primary outcome

The primary outcome was necrotizing enterocolitis (NEC) stage ≥2. A case of NEC was defined based on Bell's Modified Criteria[22]. A detailed description of the different stages can be seen in appendix figure 1. To identify all possible cases of NEC, radiology reports for all patients were scanned. When the radiological image of NEC was unclear and the radiologist could therefore not make a clear statement, the medical reports were examined further. In addition, 2 other researchers helped decide on the unclear cases. After checking the medical records there were still 23 cases unclear. It was decided to include the unclear cases as NEC cases in the analysis.

The cardiac lesions were categorized as seen in table 1.

Category	Examples
1. Left ventricle outflow tract obstruction	Interrupted aortic arch, aorta stenosis, coarctation of aortae
2. Transposition of great arteries	With or without ventricle septum defect and/or arterial septum defect
3. Single ventricle	Hypoplastic left heart syndrome, hypoplastic right heart syndrome
4. Others	Double outlet left ventricle, double inlet left ventricle, truncus arteriosus, tetralogy of Fallot, pulmonalis stenosis, morbus Ebstein

Table 1: Categorization of cardiac lesions

Type of feeding was defined as mother's milk regardless of feeding route (i.e. breastfed or given by bottle or tube), formula or a combination of the two. Human milk with fortifiers or other additions was regarded as mother milk. A combination was defined as mother's milk and formula together.

Data analysis

Statistical analysis

Quantitative variables were summarized using the median and mean with standard deviation and Q1-Q3, separately for the patients with and without NEC. Birth weight was compared for patients with and without NEC using the unpaired t-test. Gestational age was compared with the Mann-Whitney U test. Sex and type of congenital heart disease were

compared with the Chi²-test. The type of feeds given per period was compared between the groups using the Chi²-test. These results are summarized in graphs. The Fisher's Exact test was used to compare each type of feeding pairwise between the patients with and without NEC. The mean value (ml/kg/day) for the patients with NEC versus without NEC was shown in graphs, calculated per period (postnatal, post first surgery, post second surgery). The birth weight was used to convert the value to ml/kg/day.
A p-value of <0.05 was considered statically significant.
All descriptive and statistical analysis were performed using GraphPad Prism.

Results

Descriptive data
270 patients met the inclusion criteria. There were 36 patients with NEC versus 234 patients without NEC. The characteristics of the cohorts are summarized in table 2. The total cohort was predominantly male (64%). The mean birth weight was 3240 grams (± 601). The median gestational age was 38.8 weeks (38.1-39.7). The classification of the type of heart disease was as follows, 28% left ventricular outflow tract obstruction, 21% TGA, 17% single ventricle and de rest group was 34%.

Characteristics	**Total (n=270)**	**NEC (n=36)**	**No NEC (n=234)**	**P-value**
Sex				0.1292
Male	173 (64%)	17 (7%)	154 (57%)	
Female	97 (36%)	19 (6%)	80 (30%)	
Birth weight				0.0432
Mean (grams) ± sd	3240 (± 601)	3052 (± 704)	3269 (± 580)	
Type congenital heart disease				0.1550
1: Left ventricular outflow tract obstruction	76 (28%)	9 (3%)	67 (25%)	
2: TGA (+ VSD/ASD)	57 (21%)	4 (1%)	53 (20%)	
3: Single ventricle	45 (17%)	10 (4%)	35 (13%)	
4: Rest	92 (34%)	13 (5%)	79 (29%)	
Gestational age	**Total (n=264)**	**NEC (n=35)**	**No NEC (n=229)**	0.5020
Median (weeks) Q1-Q3	38.83 (38.14-39.71)	38.65 (37.57-39.57)	38.86 (38.14-39.79)	

Table 2: Baseline characteristics

Outcome data
Thirty-six patients (13%) developed NEC, post- or pre-operative. Of those thirty-six patients, thirteen patients had a clear NEC diagnosis (stage ≥2). In this group, nine patients developed preoperatively NEC, four postoperatively and one patient developed pre- and

postoperatively NEC. No distinction between pre- and postoperatively NEC was made for the unclear cases.
The mean birth weight was 3052 grams (± 704) versus 3269 grams (± 580) (p= 0.0432), the median gestational age was 38.7 (37.57-39.57) versus 38.9 (38.14-39.79) (p= 0.5020) in the NEC and no NEC cohorts, respectively.

Main results
Figures 1-4 and tables 3-6 show the different feeding types between the patients with and without NEC. Tables 7-10 show the pairwise comparison for significant difference.

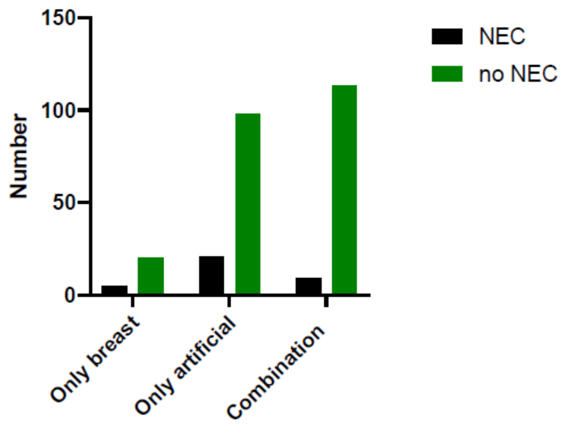

Figure 1: Overall type of feeding

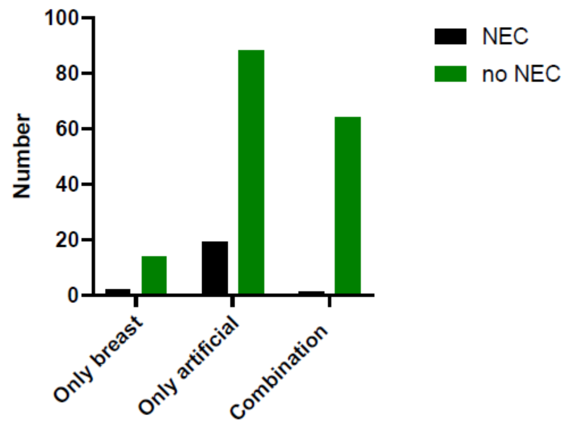

Figure 2: Type of feeding postnatal

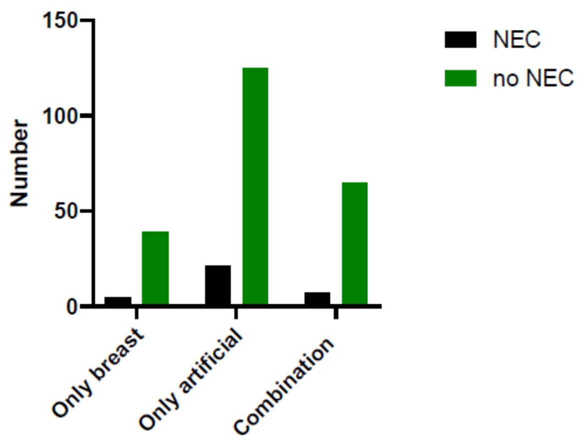

Figure 3: Type of feeding post first surgery

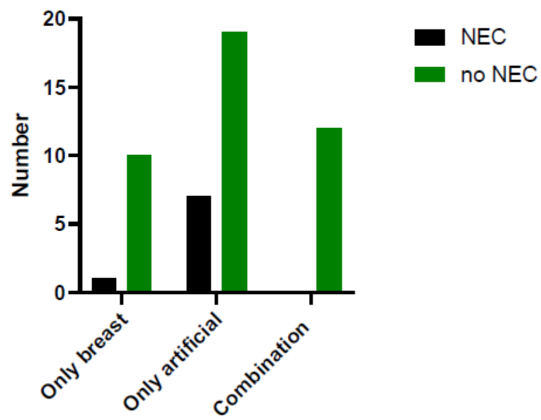

Figure 4: Type of feeding post second surgery

When looking at all periods together (overall) there is a significant difference in type of feeding between the patients with and without NEC (p= 0.0352) (table 3). The postnatal period shows also a significant difference (p= 0.0058) (table 4). The periods post first surgery and post second surgery show no significant difference in type of feeding between the two groups (p= 0.5991 respectively p= 0.0863) (table 5 and 6).

Type	NEC (N=35)	no NEC (N=231)	Total (N=266)	P-value = 0.0352
Only mother milk	5 (2%)	20 (8%)	25 (9%)	
Only formula	21 (8%)	98 (37%)	119 (45%)	
Combination	9 (3%)	113 (43%)	122 (46%)	

Table 3: Type of feeding overall

Type	NEC (N=22)	no NEC (N=166)	Total (N=188)	P-value = 0.0058
Only mother milk	2 (1%)	14 (7%)	16 (9%)	
Only formula	19 (10%)	88 (47%)	107 (57%)	
Combination	1 (1%)	64 (34%)	65 (35%)	

Table 4: Type of feeding postnatal

Type	NEC (N=33)	no NEC (N=229)	Total (N=262)	P-value = 0.5991
Only mother milk	5 (2%)	39 (15%)	44 (17%)	
Only formula	21 (8%)	125 (48%)	146 (56%)	
Combination	7 (3%)	65 (25%)	72 (27%)	

Table 5: Type of feeding post first surgery

Type	NEC (N=8)	No NEC (N=41)	Total (N=49)	P-value = 0.0863
Only mother milk	1 (2%)	10 (20%)	11 (22%)	
Only formula	7 (14%)	19 (39%)	26 (53%)	
Combination	0 (0%)	12 (24%)	12 (24%)	

Table 6: Type of feeding post second surgery

After pairwise comparing between the different types of feeding. A significant difference is seen between only formula and a combination (OR 2.69 95% CI 1.20-6.38, p=0.019) in the overall period (table 7). And there is a significant difference seen between only formula and a combination (OR 13.82 95% CI 2.31-146.4, p=0.00) in the postnatal period (table 8). The other pairwise comparisons did not show any significant difference (table 9 and 10).

	P-value	Odds (95% CI)
Only mother milk versus only formula	0.78	1.17 (0.44-3.33)
Only mother milk versus combination	0.0642	3.24 (1.01-10.78)
Only formula versus combination	0.019	2.69 (1.20-6.38)

Table 7: Type of feeding overall period

	P-value	Odds (95% CI)
Only mother milk versus only formula	>0.99	0.66 (0.14-3.02)
Only mother milk versus combination	0.10	9.14 (0.98-133.9)
Only formula versus combination	0.0009	13.82 (2.31-146.4)

Table 8: Type of feeding postnatal

	P-value	Odds (95% CI)
Only mother milk versus only formula	0.80	0.76 (0.30-2.14)
Only mother milk versus combination	0.76	1.19 (0.40-3.78)
Only formula versus combination	0.40	1.56 (0.62-4.07)

Table 9: Type of feeding post first surgery

	P-value	Odds (95% CI)
Only mother milk versus only formula	0.39	0.27 (0.02-2.17)
Only mother milk versus combination	0.39	0.27 (0.02-2.17)
Only formula versus combination	0.48	∞ (0.12-∞)

Table 10: Type of feeding post second surgery

Other analyses

Figures 5-10 show the mean value per ml/kg/day for the patients with versus without NEC. As shown, the mean value for the patients with NEC was lower, seen in all periods. In the postnatal period, it is seen that mean value (ml/kg/day) first increases, but then decreases after day 8. In the period after first surgery it can been seen that the mean value increases towards day 7, both for the patients with and without NEC. This is also visible in the period post second surgery.

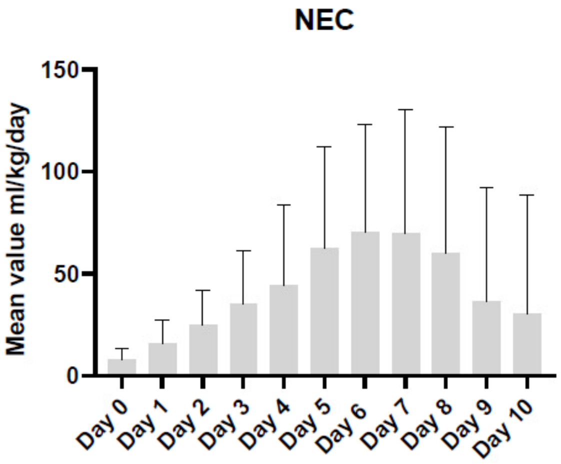

Figure 5: Postnatal period, patients with NEC

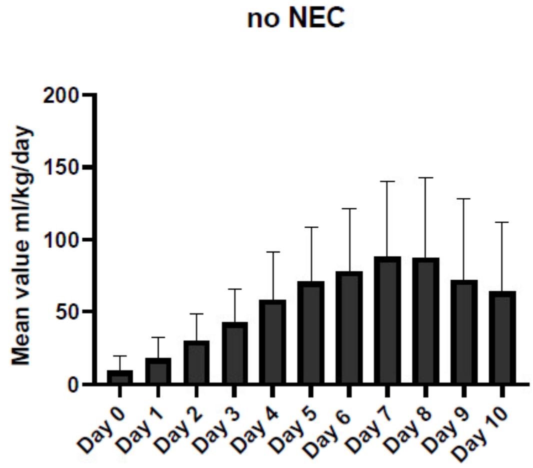

Figure 6: Postnatal period, patients without NEC

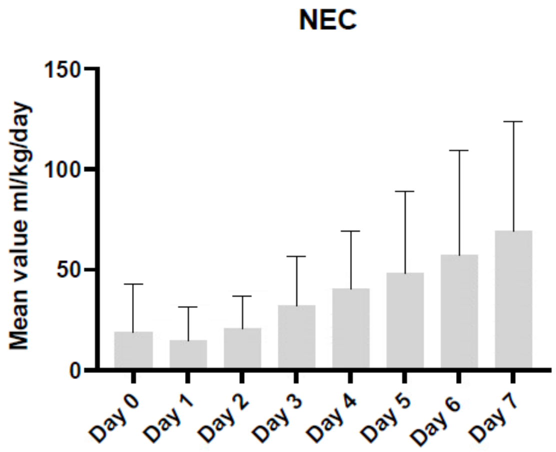

Figure 7: Post first surgery, patients with NEC

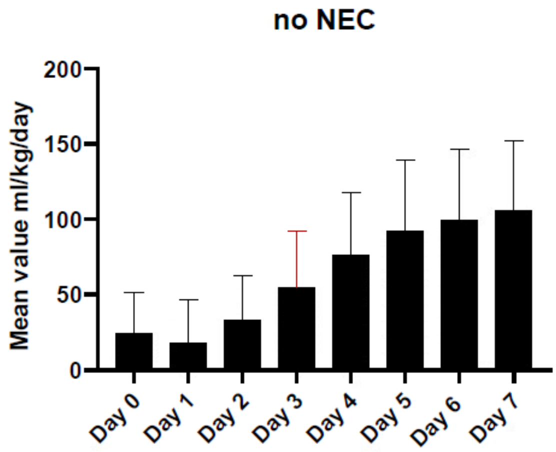

Figure 8: Post first surgery, patient without NEC

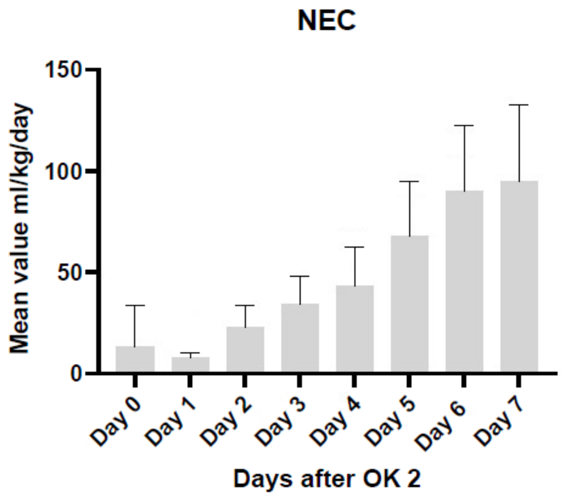

Figure 9: Post second surgery, patients with NEC

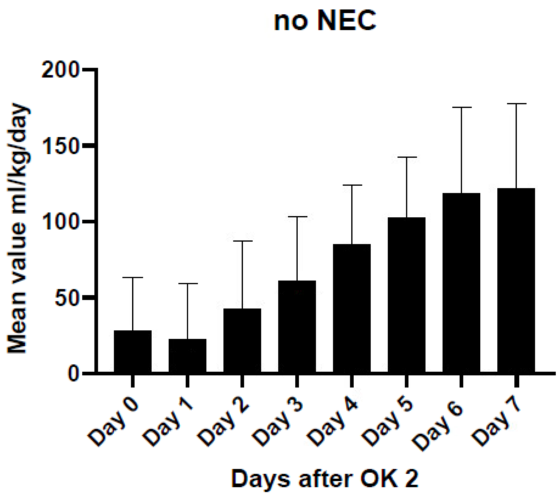

Figure 10: Post second surgery, patients without NEC

Discussion

In this study, we investigated whether mother milk in children with a congenital heart disease is associated with a lower risk on the development of NEC. In addition, we compared the mean value (ml/kg/day) between patients with and without NEC. We found that patients who received only formula compared to a combination of formula and mother milk, in the overall period, were more likely to develop NEC (OR 2.69, 95% CI 1.20-6.38, p=0.019). In the postnatal period the same trend was shown (OR 13.82 95% CI 2.13-146.4, p=0.00.). We also found that patients with NEC had a lower mean value intake over the days compared to patients without NEC.

NEC cases from stage II were included. Firstly, because from stage II there are radiological signs which make it easier to diagnose NEC. Second, because from stage II there is more clarity that the nutritional policy has been adjusted because of the development of NEC. And not whether it is because the neonate is generally not feeling well and therefore consumes/tolerates less nutrition.

Other studies showed the general benefits of mother milk[1,2,18] (e.g. contributing for gastrointestinal function, contributes to mount an immune response, beneficial for growth[2]) as well. These benefits have been known for a long time and are well documented in literature. However, the benefits of mother milk in a specific population such as neonates with a congenital heart disease are scarce.

We found that patients who received only formula compared to a combination of formula and mother milk, in the overall period and postnatal period, were more likely to develop NEC. This is consistent with Lambert et al. They found in their retrospective cohort study of patients admitted to the NICU, that patients who were fed formula exclusively were more likely to develop NEC (p= 0.000). However, the cohort consisted of only 30 patients. And did not exist of patients with a congenital heart disease[23]. In addition, Lopez et al. reported an unexpected finding that patients with a hypoplastic left heart syndrome who were formula fed developed higher rates of NEC.[24]
Cognata et al, found an association as well. They found in their retrospective cohort study with 546 newborns with CHD that an exclusive unfortified human milk diet lowered the risk for preoperative NEC (stage 1-3) (OR 0.17, 95% CI 0.04-0.84, P= 0.03). But when they excluded NEC stage 1 from the analysis, no significant difference was found.[19]
Tan et al, found in their retrospective cohort study of low birth weight patients that CHD (OR 2.13, 95% CI 1.10-3.51) was an independent risk factor for the development of NEC. And that breastfeeding (OR 0.49, 95% CI 0.02-0.93) was protective against NEC.[25]

We also looked at the mean value intake over the days. The patients with NEC had a lower value intake compared to the patients without NEC. This is most likely due to a change in nutritional policy when a suspicion of NEC is made. It is known that patients do tolerate their nutrition less well when they develop NEC. This is in contrast with Cognata et al, they found that feeding volumes exceeding 100 ml/kg/day were associated with a significant greater risk of preoperative NEC (OR 3.05, 95% CI 1.19-7.90, P= 0.02)[19]

The mean value in the postnatal period shows an increased trend towards day 7 and then it decreases. This can be explained by the fact that most neonates with a congenital heart disease are operated when they are one week old. These neonates are no longer included in the postnatal analysis because they fall into the post first surgery period. This created a select group of neonates who were weaker, less able to tolerate food and who had delayed surgery.

The analysis also shows that the value on day 0 is higher than on day 1 in the periods post first surgery and post second surgery. This can be explained by the fact that the operation (day 0) was performed at different times. As a result, the value of the day before the operation can sometimes be included in the analysis, resulting in higher values.

Limitations
The retrospective design of this study caused some limitations. First, it led to missing data. For six patients, there was no exact data of gestational age, but these six patients were born a term. In addition, there was missing information about type of feeding. Therefore, we made some assumptions during the analysis. These assumptions negatively affected the reliability of this study.

Second, the diagnosis of NEC was sometimes unclear from the medical records. The unclear cases of NEC have been included in the analysis as NEC cases. This could have led to bias and influenced the results. It is possible that those patients with an unclear NEC diagnosis are less sick than those with a clear NEC diagnosis. Therefore, the mean value of the patients with NEC could have turned out higher than it is. The reason to include these unclear cases is because when NEC is suspected, the feeding protocol is usually adjusted. And for those patients these nutritional changes are important as well.

Third, for the analysis of the mean value, the available information from MetaVision was used. However, not all patients had the same amount of information available. For example, patients with a nothing per mouth treatment (because of the suspicion of NEC) were not included in the analysis. As result, the mean value of the NEC group may be higher than it is.

Another limitation is that birth weight was used to convert the value to ml/kg/day, for each period the same weight was uses. Ideally, post first surgery and post second surgery analyses were done with more recent weight. As result, the mean value can be affected.

Strengths
The main strength of this study is the extensive and detailed data collection. Nutritional data consisting the amount and type of feeding was collected per hour per patient.

As seen in this research and in other studies described above, the limitations and retrospective design make it hard to draw firm conclusions for this specific patient group. There is a need for prospective cohort studies and randomized controlled trials to investigate the effect of mother milk in patients with a congenital heart disease. With an extensive analysis of the type and value of feeding in these children and the risk of developing NEC.

Conclusion

Patients with NEC are more likely to be formula fed. And patients with NEC have a lower mean value (ml/kg/day) intake compared to patients without NEC.
But due to the limitations of this retrospective cohort study no firm conclusion can be drawn about an association between type and/or amount of feeding between patients with and without NEC.

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Appendix

Stage	Classification of NEC	Systematic symptoms	Abdominal signs	Radiographic signs
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distension, emesis, heme-positive stool	Normal or mild intestinal dilatation, mild ileus
IB	Suspected	Same as above	Grossly bloody stool	Same as above
IIA	Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilatation, ileus, pneumatosis intestinalis
IIB	Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA	Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distension	Same as IIA, plus ascites
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum

Appendix figure 1: Modified Bell staging criteria for necrotizing enterocolitis (NEC) in neonates[22]