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Low risk of necrotising enterocolitis in enterally fed neonates with critical heart disease: an observational study

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ABSTRACT

Objective We aimed to investigate the frequency of necrotising enterocolitis (NEC) in infants with critical congenital heart disease (CCHD) hypothesising that preoperative enteral feeding does not increase the risk of NEC.

Background When NEC affects term infants, underlying risk factors such as asphyxia, sepsis or CCHD are often found. Due to fear of NEC development in infants with CCHD great caution is practised in many countries to defer preoperative enteral feeding, but in Sweden this is routinely provided.

Design, setting and patients An observational study of all infants born with CCHD who were admitted to Queen Silvia Children's Hospital in Gothenburg between 2010 and 2017. The International Classification of Diseases 10th Revision diagnosis code of NEC was used to identify NEC cases in this group. Infants described as 'fully fed' or who were fed at least 45 mL/kg/day before cardiac surgery were identified.

Main outcome measures NEC in infants with CCHD in relation to preoperative enteral feeding.

Results There were 458 infants with CCHD admitted during the study period. 408/458 were born at term and 361/458 required prostaglandin E1 before surgery. In total, 444/458 infants (97%) were fully fed or fed at least 45 mL/kg daily before cardiac surgery. Four of 458 infants developed NEC (0.9%). All four had other risk factors for NEC.

Conclusions This study showed a low risk of NEC in term infants fed enterally before cardiac surgery. We speculate that preoperative enteral feeding of neonates with CCHD does not increase the risk of NEC development.

INTRODUCTION

Necrotising enterocolitis (NEC) is a serious bowel disease that mainly affects preterm infants, usually at 1–2 weeks of age. Infants born preterm have an immature immune response, a weak barrier function and an abnormal intestinal bacterial microflora. These circumstances are thought to increase the risk for NEC. The disease is characterised by inflammation in the wall of the bowel that may lead to ischaemia and perforation.^{1–3} The immaturity of the epithelial barrier and damage to the mucosa, for example, caused by ischaemia, provides conditions that facilitate intestinal bacterial invasion through the bowel wall resulting in inflammation.⁴

When NEC affects term infants, underlying factors such as asphyxia, sepsis and critical congenital heart

What is already known on this topic?

- ▶ Many practitioners avoid enteral feeding before cardiac surgery in newborns with critical congenital heart disease due to concern of the development of necrotising enterocolitis.
- ▶ Swedish infants with critical congenital heart disease are routinely fed enterally before cardiac surgery.

What this study adds?

- ▶ In a large Swedish cohort of newborns with critical congenital heart disease who received enteral feedings prior to cardiac surgery, the rate of necrotising enterocolitis was very low.
- ▶ This suggests that preoperative enteral nutrition in this population is not associated with the development of necrotising enterocolitis.

disease (CCHD) are often to be found.^{5,6} Due to fear of NEC development in infants with CCHD, great caution to defer preoperative enteral feeding is practised in many countries and total parental nutrition (TPN) is provided instead.⁷ In previous studies, the frequency of NEC in infants with CCHD varies between 3% and 9%, with no clear relationship to preoperative feeding practices.^{8–11}

In Sweden, preoperative enteral feeding, with breast milk or formula, is routinely provided to stable infants with CCHD. Postoperative enteral feeding is initiated as soon as possible after surgery, usually within the first 1–2 days. We aimed to study whether infants born with CCHD who were enterally fed prior to cardiac surgery had an increased risk of NEC compared with the results of previous studies.

We hypothesised that preoperative enteral feeding does not increase the risk of NEC in infants with CCHD.

METHODS

For the purpose of this study, CCHD was defined as cardiac defects requiring cardiac surgery and/or interventional catheterisation before 2 months of age or causing death before 2 months of age without such treatment. The infants were identified using the International Classification of Diseases 10th Revision (ICD-10) codes for the following diagnoses: aortic stenosis, coarctation of the aorta



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(CoA), interrupted aortic arch, hypoplastic left heart syndrome (HLHS), mitral stenosis, transposition of the great arteries (TGA), pulmonary stenosis, tetralogy of Fallot (ToF), double outlet right ventricle, pulmonary atresia (with or without ventricular septal defect), tricuspid atresia, hypoplastic right ventricle, truncus arteriosus, double inlet left ventricle, total anomalous pulmonary venous return and Ebstein's anomaly. Between 1 January 2010 and 31 December 2017, a total of 860 infants with at least one of these diagnoses were admitted to either the cardiac unit, neonatal intensive care unit or paediatric intensive care unit at the Queen Silvia Children's Hospital in Gothenburg, Sweden. All subjects were either inborn or transferred from other hospitals within our referral area for paediatric cardiac surgery corresponding to approximately half of the Swedish population. From this group, 458 infants satisfying the above criteria for CCHD were identified. We did not search for infants who died at home who were diagnosed with CCHD postmortem, or infants with CCHD who died in a referring hospital before referral.

Infants who had been fed significant amounts of either breast milk or formula enterally before heart surgery were identified. In the hospital charts they were described as 'fully fed' (100–150 mL/kg daily) or fed at least 45 mL/kg daily. The ICD-10 diagnostic code for NEC (P779), which includes both medically and surgically treated NEC, was used to investigate the NEC frequency. This was crosschecked against the local paediatric surgery register without any additional NEC or suspected NEC cases being found. A chart review was performed, collecting demographic data including gestational age, birth weight, prenatal diagnosis of the cardiac defect, treatment with prostaglandin E1 (PGE1), feeding regimen, age at surgery or catheter intervention, and mortality.

RESULTS

The largest diagnostic groups among the 458 infants with CCHD were CoA (n=126), TGA (n=103), HLHS (n=47), pulmonary atresia (n=34), pulmonary stenosis (n=33) and aortic stenosis (n=32) (table 1). The total study group either underwent cardiac surgery (n=398), interventional catheterisation (n=48) or died without such treatment (n=12) before 2 months of age (table 1). Of the 458 infants, 19 patients had their first cardiac intervention within the first 2 days of life, 209 within the first week, 290 during the first 10 days and 391 during the first 31 days. The median postnatal age in days at cardiac surgery/catheter intervention for each diagnostic group is shown in table 1. The total number of deaths in the cohort was 46/458, of whom 34/46 had undergone either surgery or interventional catheterisation. Twelve of 34 died within 30 days of surgery and 22/34 died later. Last follow-up was in May 2018. The median follow-up time was 4 years (range 0.5–8 years). Eighty-nine per cent (408/458) of the infants in the cohort were born at term ($\geq 37+0$ weeks). No infant was born before 28+0 weeks, 4 between 28+0 and 29+6 weeks, 19 between 30+0 and 34+6 weeks and 22 between 35+0 and 36+6 weeks. Data on gestational age and birth weight were missing in five cases. Twenty-eight per cent (127/458) were prenatally diagnosed and HLHS was the diagnostic group in which the frequency of prenatal diagnosis was most prevalent (34/47) (table 1).

In total, 97% (444/458) received significant enteral feeding volumes before cardiac intervention or death. Of these, 91% (404/444) were fully fed and 9% (40/444) were fed at least 45 mL/kg daily. Three per cent (14/458) were not fed enterally at all before cardiac intervention or received amounts less than 45 mL/kg/day. Thirty-four per cent were fed breast milk

only, 12% formula only and the rest a mix of breast milk and any amount of formula. The majority of these infants received minimal amounts of formula initially, and were then fully breast fed. Hence, 88% of the infants were at least partially receiving breast milk. The formula used was regular formula for newborn infants. The breastfed infants were fed on demand. The bottle, or gastric tube fed infants were fed every third hour, with amounts increased as tolerated.

Of the 458 patients, 181 (40%) were inborn at the Queen Silvia Children's Hospital in Gothenburg. The remaining patients were transferred from other hospitals. Outborn patients were with few exceptions diagnosed in the referring hospital by a paediatrician trained in echocardiography and then discussed with the paediatric cardiac centre via a video conference system. PGE1 was administered before and during transport when indicated. Preoperative treatment with PGE1 was administered in 79% (361/458). The initial preoperative care at the Queen Silvia Children's Hospital was undertaken in the paediatric intensive care unit in 83/458 (18%) infants. The remaining infants did not need initial intensive care. The proportion in each diagnostic group that received PGE1 is shown in table 1. Two hundred and six infants had definitive or potential ductal-dependent systemic circulation, consisting of the diagnoses of HLHS, interrupted aortic arch, CoA and aortic stenosis. Of them, 96% (198/206) were enterally fed before cardiac intervention and 85% (169/198) of these reached full feeds. One infant in this group developed NEC (1/206, 0.5%). There were 103 infants with TGA (96% on PGE1), and of these 99% (102/103) were enterally fed before heart surgery, all reaching full feeds. One infant with TGA developed NEC (1/103, 1.0%). Among the remaining diagnoses, 97% (144/149) were enterally fed before heart surgery, 92% (133/144) reached full feeds and two developed NEC (tables 1 and 2).

In total, 4 of 458 (0.9%) infants developed NEC. As shown in table 2, all four reached full enteral feeds prior to cardiac surgery, met Bell's stage IIIB diagnostic criteria for NEC and three of four were born at term.¹² One had ToF and was small for gestational age, born at 38+0 weeks with birth weight of 1716 g. This infant received a combination of breast milk and formula prior to NEC development. The second infant, born at 39+1 weeks (2820 g), also had ToF and, in addition, 22q11 deletion syndrome, hypoparathyroidism and was vulnerable to infections due to immunodeficiency. Prior to NEC diagnosis, this infant was fed with formula only, and received no breast milk.

The third infant diagnosed with NEC was prenatally diagnosed with TGA, and born at 35+4 weeks with a birth weight of 2750 g. In addition to TGA, there was complicated coronary anatomy, a restrictive ventricular septal defect and subvalvular pulmonary stenosis. Therefore, it was decided to give time for growth before proceeding with cardiac surgery. By 3 weeks of age, a Rashkind septostomy was done, and by 3 months of age cardiac surgery with a Blalock-Taussig shunt. Hence, during the first 3 months of life this child had a saturation between 50% and 70%. One day after surgery, there were evident signs of NEC. Bowel necrosis and perforation was found at laparotomy. This infant received full enteral feeds with formula only prior to cardiac surgery. The final surgical procedure was a total cavopulmonary communication. Of the 45 preterm infants in this study, 40 received enteral feeds before cardiac surgery, but only this one developed NEC.

A fourth infant, born at term, developed intestinal necrosis and perforation during the first hours of life. This infant was born with CoA, Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, limb abnormalities

Table 1 Data on all infants subdivided by diagnosis

| Diagnosis | n (%) | Born at term | Prenatal diagnosis | Death <2 m without cardiac intervention | Cardiac surgery <2 m | Catheter intervention <2 m | Postnatal age at surgery/catheter intervention Median (range) | PGE1 | Postoperative mortality <30 days | Total deaths until last follow-up | Preoperative enteral feeds >45 mL/kg | Preoperative full feeds | NEC |
|-----------|------------|--------------|--------------------|---|----------------------|----------------------------|---|------|----------------------------------|-----------------------------------|--------------------------------------|-------------------------|-----|
| CoA | 126 (27.5) | 110 | 13 | 2 | 124 | 0 | 9 (2–61) | 102 | 1 | 4 | 123 | 99 | 1 |
| TGA | 103 (22.5) | 102 | 27 | 0 | 102 | 1 | 7 (1–57) | 99 | 1 | 2 | 102 | 102 | 1 |
| HLHS | 47 (10.3) | 41 | 34 | 7 | 40 | 0 | 6 (2–16) | 45 | 6 | 24 | 46 | 45 | 0 |
| PA | 34 (7.4) | 27 | 13 | 0 | 26 | 8 | 7 (2–42) | 32 | 1 | 5 | 33 | 33 | 0 |
| PS | 33 (7.2) | 31 | 1 | 0 | 2 | 31 | 8 (1–56) | 16 | 0 | 0 | 33 | 28 | 0 |
| AS | 32 (7.0) | 27 | 1 | 0 | 31 | 1 | 8 (0–61) | 19 | 2 | 3 | 28 | 24 | 0 |
| ToF | 23 (5.0) | 19 | 7 | 1 | 17 | 5 | 13 (2–61) | 12 | 0 | 2 | 22 | 19 | 2 |
| DORV | 19 (4.1) | 13 | 10 | 1 | 16 | 2 | 22 (4–60) | 14 | 1 | 2 | 17 | 15 | 0 |
| DILV | 14 (3.1) | 13 | 10 | 0 | 14 | 0 | 6 (4–60) | 12 | 0 | 0 | 14 | 14 | 0 |
| Truncus | 14 (3.1) | 13 | 5 | 0 | 14 | 0 | 9 (3–46) | 3 | 0 | 2 | 13 | 13 | 0 |
| TAPVR | 6 (1.3) | 5 | 1 | 1 | 5 | 0 | (5–56) | 1 | 0 | 1 | 6 | 5 | 0 |
| MS | 3 (0.6) | 3 | 2 | 0 | 3 | 0 | 6 (3–11) | 2 | 0 | 0 | 3 | 3 | 0 |
| HRV | 2 (0.4) | 2 | 2 | 0 | 2 | 0 | (4–8) | 2 | 0 | 0 | 2 | 2 | 0 |
| Ebstein | 1 (0.2) | 1 | 1 | 0 | 1 | 0 | 5 | 1 | 0 | 1 | 1 | 1 | 0 |
| IAA | 1 (0.2) | 1 | 0 | 0 | 1 | 0 | 8 | 1 | 0 | 0 | 1 | 1 | 0 |
| TA | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 458 | 408 | 127 | 12 | 398 | 48 | | 361 | 12 | 46 | 444 | 404 | 4 |

AS, aortic stenosis; CoA, coarctation of the aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; Ebstein, Ebstein's anomaly; HLHS, hypoplastic left heart syndrome; HRV, hypoplastic right ventricle; IAA, interrupted aortic arch; MS, mitral stenosis; NEC, necrotising enterocolitis; PA, pulmonary atresia; PGE1, prostaglandin E1; PS, pulmonary stenosis; TA, tricuspid atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; Truncus, truncus arteriosus.

Table 2 Description of the four NEC cases

| NEC case | Gestational age at birth (weeks+days) | Birth weight (g) | Main cardiac diagnosis | Other significant diagnoses | Preoperative PGE1 | Enteral feeding before cardiac surgery | Age at cardiac surgery (days) | Age at NEC diagnosis (days) |
|----------|---------------------------------------|------------------|------------------------|--|---------------------|---|-------------------------------|-----------------------------|
| 1 | 38+0 | 1716 | ToF | Intrauterine growth restriction | No | Full feeds (breast milk+formula) | 44 | 60 |
| 2 | 39+1 | 2820 | ToF | 22q11 Hypoparathyroidism | Yes | Full feeds (formula) | 11 | 18 |
| 3 | 35+4 | 2750 | TGA | Preterm birth. Complicated coronary anatomy, ventricular septal defect and subvalvular pulmonary stenosis. | Yes, for a few days | Full feeds (formula) | 90 | 91 |
| 4 | 40+0 | 3098 | CoA | VACTERL association, sepsis at birth | Yes | Full feeds (breast milk, no feeds before NEC diagnosis) | 18 | 1 |

.CoA, coarctation of the aorta; NEC, necrotising enterocolitis; PGE1, prostaglandin E1; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies, limb abnormalities.

(VACTERL) association and sepsis. Abdominal signs occurred 3 hours after birth, before initiation of enteral feeding. Laparotomy showed bowel necrosis and perforation. This infant received preoperative treatment with PGE1, underwent cardiac surgery 18 days later and reached full feeds prior to cardiac surgery. Since no enteral feeds were initiated until 4 days after laparotomy and bowel resection, enteral feeding could not have been a factor contributing to development of bowel necrosis in this particular case. Furthermore, diagnosing this case with NEC can be questioned since the extremely early onset of alarming abdominal signs considerably differs from the usual pattern of the disease. When feeding was initiated this infant received only breast milk and no formula.

DISCUSSION

This study showed that in a group of 458 infants with CCHD, of whom 97% were enterally fed before cardiac intervention, the frequency of NEC was low ($n=4$, 0.9%). The four infants with NEC were all enterally fed prior to cardiac surgery, and all four had other risk factors such as chromosomal aberration, immunodeficiency, small for gestational age and sepsis. Three of four were born at term and one was late preterm. One term infant was diagnosed with NEC on day 1, prior to enteral feeding and cardiac surgery. The remaining three were enterally fed prior to cardiac surgery, and developed NEC after the procedure. Prior to development of NEC, all three infants received formula feeding, either formula only (two infants) or mixed with breast milk (one infant). Thus, there were no cases of preoperative NEC after initiation of preoperative enteral feeds which suggests safety of this practice. Our study covers the period from birth until discharge from hospital, therefore the risk of undetected cases of NEC in our study is small.

Frequency of NEC among neonates with CCHD and the role of preoperative enteral feeds

De la Torre *et al*¹⁰ found a NEC frequency of 7.3% among 935 neonates with CCHD. Lau *et al*⁹ studied neonates with CCHD grouped by Risk Adjustment for Congenital Heart Surgery and 61/1811 (3.4%) developed NEC. Eighty-six per cent were on enteral feeds at the time of NEC diagnosis. McElhinney *et al*¹¹ found a similar NEC frequency (3.3%) in a group of 643 neonates with CCHD, 7% had received enteral feeds preoperatively. Becker *et al*¹³ found NEC in 0.3% of 6710 neonates with ductal-dependent CCHD of whom 14% were enterally fed while on PGE1. However, in that study, only NEC developing during

ongoing PGE1 treatment, before cardiac surgery, was registered. Iannucci *et al*¹⁴ showed a NEC frequency of 3% among 1551 infants with CCHD. Eighty-two per cent were diagnosed in the postoperative period. This is consistent with our study where three of four NEC cases were postoperative. In a recent study, Day *et al* could not show any association between enteral feeding and NEC in infants with duct-dependent congenital heart disease.¹⁵ They found a NEC incidence in their cohort of 10.1%.

Scahill *et al*⁸ reported that 61% of neonates who required cardiac surgery were enterally fed before surgery and 9% developed NEC. The study showed no difference in the prevalence of NEC between the groups with and without preoperative enteral feeding. In a study by Natarajan *et al*,¹⁶ 62 of 67 neonates with CCHD were enterally fed before cardiac surgery, of them 75% (47/62) obtained at least 100 mL/kg/day and 35% (22/62) full feeds. The incidence of NEC was 3% (2/67). The rate of preoperative enteral feeding is comparable to our cohort.

In summary, the previously reported frequency of NEC in infants born with CCHD varies between 3% and 9%, with no obvious relationship to preoperative feeding practices. In our study, the frequency of NEC was much lower despite routine preoperative feeding and three of four cases had other risk factors for NEC.

There is no uniform definition of CCHD which complicates comparison between different studies. However, the majority of the neonates in this study had well-defined critical cardiac diagnoses such as HLHS, aortic arch obstruction, TGA and pulmonary atresia. Preoperative circulatory instability with hypoxia, poor intestinal perfusion and acidosis likely increases the risk of NEC in neonates with CCHD.^{13 17 18} Although this Swedish cohort includes only infants with CCHD we cannot exclude that they were in a more stable condition preoperatively compared with published cohorts with a higher frequency of NEC. The proportion of neonates with a prenatal diagnosis was rather low overall, but a well-developed referral and transport system in Sweden for infants with suspected CCHD, and access to paediatricians with some training in cardiology and paediatric echocardiography in almost all delivery units may have contributed to the low frequency of NEC compared with previous studies.

Ductal-dependent systemic circulation and NEC

HLHS, critical aortic stenosis, interrupted aortic arch and CoA are cardiac defects in which systemic circulation may remain compromised even after initiation of PGE1. Previous studies

have shown that the risk of NEC is increased in infants with these diagnoses compared with other CCHD. Reduced mesenteric perfusion is thought to be the underlying cause of this association,^{13 17 18} and it is in infants with these diagnoses that the practice of avoiding preoperative enteral feeding is most widespread.^{7 19} ElHassan *et al*¹⁷ found that NEC developed in 6% of 5720 neonates with HLHS, which provides a benchmark of the incidence in that group. The proportion receiving enteral feeds before surgery was not described. McElhinney *et al*¹¹ reported a similar NEC frequency (7%) among infants with HLHS. In our study, 46 of 47 infants with HLHS were enterally fed before cardiac surgery and there were no cases of NEC. In our cohort of infants with ductal-dependent systemic circulation 96% (198/206) were enterally fed before cardiac intervention and one infant was diagnosed with NEC. This indicates that the practice of not offering enteral feeds before cardiac surgery to infants with CCHD and ductal-dependent systemic circulation needs to be re-evaluated. Breast milk constitutes a protective factor against the development of NEC,^{20 21} which is an advantage compared with TPN. It also enhances the infant's innate immune system by facilitating pathogen recognition and anti-inflammatory response.^{22 23} In addition, by increasing enteral feeds, the risks associated with prolonged TPN are avoided. All this should be of benefit to these infants who are at risk of developing postoperative severe bacterial infections.²⁴ As described in a review by Niño *et al*, multiple randomised clinical trials have now validated the observation that breast milk reduces the incidence of NEC.²⁵ Human milk contains a variety of beneficial factors, among which several have been shown to reduce NEC incidence. Whether the development of NEC in association with formula feeding is due to an injurious agent in infant formula, or the lack of a protective component only present in breast milk remains to be determined.²⁵ The use of standardised feeding guidelines has been proven to be effective to reduce the incidence and severity of NEC.²⁵ Several studies from infants born preterm show that it is safe and even beneficial with early introduction and fast advancement of enteral breast milk.^{26 27} An initial fasting period is not recommended in these studies on preterm infants.^{26 27} The effects on intestinal maturation in combination with a shorter need for parenteral nutrition are some of the positive effects noted.

Strengths and limitations

The study presents a large cohort of neonates with CCHD, and information on enteral feeding before cardiac surgery was carefully investigated.

This study is limited by the inherent limitations of retrospective studies. We used the ICD-10 code to identify cases of NEC. Thus, the results rely on correct diagnostic coding. However, we crosschecked against the paediatric surgery register which should minimise the risk of under-reporting. Neonates who died at a referring hospital or after admission to our hospital with undiagnosed CCHD (detected only at a postmortem examination) were not searched for. They should however be very few, if any.

CONCLUSION

This study has demonstrated that preoperative enteral feeding in infants with CCHD is safe in our institution. Of the four NEC cases in our entire cohort there were no cases of preoperative NEC after initiation of preoperative enteral feeds. This includes 206 infants with ductal-dependent systemic blood flow.

We speculate that the Swedish practice to provide preoperative enteral feeding in these patients does not increase the risk of NEC.

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