Original Article

Analysis of clinical features of neonates with congenital heart disease who develop necrotizing enterocolitis: a retrospective case-control study

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Background: Infants with congenital heart disease (CHD) are known to have higher rates of necrotizing enterocolitis (NEC). Although the etiology is recognized as distinct from the premature neonatal population, there is not a universal consensus regarding etiology or specific risk factors. To analyze the clinical features of neonates with CHD who develop NEC.

Methods: A retrospective study of neonates with CHD in the cardiac intensive care unit (ICU) between 2015 and 2018 was performed, and modified Bell's criteria were used to diagnose NEC. Patients were divided into 2 groups according to ductal-dependent (DD) lesions, and were further stratified by Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) score and Aristotle score, to compare the differences.

Results: Among 412 patients with CHD, 69 (16%) developed NEC. The incidence of NEC was notably higher among DD patients than among non-DD (nDD) patients (18.7% *vs.* 11.1%; P=0.04). Patients with RACHS-1 >2 also had a higher rate of NEC than did those with RACHS-1 ≤2 (19.49% *vs.* 9.29%; P=0.01). nDD patients who developed NEC were younger, had a lower gestational age (36.25±1.88 *vs.* 38.10±1.28 weeks; P=0.00), a lower weight (2.86±0.85 *vs.* 3.33±0.55 kg; P=0.01), and a lower birth weight (2.79±0.79 *vs.* 3.26±0.55; P=0.01) compared to the DD group. All nDD patients developed NEC after congenital heart surgery, while only 38 cases (76%), NEC occurred after heart surgery in the DD group. Four patients needed surgery for NEC in the DD group and RACHS-1 >2 group. Presence of NEC was not associated with an increased risk of mortality in any group.

Conclusions: NEC is a common complication in neonates with CHD and can occur both before and after CHD operations. Likely there are varying mechanism for NEC in different forms of CHD. While NEC is more common in patients with DD CHD and those with more complex forms of CHD, there was no significant difference observed in weight-for-age Z-score (WAZ) between the DD group during follow-up.

Keywords: Necrotizing enterocolitis (NEC); congenital heart disease (CHD); neonates

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Introduction

Necrotizing enterocolitis (NEC) is a type of intestinal inflammation that occurs in newborns. NEC is characterized by extensive hemorrhage and necrosis of the small intestine and colon and is currently one of the main causes of death in newborns (1). Even with surgical intervention, the mortality rate is still as high as 20–30% (2). The incidence of neonatal NEC in congenital heart disease (CHD) patients is significantly higher than in other infants, reaching 3.3–11% (3). The mechanism relevant to neonates with CHD is still unclear, but it is commonly believed to be related to decreased intestinal perfusion secondary to low cardiac output either due to systolic cardiac dysfunction or systemic outflow tract obstruction, lower diastolic blood pressures, especially in infants with ductal-dependent (DD) CHD, and/or hypoxia in infants with cyanotic CHD (4,5). There is a substantial body of scientific literature, consisting of retrospective cohort studies, which have reported evidence of both term and preterm infants with CHD (3,6,7). However, concerns related to the onset of NEC should lead to the analysis of multiple preoperative and postoperative status including comorbidities, haemodynamic instability, cardiopulmonary bypass surgery and enteral feeding mode. Therefore we sought to describe the clinical characteristics of neonates with CHD who develop NEC, specifically looking to examine the difference in those patients with and without DD CHD and those patients with more complex CHD. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3248/rc).

Methods

Study design

This study was a retrospective case-control study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Health Research Ethics Board of Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine (No. SCMCIRB-K2015003), and informed consent was taken from guardians of the patients.

We performed a retrospective study of all newborns with CHD admitted to the Shanghai Children's Medical Center's Cardiac Intensive Care Unit (ICU) from 2015 to 2018 who were diagnosed as NEC. The diagnosis of NEC was made using the modified Bell standard (8), which is based on clinical manifestations of abdominal distension, feeding difficulties, a positive stool occult blood test, and corresponding responses. Imaging findings, including intestinal gas accumulation, portal vein gas accumulation, and/or pneumoperitoneum, were used to confirm the presence and assess severity of NEC.

Data collection

Patient demographic data were collected including gestational age, birth weight, diagnosis of CHD, and presence of arterial DD. In addition, operative characteristics, including CHD risk score [Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1)] and Aristotle Score, cardiopulmonary bypass times, and aortic cross clamp time were collected. At the time of diagnosis of NEC, age, vasoactive inotropic score (VIS), Bell staging, NEC treatment, and feeding method were collected. RACHS-1 and Aristotle Score were classified according to the literatures (3). Early enteral nutrition (EN) was defined as enteral feeding started within 24 hours after ICU admission or 24 hours after cardiac surgery. All infants were followed up by telephone, and the main follow-up information was current age and weight. The long-term indicators were weight-for-age Z-score (WAZ) calculated from the last follow-up.

Data analysis

Neonates with NEC were divided into two cohorts based on presence of DD CHD. Further, patients were stratified by RACHS-1 score, which was dichotomized as ≤2 or >2. Clinical characteristics and incidence of NEC were compared between groups.

Statistical analysis

The SPSS v. 21.0 statistical software package (IBM

Table 1 Distribution of necrotizing enterocolitis congenital heart disease

Congenital heart disease type	Number of patients (n=66)
Transposition of the great arteries with atrial septal defect	15
Coarctation of the aorta	12
Interruption of aortic arch	11
Total anomalous of pulmonary veins connection	10
Pulmonary atresia with intact ventricular septal	6
Double outlet of right ventricle, coarctation of the aorta, ventricular septal defect	4
Transposition of the great arteries with ventricular septal defect	3
Pulmonary atresia with ventricular septal defect	2
Severe pulmonary stenosis	2
Tetralogy of Fallot	1

Corporation, Armonk, NY, USA) was used for statistical processing. All statistical data were assessed using 2-sided tests, and type I errors were controlled to within 0.05. If the measurement data of a group conformed to a normal distribution, the mean ± standard deviation was used to describe the difference between groups. Comparison between groups was performed with an independent samples *t*-test. If the data were not normally distributed, the median (minimum–maximum) is provided. The comparison between groups was performed using the Mann-Whitney U test. The count data are expressed by frequency (percent). The comparison between groups was performed with Pearson's χ^2 test. When the theoretical frequency of more than 25% of the cells was less than 5 and greater than 1, the continuous correction chi-square test was used. When the theoretical frequency of more than 25% of the cells was less than 1, the Fisher exact probability method was used.

Results

From January 1, 2015 to June 30, 2018, a total of 412 newborns with CHD were admitted to our department, and 66 (16.0%) developed NEC. The average birth weight was 3.2±0.7 kg, the average gestational age was 37.7±1.6 weeks, and the mean age at diagnosis of NEC was 14.8±7.2 days. The overall survival rate was 84.8% (n=56). According to the modified Bell staging, the most common severity of NEC was stage I (n=55, 83.3%), followed by stage II (n=8, 12.1%) and stage III (n=3, 4.5%). Four patients required abdominal surgery. The average ICU stay time in surviving patients was 13.6±12.1 days.

The distribution of NEC by diagnosis of CHD is shown in *Table 1*. Transposition of the great arteries with atrial septal defect accounted for the highest proportion in this study, reaching 22.7% (n=15). The 3 infants diagnosed with the most severe form of NEC (stage III) had the following types of CHD: transposition of the great arteries with atrial septal defect, pulmonary atresia with ventricular septal defect, and coarctation of the aorta with ventricular septal defect.

Of the 268 total patients with DD CHD, 50 (18.7%) developed NEC, compared to 16 of the 144 (11.1%) patients with non-DD CHD (χ^2=3.964; P=0.04). Among the newborns with NEC, the nDD group had earlier gestational age, lower body weight, and lower birth weight. NEC occurred most commonly 2 weeks after birth (*Table 2*). Most of the infants in the NEC group developed NEC after cardiac surgery. Notably all the nDD infants developed NEC after cardiac surgery, whereas 24% of the infants in the DD group had NEC before cardiac surgery. At the time of diagnosis, there were no significant differences in VIS, blood lactic acid (Lac), cardiopulmonary bypass time, or aortic cross clamp time. Further, there was no difference in duration of mechanical ventilation, ICU length of stay, or in hospital mortality between the 2 groups (*Table 2*).

In the patients who developed NEC, four infants needed abdominal surgery, all of whom were in the DD group. One patient had stage IIb disease requiring an ileostomy and survived. Three patients had stage IIIb disease, 2 of whom died after ileostomy and 1 whom survived after sigmoidostomy with appendectomy. No significant difference was found in early EN, total EN, or parenteral nutrition (PN) usage between the 2 groups.

Table 2 Clinical characteristics of infants with NEC in the nDD and DD groups

Variables	nDD (n=16)	DD (n=50)	Statistics	P
Clinical characteristics				
Gestational age (w) (± SD)	36.25±1.88	38.10±1.28	−3.67	0.00*
Sex: female, n (%)	4 (25.00)	12 (24.00)	0.13	0.72
Weight (kg) (± SD)	2.86±0.85	3.33±0.55	−2.57	0.01*
Birth weight (kg) (± SD)	2.79±0.79	3.26±0.55	−2.64	0.01*
NEC				
Age at NEC diagnosis (days) (± SD)	15.50±7.92	14.62±7.09	0.42	0.68
VIS at NEC diagnosis [range]	14.25 [0–31.40]	18 [0–85]	455.00	0.21
Lactate level (mmol/L) [range]	2.05 [0.9–5.7]	2.5 [0.7–30]	468.00	0.15
ICU length of stay (days) [range]	13 [7–65]	10 [2–73]	350.00	0.68
Cardiopulmonary bypass time (min) [range]	90.5 [0–302]	125 [0–328]	464.50	0.09
Aortic cross clamp time (min) [range]	45.5 [0–148]	67 [0–193]	449.00	0.14
Mechanical ventilation duration (hours) [range]	208.65 [49.3–866.20]	122.35 [27–858.5]	276.00	0.14
NEC after cardiac surgery, n (%)	16 (100.00)	38 (76.00)	0.03	0.03*
Outcomes				
NEC abdominal surgery, n (%)	0	4 (8.00)	0.57	0.32
Mortality, n (%)	3 (18.80)	9 (18.00)	0.00	1.00
Early EN, n (%)	14 (87.50)	36 (72.00)	0.85	0.36
Full EN, n (%)	8 (50.00)	15 (30.00)	2.14	0.14
PN, n (%)	7 (43.75)	32 (64.00)	2.06	0.15
Age at follow-up (months) [range]	17 [11–38]	20 [11–46]	134.50	0.39
WAZ at follow-up [range]	0.52 [−3.45 to 1.28]	0.48 [−0.92 to 2.11]	122.50	0.70

*, P<0.05. NEC, necrotizing enterocolitis; nDD, non-ductal-dependent; DD, ductal-dependent; VIS, vasoactive inotropic score; EN, enteral nutrition; PN, parenteral nutrition; WAZ, weight-for-age Z-score.

When comparing incidence of NEC by complexity of CHD using the RACHS-1 score (*Table 3*), the incidence of NEC in those with RACHS-1 ≤2 was 9.29% (n=13/140), while the incidence of NEC was 19.49% (n=53/272) in the RACHS-1 >2 group (χ^2=7.15, P=0.01). The only difference between the two RACHS-1 cohorts was infants in the RACHS-1 ≤2 group had a slightly higher birth weight than did those in the RACHS-1 >2 group. No other differences were observed in clinical characteristics or outcome measures between groups.

A total of 66 infants with NEC were divided into 2 groups according to the Aristotle score. Half had an Aristotle score ≤2, and the rest had an Aristotle score >2. *Table 4* shows the statistical results of the clinical characteristics between two groups. The gestational age, weight, birth weight, and VIS at diagnosis were higher and the Lac was lower in the Aristotle ≤2 group. There was no significant difference between the 2 groups in regard to other clinical characteristics.

Of those patients who survived to hospital discharge, 34 had follow-up after hospital discharge for a follow-up rate of 88.9% (n=48/54). The median age at follow-up was 18.5 [5–46] months, and the average WAZ was 0.28±0.17. There was no significant difference observed in WAZ between the DD group, RACHS-1 ≤2 group, or RACHS-1 >2 group during follow-up.

Table 3 Clinical characteristics of different groups of infants with NEC

Variables	RACHS-1 ≤2 (n=13)	RACHS-1 >2 (n=53)	Statistics	P
Gestational age (w) (± SD)	37.00±1.73	37.81±1.59	−1.62	0.11
Sex: female, n (%)	6 (46.15)	15 (28.30)	1.53	0.22
Weight (kg) (± SD)	3.17±0.77	3.23±0.64	−0.29	0.77
Birth weight (kg) (± SD)	3.18±0.86	3.13±0.58	0.24	0.04*
Age at NEC diagnosis (d) (± SD)	16.62±8.31	14.40±7.00	0.99	0.33
VIS at NEC diagnosis [range]	16.75 [0–34]	18 [0–85]	318.00	0.83
Lactate level (mmol/L) [range]	3.3 [1.1–30]	2.4 [0.7–20]	250.50	0.33
ICU length of stay (days) [range]	7 [2–23]	11 [3–73]	374.00	0.11
Cardiopulmonary bypass time (min) [range]	41 [0–310]	126 [0–328]	407.50	0.00*
Aortic cross clamp time (min) [range]	54 [0–169]	78 [0–193]	426.50	0.00*
Mechanical ventilation duration (h) [range]	120.4 [27.8–458.1]	142.1 [27–866.20]	339.00	0.28
NEC after cardiac surgery, n (%)	11 (84.6)	43 (81.1)	0.00	1.00
NEC abdominal surgery, n (%)	0	4 (7.54)	0.58	0.41
Mortality, n (%)	2 (15.38)	10 (18.87)	1.00	0.56
Early EN, n (%)	9 (69.23)	41 (77.36)	0.06	0.80
Full EN, n (%)	5 (38.46)	18 (33.96)	0.09	0.76
PN, n (%)	7 (53.84)	32 (60.38)	0.18	0.67
Age at follow-up (months) [range]	17 [12–38]	20 [11–46]	81.50	0.67
WAZ at follow-up [range]	−0.02 [−3.45 to 1.14]	0.58 [−0.92 to 2.11]	99.50	0.20

*, P<0.05. NEC, necrotizing enterocolitis; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1; VIS, vasoactive inotropic score; ICU, intensive care unit; EN, enteral nutrition; PN, parenteral nutrition; WAZ, weight-for-age Z-score.

Discussion

NEC is associated with a high rate of morbidity and mortality and occurs when the gastrointestinal region of an immature or compromised infant acts as a gateway for bacteria to breach the mucosal barrier. This clinical-pathological entity leads to an uncontrolled inflammatory reaction which evolves towards ischemia and perforation.

Although NEC occurs more frequently in premature infants, it cannot be considered distinctive for this population of patients. In fact, the existence of CHD is a well-known risk factor for the development of NEC in both the full-term and preterm population. In this study, we found the incidence of NEC in our patients to be 16%, seems to be slightly higher than that reported in the literature (9). The possible reason for the high incidence of NEC in our patients is a high number of patients with complex congenital disease, and patients with DD CHD accounted for 65% of the study population. The incidence of NEC in infants with DD CHD was 18.7%, which was significantly higher than that in infants with nDD CHD (11.1%) and this is consistent with the incidence reported in the literature (10). The mechanism of NEC in newborns with DD CHD is likely different from that in newborns with nDD CHD, and may be related to the type of cardiac operation required in DD CHD, or reduced postoperative cardiac output (11). As expected based on prior literature, risk factors for NEC in nDD heart disease includes lower gestational age and birth weight (12-14).

It was previously believed that NEC occurs in neonates with CHD mostly before cardiac surgery (15), in a systematic review reported NEC occurred before cardiac surgery in 48% in CHD (16). However, the results of this study showed that all patients in the nDD group developed NEC after cardiac surgery, while 76% of patients in the DD group were diagnosed after cardiac surgery, which is

Table 4 Clinical characteristics of infants with NEC in different Aristotle score groups

Variables	Aristotle ≤2 (n=33)	Aristotle >2 (n=33)	Statistics	P
Gestational age (w) (± SD)	39.67±1.08	38.52±2.15	2.747	0.008*
Sex: female, n (%)	10 (30.3)	11 (33.3)	0.070	0.792
Weight (kg) (± SD)	3.47±0.55	2.92±0.63	3.742	0.001*
Birth weight (kg) (± SD)	3.40±0.52	2.90±0.68	3.328	0.001*
Age at NEC diagnosis (d) (± SD)	16.87±16.43	15.58±6.98	0.415	0.68
VIS at NEC diagnosis [range]	20 [3–85]	11.5 [0–31.5]	2.457	0.014*
Lactate level (mmol/L) [range]	1.90 [0.7–6.9]	2.6 [0.9–20]	2.008	0.045*
ICU length of stay (days) [range]	11 [5–32]	10 [2–73]	0.088	0.93
Cardiopulmonary bypass time (min) [range]	125 [0–310]	108 [0–328]	0.500	0.617
Aortic cross clamp time (min) [range]	66 [0–169]	66 [0–193]	0.058	0.954
Mechanical ventilation duration (h) [range]	122.5 [67.8–858.5]	142.55 [26–866.2]	0.399	0.690
NEC after cardiac surgery, n (%)	33 (100.0)	30 (90.9)	3.143	0.076
NEC abdominal surgery, n (%)	1 (3.0)	2 (6.1)	0.349	0.555
Mortality, n (%)	4 (12.1)	10 (30.3)	3.264	0.071
Early EN, n (%)	31 (100.0)	29 (90.6)	3.052	0.081
Full EN, n (%)	15 (48.4)	8 (25.0)	3.715	0.054
PN, n (%)	16 (51.6)	21 (65.6)	1.276	0.259
Age at follow-up (months) [range]	19 [7–46]	18 [5–44]	0.652	0.514
WAZ at follow-up [range]	0.28 [–2.76 to 1.97]	–0.09 [–3.17 to 1.21]	1.528	0.126

*, P<0.05. NEC, necrotizing enterocolitis; VIS, vasoactive inotropic score; ICU, intensive care unit; EN, enteral nutrition; PN, parenteral nutrition; WAZ, weight-for-age Z-score.

consistent with the results of a study published by Iannucci *et al.* (17). Patients in the nDD group suffered from low cardiac output, which might have caused multiple organ dysfunction, with NEC being one component of the intestinal manifestation of multiple organ dysfunction. For these infants, timely improvement in low cardiac output syndrome and tissue perfusion may be keys to preventing severe NEC. In addition, due to a more embedded understanding of NEC emerging in recent years, some infants with DD in our study were cautiously provided with EN, especially during the period of PGE1 usage, which might also have been the reason for the incidence of preoperative NEC was low in the DD group. Furthermore, there were fewer premature and low birth weight infants in this group, which could also by a reason why NEC rarely occurred before surgery. It is important to evaluate the differences in clinical presentation between children with CHD and NEC compared with those with prematurity, but the distribution of characteristics in this population are related to the current national conditions.

Concerns about the newborn's weight at birth and the manifestation of CHD are two determining factors to focus on, as eminently highlighted in our report. As regard the infant's weight, Velazco *et al.* (18) revealed that among infants who have a normal birth weight (>2,500 g), the rate of CHD occurs for 18% of cases. While the results reported in our cohort of patients who had low birth weight (<1,500 g) both with and without CHD reliably supported that the presence of CHD significantly increases the risk of NEC (13% *vs.* 9%). Despite evidence of a CHD being one of the most common risk factors for NEC in both term infants, the pathophysiology has not yet been fully elucidated.

EN in newborns with high-risk factors for NEC is still a controversial issue. Scahill *et al.* (14) posited that EN before surgery does not increase the incidence of NEC in neonates

with CHD. In recent years, more studies have suggested that the occurrence and development of NEC are caused by multiple factors. There is not enough evidence to show that NEC is absolutely related to feeding (17,19-21) or the usage of PGE1 before surgery (22), and one study has suggested that fasting cannot prevent NEC (23). Rather, an increasing amount of evidence supports early EN in neonates with CHD (24,25). One nutritional questionnaire study (26) suggested that 76% of pediatric intensive care units (PICUs) in Europe routinely provide EN within 24 hours of surgery in infants with CHD. These findings suggest that early EN may be safe for newborns with CHD. In our study, there was no significant difference between the nDD group and the DD group in early enteral feeding and complete enteral feeding, and the same results were seen in the RACHS-1 <2 and RACHS-1 ≥2 groups. A study (27) of early and late PN for pediatric critical patients showed that delaying the use of PN for 1 week can reduce the infection rate and accelerate the recovery of critically ill infants. Another recent study (28) examined the long-term effects of early and late PN on growth and development, suggesting that limiting early PN for 1 week does affect survival rate, growth, or development. In our study, among those who were followed up via telephone, there was no significant difference in WAZ between the 2 groups with or without PN (u=117.00; P=0.74). Although there are many research results suggesting the safety of early EN in neonates with CHD, the clinical characteristics of NEC showed that those in the DD group were more likely to develop NEC. Newborns with CHD with risk factors should be carefully provided with EN, and close attention should be paid to the evaluation of abdominal signs to prevent severe NEC.

Conclusions

NEC is a common complication in neonates with CHD and can occur both before and after CHD operations. Likely there are varying mechanism for NEC in different forms of CHD. While NEC is more common in patients with DD CHD and those with more complex forms of CHD, most patients recover without major issues in the neonatal period.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3248/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3248/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3248/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Health Research Ethics Board of Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine (No. SCMCIRB-K2015003), and informed consent was taken from guardians of the patients.

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