Necrotizing Enterocolitis Associated with Congenital Heart Disease—A Review Article

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Abstract
Necrotizing enterocolitis (NEC) is a relatively rare but devastating entity associated classically with the preterm cohort in the neonatal intensive care unit. Preterm and term babies with congenital heart disease are at risk of a number of comorbidities because of the hemodynamic derangements due to a structurally abnormal heart and the corrective procedures adopted. Necrotizing enterocolitis is one of the dreaded complications associated with this cohort and impacts the course of these babies in the hospital in a major way. A large majority of term babies with NEC are in the backdrop of a significant congenital cardiac lesion. This review article summarizes the literature and elaborates this entity including its specific features, risk factors associated with its causality, histopathology and related aspects of hemodynamics, and feeding in this vulnerable population. It also provides insight into modifiable risk factors and early markers of detection of gut necrosis to facilitate prevention and early detection. It highlights the subtle but definite difference in outcome variables to help physicians enable the parents of babies with heart disease to develop a better understanding of the entity and its expected course while counseling.

Keywords: Congenital heart disease, Necrotizing enterocolitis, Neonatal mortality, Preterm newborns.
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Introduction
Necrotizing enterocolitis (NEC) is one of the most severe gastrointestinal emergency conditions in the neonatal period, with high morbidity and mortality rates. Nearly 85–97% of all cases of NEC occur in premature infants.1 The other 3–15% occur in full-term infants with predisposing factors such as maternal cocaine exposure, intraterine growth retardation, birth asphyxia, and congenital heart disease (CHD).2–5

Any cardiac lesion causing hemodynamic alterations in the gut could cause ischemia and NEC.6 Poor outflow and poorly oxygenated systemic circulation, due to left-sided cardiac lesions, heart failure, or congenital cyanotic heart disease could all result in gut necrosis.4,5 Consequently, the severity and complexity of cardiac lesions seem to have a major impact on the causality of NEC. The rate of NEC in term newborn infants with symptomatic CHD has been estimated to be 10–100 times higher than in those with structurally normal hearts,1 with an estimated incidence ranging from 1.6 to 9%.3,7–10 The mortality rates in infants who are born with CHD and go on to develop surgical NEC can be as high as 20–30%.11 Infants with single ventricular physiology are at the greatest risk, and NEC can be fatal in up to 97% of these infants.12–14 These infants also have considerable morbidity related to severe intestinal injury, and many develop intestinal strictures, short bowel syndrome, and neurodevelopmental delay.12,14

In a systematic review, Siano et al.1 described cardiogenic NEC to be an entity that was distinct from the classical, idiopathic NEC seen in the preterm gut. The demographics, pathogenic mechanisms, and outcomes differ in the two cohorts. They showed that the presence of a CHD increased the incidence of NEC in very low birth weight (VLBW) infants only slightly from 6.3 to 8.9%. Fewer infants with CHD and NEC required surgery (31 vs 66% in classical NEC), but the overall mortality in these infants was higher.15 Most cardiogenic NEC (50–70%) occurred in the postoperative period.8,15

Prematurity continues to be an independent risk factor for NEC, where the likelihood of developing NEC remains higher in preterm infants recovering after surgery for CHD, even mild medical NEC impeded feeding and weight gain resulting in prolonged hospital stay.19–21 The pathophysiology of NEC in CHD patients is still unknown, but is thought to be multifactorial with lower bowel perfusion pressures due to poor diastolic pressures along with lower systemic oxygenated blood flow. This may have caused bowel ischemia, loss of gut wall integrity, and bacterial overgrowth.9,12

Histopathological Characteristics of NEC in Infants with CHD
The pathophysiology of NEC in infants with CHD which is likely to develop primarily due to gut ischemia may differ from that of NEC in preterm infants, which is thought to result from a mixture of inflammatory and vascular injury.22 The incidence of NEC in premature infants with CHD is actually higher than those with...
Necrotizing Enterocolitis Associated with Congenital Heart Disease

Idiopathic NEC, presumably because these infants not only have the classic risk factors of preterm babies but also the hemodynamic changes observed in CHD.  

Existing studies on cardiogenic NEC emphasize the importance of vascular phenomena involving mesenteric hypoperfusion from diastolic steal and flow reversal in the abdominal aorta.  

A recent retrospective case–control study revealed that postnatal age at onset was lower in CHD NEC patients than in preterm infants (4 [2–24] vs 11 [4–41] days, p < 0.001). The pH nadirs were lower in the CHD cohort (7.21 [7.01–7.47] vs 7.27 [6.68–7.39], p = 0.02) in the one with structurally normal heart.  

Interestingly, the contribution of inflammation and bacterial colonization may not be different between cardiogenic and idiopathic NEC, although there may be more neutrophils in the lesions of NEC associated with CHD. In one study, the highest C-reactive protein levels were higher in cardiogenic NEC (112.5 mg/L [5.0–425.0] vs 66.0 [5.2–189.0], p = 0.05). The anatomic localization of the disease may be different, with some studies showing more lesions in the colon, but not others. The colon can be involved more often than would be predicted based on the gestational age (86 vs 33%, p = 0.03). Mortality caused by NEC was not different (22 vs 11%, p = 0.47).

The histopathological characteristics of NEC in infants who have CHD vs those who have a structurally normal heart are not markedly different. Diez et al. described that infants with cardiogenic NEC seemed to have more prominent macroscopic necrosis, but also had a higher bacterial load noted on histopathology. One example of CHD-related NEC is shown in Figure 1.

**Specific Cardiac Abnormalities Associated with NEC**

Many cardiac anomalies are associated with increased risk of NEC (Table 1). Infants with single ventricular physiology are at the greatest risk of intestinal injury and NEC, which can be fatal in up to 97% of these infants. Hypoplastic left heart syndrome (HLHS), which constitutes 7% of all CHD, is the single most common heart lesion associated with NEC. Infants with HLHS and other single ventricle defects sustain dramatic hemodynamic challenges in the first few days after stage 1 palliative shunt surgery which aims to improve the systemic perfusion by shunting it from the pulmonary circulation. In this process, the gut undergoes periods of hypoperfusion and is at risk of ischemic injury.

Table 1: Outcomes in mild and severe CHD vs controls

<table>
<thead>
<tr>
<th></th>
<th>Mild CHD, n = 130</th>
<th>Severe CHD, n = 40</th>
<th>Controls, n = 4508</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC (%)</td>
<td>5 (4)</td>
<td>4 (10)*</td>
<td>109 (2)</td>
<td>0.014</td>
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<tr>
<td>Mortality (%)</td>
<td>22 (17)*</td>
<td>16 (40)*</td>
<td>234 (5)</td>
<td>&lt;0.001</td>
</tr>
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*p value corresponds to χ² analysis (exact test) or analysis of variance including all groups. *Pairwise comparison vs controls, p < 0.025 (Fischer’s exact test with Bonferroni correction). (From: Motta et al. Journal of Perinatology 2015;35:949–953. CHD, congenital heart disease; NEC, necrotizing enterocolitis)

Diez et al. examined the National Pediatric Cardiology-Quality Improvement Collaborative (NPC-QIC) database to compare mid-term that is interstage outcomes for NEC in infants with HLHS. NEC was seen in 5.8% (68 of 1163) with preterm infants with HLHS. The incidence was higher in those born at <37 weeks (18.3%, 11 of 60) compared to 5.2% (57 of 1103) in gestational age >37 weeks. ElHassan et al. examined a larger retrospective cohort of HLHS babies who went on to develop NEC in 41 hospitals over 10 years. Of the 5720 infants with HLHS, 349 patients (6.1%) were diagnosed with medical or surgical NEC. Fifty-two patients (9%) required laparotomy or percutaneous abdominal drainage.

Bain et al. looked at the incidence of NEC in VLBW infants with atrial and ventricular septal defects (ASDs and VSDs), or both, and found that the incidence of NEC was 6.2% in infants without septal defects, 9.3% in those with an ASD, 7.8% in those with a VSD, and 10.3% in infants with both an ASD and a VSD. Compared with infants without septal defects, the adjusted odds ratios for developing NEC for each group, ASD alone, VSD alone, and those with both an ASD and a VSD were 1.26 (95% confidence interval (CI) 1.07–1.49), 1.27 (1.07–1.51), and 1.79 (1.03–3.12), respectively. They concluded that septal defects did increase the risk of NEC. The association could be due to direct factors causing hemodynamic alterations like cardiac surgery and cardiopulmonary bypass or due to other factors like an elevated circulating endotoxin and proinflammatory cytokines in the background of altered mesenteric blood flow leading to intestinal ischemia thus encouraging bacterial overgrowth with intestinal breakdown.

Diez et al. looked into the characteristics of preterm newborns with NEC with or without a patent ductus arteriosus (PDA) or a CHD. Lesions causing a diastolic steal commonly seen in hemodynamically significant PDAs are often implicated in NEC. In another study, Harkin et al. noted increased risk of NEC following ligation of PDA.

Figs 1A and B: Hematoxylin and eosin-stained microphotographs of resected (A) Distal jejunum; and (B) Colon from a 28-week gestation infant with HLHS show typical features typical of NEC, including necrosis, inflammation, and interstitial hemorrhages. Scale bars: 100 µm

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Becker et al. 14 examined a large multicenter cohort with CHD, and noted the risk of NEC to be higher in infants with various forms of duct-dependent CHD and were on prostaglandin E infusion. This association was the strongest in those with single ventricle heart defects such as HLHS, tricuspid atresia, and hypoplastic right ventricle syndrome. They also examined this cohort for the association of NEC with feeding, and noted that the risk was highest in infants with HLHS. The incidence of NEC was higher in any single ventricle heart disease, even after adjusting for gestational age. In their own cohort, infants born at an earlier gestational age and with lower birth weights had a higher incidence of NEC. 15, 21 Enteral feeding seemed to increase the odds of NEC but the difference was not statistically significant. The median time of starting feeds was seen to be later in patients who went on to develop NEC as compared to those who did not (5 days vs 2 days postoperative). NEC occurred mostly in the postoperative period after feedings were started but did not seem to be related to feeding regimens. 3  

HLHS, which causes major hemodynamic compromise and may need multiple surgeries, had a major impact on the quality of life with a 9% incidence of NEC. 15 In other duct-dependant lesions, NEC was seen in 5% infants. When the complexity of the cardiac anomaly was quantified using the Risk Adjustment for Congenital Heart Surgery criteria, a score ≥2 was more likely to develop NEC. 26 Motta et al. 37 examined a cohort of preterm infants to determine whether severe CHD had an independent association with NEC. They defined severe lesions as cyanotic or left-sided obstructive lesions, or those associated with congestive heart failure. Mild lesions included septal defects and various other lesions not included in the list of severe ones. Among 4678 infants, 170 (3.6%) had CHD and 118 (2.5%) developed NEC. The risk for NEC increased with severe CHD (adjusted relative risk (RR) = 3.72; 95% CI = 1.37–10.10) but not with mild CHD (RR = 0.65; CI = 0.27–1.55).

**Hemodynamic Changes and Gut Perfusion in CHD**

The risk of NEC in infants with CHD suggests that altered intestinal perfusion and consequent gut wall ischemic–reperfusion injury may trigger the cascades of mucosal breakdown and bacterial translocation typically associated with NEC. 38, 39 The histopathological changes of NEC do not differ from those who developed NEC related to prematurity and did not have CHD.  

The specific hemodynamic changes that increase the incidence of NEC in infants with HLHS still remain unclear. Diez et al. 38 described how reduced perfusion is documented in a large number of infants with CHD or PDA who developed NEC. The location of gut necrosis in CHD vs patients with normal cardiac anatomy was noted to be similar, in the small intestine. In other studies, Biglieri et al., 23 Diez et al., 38 and Giannone et al. 3 found most lesions in the colon. The risk of ileal and colonic injury might be related to inferior collateral blood supply and consequent tissue hypoxia.  

In patients who develop NEC, the diastolic velocities of DA were significantly lower, and were even reversed in some. The ratio of diastolic reverse to systolic forward flows was significantly increased in the NEC group. In addition, the resistive index of DA was an independent risk factor for the development of NEC. 12 In another study, Papneja et al. 40 noted that lower descending artery flows in ultrasound Doppler studies in infants with small left-sided heart structures were associated with feeding intolerance and NEC. Figure 2 shows typical Doppler changes related to a large PDA with systolic steal, compared to those from a structurally normal heart with no PDA.  

Two separate studies by Cheung et al. 41 and Castillo et al. 42 examined the postprandial mesenteric blood flow velocities in cohorts with palliative shunts for single ventricle physiology. Cheung compared the basal and postprandial mesenteric blood flow velocities and vascular resistance in infants after shunt palliation with those in non-shunted infants with underlying heart disease. They selectively looked at the systemic to pulmonary or the modified-blalock taussig shunt (m-BTS) which is known to reverse diastolic flow in the mesenteric vasculature. The correlation between these factors was complex. Disturbances of splanchic perfusion were noted in the shunted cohort with their superior mesenteric artery (SMA) blood flow being either absent or reversed during diastole both prior to, and after feeding. However, there was also some compensatory lowering of resistance of the splanchic circulation in the shunted population. Johnson et al. 43 compared mesenteric blood flow in m-BTS cohort to the right ventricle-to-pulmonary artery conduit or the Sano shunt population, postprandially. The Sano shunt was expected to improve systemic including mesenteric perfusion due to better diastolic blood flow in the descending aorta. However, they saw similar changes in the SMA and celiac artery blood flow, and an unexpected absence of increase in forward flow in the postprandial period in the Sano cohort. Thus, the risk of NEC was higher in infants with palliative shunts in both studies.

Miller et al. 43 noted that low cardiac output and diastolic run-off in HLHS might be only inconsistently associated with NEC. They suggested these defects may alter the development of systemic vascular beds, and that those with low abdominal aorta pulsatility index have significantly higher chances of developing NEC. Univentricular physiologies presenting with heterotaxy syndromes pose the complex scenario of unstable hemodynamics with intestinal malposition. Sharma et al. 44 showed that the timing of Ladd’s procedure in such babies needs careful consideration as the chances of NEC increases if it was done prior to establishing a more balanced circulation, ideally after cavopulmonary connection. In another study, Van der Heide et al. 27 looked at two decades of retrospective data of near-term infants with CHD. They noted that infants who had birth asphyxia with lower Apgar scores were at higher risk of NEC.  

**Cardiac Surgery, Perioperative Risk Factors, and NEC**

Other than critical cardiac lesions, NEC can also result due to other associations of CHD like prostaglandin therapy, inotrope use, 14 cardiopulmonary bypass (CPB), extracorporeal membrane use, 45 red cell transfusions, especially if multiple. 19 The postoperative period is particularly vulnerable for gut necrosis resulting in significant morbidity and mortality. 3, 38, 66 The surgical procedure for the cardiac lesion itself compromises the gut flow with patients needing longer times of cardiopulmonary bypass having increased chances of NEC in the postoperative period. 47 Lopez et al. found that the incidence of extracorporeal membrane use was higher and HLHS patients who developed NEC were more likely to have moderate to severe atroventricular valve regurgitation at times of discharge from the NPC-QIC database analysis. 45 In another study, Weiss et al. 48 noted the rates of intra-abdominal complications to be more frequent in infants.
who underwent the hybrid procedure than those with the Sano or m-BTS procedure.

During the postoperative period, the diagnosis of NEC can be challenging. Clinical signs may be difficult to elicit and characteristic radiologic signs may note be notable. Delayed diagnosis and the presence of unusual pathogens may increase morbidity and mortality. The gastrointestinal (GI) system may be particularly prone to complications after cardiac surgery because of the interactions between the GI and cardiovascular systems. Complications may result from perfusion abnormalities of the splanchnic circulation, which may cause ischemia–reperfusion injury. Potential abdominal complications include NEC, GI bleeding, colitis, enteric ischemia, intestinal perforation, and pancreatitis. The gut is particularly at risk of ischemia during the postoperative low cardiac output state because of the sensitivity of the splanchnic circulation to endogenous and exogenous catecholamines, and selective vasoconstriction effects of angiotensin. Splanchnic ischemia may result in inflammation and development of endotoxemia leading to multiorgan dysfunction, and potentially death.\(^3\)

Giannone et al.\(^3\) reviewed the occurrence of NEC in newborns with CHD. They noted considerable systemic inflammation with activation of the nuclear factor-κB in these infants during both the pre- and postoperative periods. There were inflammatory changes in cardiac myocytes and higher levels of the tumor necrosis factor and endotoxin released during and after cardiac surgery, which were associated with heart failure. Contact of blood with foreign surfaces and ischemia–reperfusion injury also results in systemic inflammatory response.

The association between feeding and necrotizing enterocolitis results in frequent feed withdrawal which further contributes to malnutrition in the postsurgical cardiac neonate. Neonates with CHD manifest with early and gradual falls in their growth trajectory compared to healthy infants, increasing their length of hospital stay and risk of death postsurgery.\(^4\)

**Impact of Feeding in Infants with Cardiogenic CHD**

Golbus et al.\(^5\) did a systematic review of all literature between 1950 and 2010 for feeding issues in babies with HLHS. The rationale that it is modifiable morbidity and specific strategies if implemented could improve outcomes in this cohort. The feeding issues reported in literature range from dysphagia due to recurrent laryngeal nerve dysfunction, gastroesophageal reflux (GERD), and increased glottic gap due to weakness to complications like NEC and poor growth and development all resulting in prolonged hospital stay and increased morbidity and mortality. Insertion of a gastrostomy tube has shown to improve survival. The other two measures to show significant benefit are implementation of a standardized feeding protocol and a home-monitoring system consisting of daily weight and systemic oxygen saturation measurements. The thresholds for parents to seek medical advice included a resting SpO\(_2\) <70%, failure to gain 20 g during a 3-day period, and weight loss of >30 g during 24 hours.

A single-center retrospective study at Texas Children’s Hospital from 2010 to 2016 found that an exclusive unfortified human milk
diet was associated with a significantly lower risk of preoperative NEC (OR 0.17, 95% CI 0.04–0.84, \( p = 0.03 \)) in a multivariable regression model controlling for cardiac lesion, race, feeding volume, birth weight, SGA, inotrope use, and prematurity.\(^{11}\) Therefore, exclusive breastfeeding and an exclusive unfortified human milk diet, whether the milk is maternal or donated, is the most significant enteral feeding strategy to decrease the incidence of NEC in infants with CHD.

Standardized feeding protocols have been shown to reduce the incidence of postoperative NEC, shorten the duration of total parenteral nutrition intake days, and reach RDA in a significantly shorter time. Gephart et al.\(^{30}\) found that having a standardized feeding protocol in a unit does reduce the chances of NEC in the vulnerable population including babies with CHD. But they also agree that there is no defined way to standardize an ideal feeding regime for babies with heart disease. A unit-specific feeding policy with well-defined indications and timings to stop, hold, or progress feeds are often used to reduce the chances of NEC.\(^{9}\) Delayed feeding might also be required in low cardiac output states such as in neonates with ductal-dependent cardiac lesions or during treatment with extracorporeal membrane oxygenation or when on inotropic support.\(^{30}\)

### Investigations to Detect Early Gut Compromise in the Postoperative Period

Abdominal radiography is used as a diagnostic tool for NEC; however, its utility is limited in the early stages when pneumatosis intestinalis is absent. In recent years, there has been accumulating data regarding the benefits of using bowel ultrasound (BUS) in the diagnosis and management of NEC. Bowel ultrasonography provides a more detailed and dynamic understanding of the state of the bowel in patients with NEC and may thus make management decisions easier and potentially change the outcome. BUS can detect early signs of NEC (such as bowel wall thickening, decreases in bowel perfusion, and peristalsis), which can then translate to earlier treatment before more advanced NEC develops.\(^{32}\) In atypical presentations, abdominal CT scan is a sensitive modality to diagnose NEC.\(^{33}\)

Dewitt et al. studied the splanchnic NIRS in single ventricle physiology babies intra and postoperatively and as they were being fed in the postoperative period. They saw lower average regional oximetry \(\left( rS_O_2 \right) \) values for prolonged durations in patients who went on to develop proven NEC compared to those who did not. These \( rS_O_2 \) values were lower when they reached one-fourth feed volumes.\(^{47}\)

There has been a fair bit of work to look at specific biochemical markers in postoperative babies to predict the occurrence of NEC. O’Connor et al.\(^{49}\) found that fecal calprotectin levels were significantly increased in postop babies with NEC compared to without increased levels of intestinal-fatty acid-binding protein in the immediate postoperative period after a cardiothoracic surgery is an indicator of the degree of enteroctye injury, and is associated with subsequent development of NEC.\(^{44}\) Other biochemical markers identified in relation to NEC are FOXP3+ regulatory T-cell levels or increased levels of platelet-activating factor and increased expression of its receptor in the ileum. These factors are also more specific to small gut injuries.\(^{12}\)

### Conclusions

Neonates with CHD who go on to develop NEC are a particularly vulnerable cohort and are distinct from the typical population of preterm babies with classical NEC. As advancement in technology allows more newborns to have interim and corrective surgeries for CHD at earlier gestational ages, the likelihood for NEC increases in this vulnerable population. There is a requirement for large randomized prospective studies to understand this entity better but this is difficult as the overall incidence is low. The “high risk” in this group are the ones with complex cardiac lesions like HLHS which significantly reduce gut perfusion. Majority of the cases of NEC are seen in the postoperative period probably due to the hypoperfusion–reperfusion injuries to the intestinal cells. This mandates holding of enteral feeds, complicates recovery, delays growth, and prolongs hospital stay. This review article highlights some key areas of knowledge and gives insight into specific populations at risk, demographics, anticipated outcomes, and management strategies of cardiogenic NEC. It will be helpful to discuss course and expected trajectory of such babies while counseling parents instead of citing data more applicable to preterms with classical NEC.

### References


