Cardiology in the Young

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Outcomes and characteristics in term infants with necrotising enterocolitis and CHD

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Abstract

Background: CHD is a significant risk factor for the development of necrotising enterocolitis. Existing literature does not differentiate between term and preterm populations. Long-term outcomes of these patients are not well understood. The aim was to investigate the baseline characteristics and outcomes of term normal birth weight infants with CHD who developed necrotising enterocolitis. *Methods:* A retrospective review was performed of infants from a single tertiary centre with CHD who developed necrotising enterocolitis of Bell's Stage 1–3, over a ten-year period. Inclusion criteria was those born greater than 36 weeks' gestation and birth weight over 2500g. Exclusion criteria included congenital gastro-intestinal abnormalities. Sub-group analysis was performed using Fisher's exact test. *Results:* Twenty-five patients were identified, with a median gestational age of 38 weeks. Patients with univentricular physiology accounted for 32% (n = 8) and 52% of patients (n = 13) had a duct-dependent lesion. Atrioventricular septal defect was the most common cardiac diagnosis (n = 6, 24%). Patients with trisomy 21 accounted for 20% of cases. Mortality within 30 days of necrotising enterocolitis was 20%. Long-term mortality was 40%, which increased with increasing Bell's Stage. In total, 36% (n = 9) required surgical management of necrotising enterocolitis, the rate of which was significantly higher in trisomy 21 cases ($p < 0.05$). *Conclusion:* Not previously described in term infants is the high rate of trisomy 21 and atrioventricular septal defect. This may reflect higher baseline incidence in our population. Infants with trisomy 21 were more likely to develop surgical necrotising enterocolitis. Mortality at long-term follow-up was high in patients with Bell's Stage 2–3.

Necrotising enterocolitis is a life-threatening gastro-intestinal disorder of infancy wherein a compromised mucosal barrier of the gastro-intestinal tract leads to bacterial translocation, systemic inflammation, and localised perforation in susceptible individuals.[1] Necrotising enterocolitis is classically associated with the preterm infant.[2] However, amongst term infants, cardiovascular disease is a major frequently implicated risk factor, accounting for 18% of necrotising enterocolitis in normal birth weight (>2500g) infants.[3] So-called cardiogenic necrotising enterocolitis has been postulated to possess a unique set of risk factors and pathophysiologic mechanisms, which differentiate it from that seen in prematurity.[4,5] The incidence of necrotising enterocolitis in infants with CHD is approximately 3% with particular lesions associated with a higher incidence. Hypoplastic left heart syndrome has a strong association with necrotising enterocolitis with rates of 6.1–9% in this population.[6,7] The incidence of necrotising enterocolitis in infants with ductal-dependent lesions is reported to be 5%, with a significant proportion seemingly occurring in the post-operative period.[6] Several unanswered questions remain, including the role of pre-operative feeding in high-risk lesions with several studies suggesting that the practice may be safe, particularly with breast milk feeds.[8–10] In the published literature to date, most retrospective series do not describe the rate of genetic abnormalities amongst participants.[6,8,9,11–16] However, in infants with hypoplastic left heart syndrome, a higher rate of chromosomal anomalies has been described in infants who develop necrotising enterocolitis.[7] Furthermore, in the very low birth weight population, infants with trisomy 21 and atrioventricular septal defect have been shown to be at particularly high risk of necrotising enterocolitis, with 17.2% of such infants developing the condition in a prospective cohort,[17] with this association not described in term infants.

Our aim was to review our institutional experience with necrotising enterocolitis in term, normal birth weight infants with CHD with a focus on their mortality outcomes both during and beyond their index admission. We sought to characterise the cardiac lesions most commonly encountered within our patient group and to highlight, where known, any associated genetic anomalies.

Table 1. Modified Bell's criteria for necrotising enterocolitis

Stage	Systemic signs	Intestinal signs	Radiological signs
I. Suspected			
A	Temperature instability, apnoea, and bradycardia	Elevated pregavage residuals, mild abdominal distension, and occult blood in stool	Normal or mild ileus
B	Same as IA	Same as IA, plus gross blood in stool	Same as IA
II. Definite			
A: Mildly ill	Same as IA	Same as I, plus absent bowel sounds abdominal tenderness	Ileus, pneumatosis intestinalis
B: Moderately ill	Same as I, plus mild metabolic acidosis, and mild thrombocytopenia	Same as I, plus absent bowel sounds, definite abdominal tenderness, abdominal cellulitis, and right lower quadrant mass	Same as IIA, plus portal venous gas, with or without ascites
III. Advanced			
A: Severely ill, bowel intact	Same as IIB, plus hypotension, bradycardia, respiratory acidosis, disseminated intravascular coagulation, and neutropenia	Same as I and II, plus signs of generalised peritonitis, marked tenderness, and distension of abdomen.	Same as IIB, plus definite ascites
B: Severely ill: bowel perforated	Same as IIIA	Same as IIIA	Same as IIB plus pneumoperitoneum

NEC = necrotising enterocolitis—table compiled from references.[2,18]

Materials and methods

A retrospective study was carried out at Children's Health Ireland at Crumlin Hospital, Dublin. Ethical approval was gained for this study from the hospital ethics board. Requirement for informed consent was waived in this instance as all data collected were anonymized.

Infants with structural CHD or congenital cardiomyopathy confirmed on echocardiography and with a diagnosis of suspected or radiologically confirmed necrotising enterocolitis treated at our institution between January 2009 and December 2019. Patients were identified by searching our local hospital reporting database to The National Institute for Cardiovascular Outcomes Research or if necrotising enterocolitis was coded on discharge. Necrotising enterocolitis was defined according to Modified Bell's Staging Criteria (Table 1).[2] Where treating clinicians had not made use of this staging system at time of diagnosis, clinical examination findings, laboratory investigations, and radiology reporting were consulted to reach a consensus amongst the authors as to the appropriate stage. Infants were excluded if they were born less than 36 weeks' gestation, or had a birth weight of less than 2.5 kilograms. Also excluded were those infants with known anomalies of the lower gastro-intestinal tract. Data were collected retrospectively from both electronic medical records and physical patient charts. Baseline characteristics were collected on gestational age at birth, patient sex, and birth weight.

Infants were included depending on the presence of structural CHD, cardiomyopathy, or arrhythmia. Structural CHDs were categorised as univentricular or biventricular. Ductal dependence at the time of development of necrotising enterocolitis or prior ductal dependence was recorded. Whether the lesion was detected antenatally was recorded. Medical records were reviewed for the presence or absence of genetic conditions including chromosomal abnormalities and specific molecular gene mutations (if known). Gene variant calling was based on the American College of Medical Genetics and Genomics 2015 criteria.[19]

The following data were collected on infant feeding patterns; day of life when enteral feeds were commenced; whether the infant was fed enterally at time of development of necrotising enterocolitis; type of feed (breast milk, formula); and mode of feeding (nasogastric, oral). If infants were not enterally fed, need for parenteral nutrition or intravenous fluids was recorded and the proportion of each was quantified where possible.

Day of life at development of necrotising enterocolitis was recorded, in addition to whether it occurred pre or post-operatively. Haemodynamically instability prior to developing necrotising enterocolitis was recorded. This was considered to be present in the following circumstances; cardiorespiratory arrest requiring resuscitation; new or escalating ionotropic requirement; metabolic acidosis with pH < 7.25; pulmonary hypertensive crisis; and arrhythmia resulting in haemodynamic compromise.

The primary outcome was death within 30 days of development of necrotising enterocolitis. In this instance, whether necrotising enterocolitis was listed as the primary cause of death was also recorded. Secondary outcomes included long-term mortality beyond the 30-day period and need for surgical management of necrotising enterocolitis.

A sub-group analysis comparing infants with and without trisomy 21 was conducted. Outcomes within these two groups were analysed to assess whether there was a difference in mortality, Modified Bell's Stage, or need for surgical intervention for necrotising enterocolitis between the two groups. Fisher's *t* test was used for comparison of dichotomous variables. Significance was defined as a p value < 0.05. Statistical analysis was performed using GraphPad (Dotmatics. GraphPad. San Diego, California 2022)

Results

Baseline characteristics

Over the 10-year period, there were 25 patients who met the inclusion criteria. Mean gestational age at birth was 38 weeks

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Table 2. Primary cardiac diagnoses

Cardiac lesion	Number of patients (n = 25)
Univentricular Physiology	n = 8 (32%)
HLHS	n = *2*
Pulmonary Atresia	n = *4*
Unbalanced AVSD with LV hypoplasia	n = *2*
Atrioventricular septal defect (balanced)	n = 4 (19%)
Complete AVSD	n = *3*
Transitional AVSD	n = *1*
Left sided obstructive lesions	n = 3 (12%)
Coarctation of the aorta	n = *2*
Coarctation, TGA, DORV	n = *1*
TGA	n = 2 (8%)
VSD	n = 2 (8%)
Pulmonary venous obstructive disease	n = 2 (8%)
TOF	n = 1 (4%)
DORV	n = 1 (4%)
Hypertrophic Cardiomyopathy with SVT	n = 1 (4%)
ccTGA with atrial tachycardia	n = 1 (4%)

Table 3. Results of genetic testing

Genetic test	Test performed
Karyotype	n = 15
	Diagnostic Results n = *5*
Microarray	n = 8
	Diagnostic Results n = *2*
	Benign copy number variants n = *2*
Molecular testing	n = 2
	Diagnostic Results n = *2*

(SD 1.39). Mean birth weight was 3.11 kg (SD 0.45 kg). Cardiac diagnoses and their frequency are recorded in Table 2. Infants with single-ventricle physiology comprised the largest group of defects, accounting for 32% of the total. The most common single defect was atrioventricular septal defect, with a total of n = 6 patients (24%), including two patients with an unbalanced atrioventricular septal defect. Patients with critical CHD requiring ductal patency to maintain circulation in the neonatal period accounted for 52% (n = 13). However, only five patients (20%) were on a prostaglandin infusion at the time they developed necrotising enterocolitis, with the remaining eight patients with a duct-dependent circulation developing necrotising enterocolitis in the post-operative period or beyond (32%). Antenatal diagnosis of cardiac defect was made in 56%.

Genetic testing was not performed in all cases due to institutional practice during the time period of the review. Tests performed are listed in Table 3. Ten patients (40% of total) had a confirmed genetic diagnosis, the details of which are listed in Table 4. Infants with trisomy 21 comprised the greatest number (n = 5/25, 20%). Infants with trisomy 21 accounted for all patients with balanced atrioventricular septal defect (n = 4, 100%). One infant with phenotypic and documented trisomy 21 did not have a laboratory karyotype available for review. In this instance, initial genetic sampling may have been sent from the referring hospital.

Table 4. Cardiac defects in patients with genetic conditions

Genetic abnormality	Cardiac defect
Total (n = 10)	
Trisomy 21 (n = 5)	*AVSD* (n = 4)
	Complete AVSD (n = 3)
	Transitional AVSD (n = 1)
	Pulmonary Vein Stenosis, ASD, PDA (n = 1)
Trisomy X (n = 1)	*Pulmonary Atresia, Tricuspid Atresia, Hypoplastic RV, Single RCA* (n = 1)
Tetrasomy X (n = 1)	*Left and Right Pulmonary Vein Stenosis, Divided Left Atrium, ASD*
CHARGE Syndrome (*CHD7* pathogenic mutation) (n = 1)	*Double Outlet Right ventricle* (n = 1)
Noonan Syndrome (*PTPN11* pathogenic mutation) (n = 1)	*Hypertrophic Cardiomyopathy, Supraventricular tachycardia* (n = 1)

Timing of development of necrotising enterocolitis

The median age at development of necrotising enterocolitis was 17 days with an interquartile range of 5–61 days. A large proportion of infants developed necrotising enterocolitis within the first week of life (n = 9, 36%). In seven patients (28%), necrotising enterocolitis developed between the 2nd and 4th weeks of life. Approximately one-third (n = 9, 36%) of patients presented beyond this period with the latest presentation at 31 weeks of age. In those patients who presented beyond the neonatal period, a significant proportion occurred in the post-operative period or post-cardiac catheterisation (n = 4, 44%). The remainder (n = 5, 56%) were haemodynamically unstable prior.

In 40% of total cases, necrotising enterocolitis developed post-operatively or post-cardiac catheterisation (n = 10). The patients and procedures are listed in Tables 5 and 6. Patients with univentricular circulation accounted for the majority of these patients (n = 6, 60%). This most frequently occurred following first-stage surgical palliation (n = 4) and in one instance first-stage palliation with trans-catheter insertion of a PDA stent (n = 1). In 80% of cases (n = 8), there was pre- or post-procedural haemodynamic instability as defined above.

Feeding patterns

Nineteen patients were enterally fed at the time they developed necrotising enterocolitis. The feed type for these patients is listed in Table 7. The number of patients receiving breast milk feeds (including in combination with any formula) was low at four patients in total (21% of the enterally fed group). The majority of those infants who were enterally fed were on full enteral feeds (n = 11, 58% of enterally fed group). Four patients developed necrotising enterocolitis on advancement of feeds in the post-operative period.

Six infants were nil by mouth at the time of developing necrotising enterocolitis (n = 6/25, 24%), of whom three (n = 3/25, 12%) had never fed prior to developing necrotising enterocolitis. Those infants who had never been fed enterally all developed

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Table 5. Characteristics of patients who developed necrotising enterocolitis in the post-operative period

Diagnosis	Day of life	Procedure	Haemodynamic instability prior to development of NEC	Feed pattern
ccTGA with ventricular and atrial arrhythmias	*17*	*Permanent pacemaker insertion*	*Yes*	*Full enteral*
Pulmonary atresia	*8*	*BTT Shunt*	*Yes*	*Advancing feeds*
Pulmonary atresia	*61*	*BTT Shunt ECMO Post-operatively*	*Yes*	*Parenteral nutrition*
Coarctation, TGA, DORV	*12*	*Arterial Switch, Coarctation Repair*	*No*	*Advancing feeds*
Unbalanced AVSD with LV Hypoplasia (w/ Right Atrial Isomerism)	*47*	*BTT Shunt*	*Yes*	*Trophic feeds (20% enteral)*
Unbalanced AVSD with LV Hypoplasia	*7*	*Damus Kaye Stansel Procedure with BTT Shunt, Arch Repair*	*No*	*Advancing feeds*

Table 6. Characteristics of patients who developed necrotising enterocolitis post-cardiac catheterisation

Diagnosis	Day of life	Procedure	Haemodynamic instability prior to development of NEC (yes/no)	Feed pattern
Pulmonary atresia	*9*	*PDA Stent*	*Yes*	*Parenteral nutrition*
Pulmonary venous obstructive disease	*75*	*Diagnostic Cardiac Catheterisation*	*Yes*	*Full enteral*
Tetralogy of Fallot	*17*	*Right ventricular outflow tract stenting*	*Yes*	*Full enteral*
Hypoplastic left heart syndrome	*72*	*Diagnostic Cardiac catheterisation*	*Yes*	*Full enteral*

Table 7. Feeding patterns

Feeding pattern	Total number
Enterally fed	n = 19 (76%)
Exclusive breast milk	n = 2
Combined breast milk and formula	n = 2
Exclusive formula feeding	n = 13
Unknown	n = 2
Nil by mouth	n = 6 (24%)

Table 8. Mortality rates by stage of necrotising enterocolitis

Modified Bell's Stage	Total number (%)	Mortality at 30d (%)	Mortality at long-term follow-up (%)
Stage 1a & b	n = 10 (40%)	n = 0 (0%)	n = 1 (10%)
Stage 2a & b	n = 6 (24%)	n = 2 (33%)	n = 4 (67%)
Stage 3a & b	n = 9 (36%)	n = 3 (33%)	n = 5 (56%)

necrotising enterocolitis within the first week of life, 100% of whom (n = 3) were on prostaglandin infusion at the time. Three of the infants had been fed enterally previously all of whom had pulmonary atresia. Two were in the post-operative period. The final patient was diagnosed postnatally with pulmonary atresia and had fed enterally at birth, but feeds were held at diagnosis. Necrotising enterocolitis developed on the second day of life and this infant died with necrotising enterocolitis listed as the cause of death.

Outcomes

Death within 30 days of development of necrotising enterocolitis occurred in five patients accounting for 20% of the total. Of these, three patients (12% of total) had necrotising enterocolitis listed as the primary cause of death. Total mortality including at long-term follow-up was 40% (n = 10). Follow-up was variable between 0 and 10 years. Patients were classified according to Modified Bell's Stage and are listed in Table 8. Death within 30 days and at long-term follow-up was increased in Bell's stages 2 & 3. Patients with a univentricular circulation had total mortality of 62.5% (n = 5), and death within 30 days of necrotising enterocolitis of 37.5%.

Sub-group analysis

We conducted a sub-group analysis comparing infants with and without trisomy 21 to assess differences in outcomes between the two groups using Fisher's exact test (Table 9). We noted that while there were no significant differences in mortality between the two groups, infants with trisomy 21 were more likely to require surgical management of necrotising enterocolitis. In terms of baseline characteristics, infants with trisomy 21 had a different spectrum of cardiac diagnosis (Table 4) and none were duct-dependent.

Discussion

Diagnoses

As demonstrated in previous research on this subject, infants with a univentricular circulation accounted for a considerable proportion of the total number of term normal birth weight infants who

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Table 9. Primary and secondary outcomes—comparison of infants with Trisomy 21 and without

	Total (n = 25)	Trisomy 21 (n = 5)	Non-Trisomy 21 (n = 20)	p value
Mortality at 30 days	n = 5 (20%)	n = 1 (20%)	n = 4 (20%)	p = 1
Mortality at long-term follow-up	n = 10 (40%)	n = 2 (40%)	n = 8 (40%)	p = 1
Modified Bell's Stage 2 or higher	n = 15 (60%)	n = 5 (100%)	n = 10 (50%)	p = 0.06
Modified Bell's Stage 3	n = 9 (36%)	n = 5 (100%)	n = 4 (20%)	p = 0.002
Surgical management of NEC	n = 9 (36)	n = 5 (100%)	n = 4 (20%)	**p = 0.02**

p values derived using Fisher's exact test.

developed necrotising enterocolitis at our institution, inferring that this group are at particular risk.[6,7,11] Patients with ductal-dependent circulations in the neonatal period accounted for 52% of our total. However, many of these patients developed necrotising enterocolitis, not whilst on prostaglandin infusion, but in the post-operative period and beyond. A possible hypothesis for this is that abnormal haemodynamics including diastolic steal and episodic hypoperfusion may predispose these infants to necrotising enterocolitis.

The most common single lesion in our population was atrioventricular septal defect. The physiological effects of atrioventricular septal defects include left to right shunting, valvular dysfunction, and cyanosis.[17] It is worth noting that two patients with atrioventricular septal defect in our group had concurrent LV hypoplasia conferring additional risk. Although atrioventricular septal defects have been shown to be strongly associated with necrotising enterocolitis in preterm infants, this has not been previously demonstrated in term infants of normal birth weight.[17] Patient selection may partly explain why this association has not been demonstrated in prior work, with some studies excluding lesions not deemed to be high risk for necrotising enterocolitis with a focus on duct-dependent and univentricular lesions.[7,9,13] Ireland, where this study was performed, has rates of live-born infants with trisomy 21 syndrome that are up to 3 times higher than European counterparts in part due to restrictions on termination of pregnancy for fetal anomalies.[20] Trisomy 21 and atrioventricular septal defect are strongly associated and therefore the incidence of atrioventricular septal defect in our population may be higher when compared with previous literature on the topic.

Genetics

Infants with a confirmed genetic diagnosis accounted for 40% of our total series and infants with trisomy 21 alone accounted for 20% of the total patients. In addition to the cardiovascular effects of atrioventricular septal defect, infants with trisomy 21 are at an increased independent risk of pulmonary hypertension and myocardial dysfunction in both the neonatal period and beyond.[21] While it is not routine practice at our institution to screen for immune deficiency in this group, increasingly appreciated is the substantial immune dysregulation associated with the condition which includes impairments in both innate and adaptive immune systems. This places these infants at an increased risk of serious infection and sepsis, while dysregulated cytokine release can lead to deleterious outcomes.[22] An excessive luminal inflammatory response to bacterial stimuli is a histological feature of necrotising enterocolitis,[2] although there is no literature that demonstrates this specifically in infants with trisomy 21, there is a well-described increased incidence of congenital gastro-intestinal anomalies in this population.[23] Patients with major gastro-intestinal abnormalities were excluded from this series, however, there may be predisposing factors in the gastro-intestinal tract of patients with Trisomy 21 which makes them more susceptible. Therefore, the risk of developing necrotising enterocolitis may be multi-factorial.

The majority of previously published cohorts do not report their rates of chromosomal abnormalities.[6,8,9,11–16,24,25] El Hassan et al. in a large multi-centre cohort study of necrotising enterocolitis in infants with HLHS demonstrated that a larger percentage of infants who developed necrotising enterocolitis had chromosomal abnormalities (8.9% versus 4.7%, p,0.001) and those with chromosomal abnormalities had higher mortality (7.4% versus 4.5%).

Smaller studies have not noted this difference. A single-centre retrospective nested 2:1 matched case-control comparison of infants with CHD, both with and without necrotising enterocolitis, did not demonstrate a statistically significant difference in the rate of chromosomal abnormalities (25.9% versus 16.7% p = 0.31). Overall, patient numbers in this study (n = 81) were considerably smaller than the El Hassan cohort.[7,26]

In our series, patients with trisomy 21 were more likely to require surgical management of necrotising enterocolitis, suggesting that this is a vulnerable patient cohort. However, there was no difference in mortality. A limitation of this study is that it lacks a comparator group allowing for comparison of the background rate of chromosomal abnormalities in our CHD population.

Outcomes

The short-term mortality reported in this series is similar to previous series (20%).[6,7,11] While some series have reported higher rates, these have tended to exclude suspected necrotising enterocolitis (analogous to Modified Bell's Stage 1) from their analyses.[4,8] We have reported mortality according to Bell's stage showing increasing mortality with stage. We have not identified any previous studies looking at long-term follow-up of infants with CHD who develop necrotising enterocolitis.[4,6–8,11,12,14,16,24] Notable in this series is the high mortality rates at long-term follow-up, particularly for those patients who developed stage 2 and stage 3 necrotising enterocolitis (67 and 56%, respectively). While these deaths cannot be attributed to necrotising enterocolitis, the high rates suggest that this is a particularly vulnerable group of patients, with the development of necrotising enterocolitis a poor prognostic indicator for long-term survival.

Feeding patterns and timing

A large proportion of infants developed necrotising enterocolitis within the first week of life. However, 55% of infants presented beyond the first week of life. Particularly high-risk periods appear

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to be the post-operative period, particularly in those with a univentricular circulation. Therefore, the ability to mitigate the risk of necrotising enterocolitis development through withholding feeds may be limited. Indeed, 28% of patients were nil by mouth at the time they developed necrotising enterocolitis, and 17% had never been enterally fed. Further work is necessary to determine whether feed advancement schedules both in the early neonatal period or in the post-operative period could help to ameliorate the risk of necrotising enterocolitis. Notable in this population is the low rate of human breast milk feeds (24% of the enterally fed group). Efforts to increase the rate of human breast milk feeds at our institution are ongoing.

Limitations

This study has several limitations, which must be clearly stated. Data are derived from a single centre. Findings described pertain to the only paediatric cardiology centre providing paediatric cardiac surgical care in Ireland so the findings are representative of the national experience. However, these findings may not be generalisable to other distinct populations. This study was conducted retrospectively and therefore is exposed to inherent biases as practices have changed over time. Follow-up periods varied from between 1 and 10 years. This study is presented as a series as it lacks a comparator group of patients to act as controls. Therefore, the interpretation of the findings in a broader sense is therefore limited and the study is not constructed to demonstrate risk factors for developing necrotising enterocolitis.

Conclusion

The high rate of trisomy 21 and atrioventricular septal defect noted in this series has not been previously described in term infants with CHD and necrotising enterocolitis. There is considerable overlap between the two conditions, and it is unclear which confers the greater risk. Atrioventricular septal defect confers numerous physiological effects, and there is a notable absence of infants with trisomy 21 and isolated ventricular septal defects who developed necrotising enterocolitis. Proposed mechanisms for the increased risk in trisomy 21 include immune dysregulation, cardiac dysfunction, and elevated pulmonary pressures. Infants with trisomy 21 had higher necrotising enterocolitis-related morbidity and were more likely to require surgical management of necrotising enterocolitis. While two patients with atrioventricular septal defects did not have trisomy 21, these patients had unbalanced defects. Overall, a high proportion of patients (40%) had a confirmed genetic condition including chromosomal anomalies and specific gene mutations. High mortality at long-term follow-up was noted in patients with Bell's Stage 2–3. While the cause of death was attributable to necrotising enterocolitis in only a small number of cases, it suggests that the development of necrotising enterocolitis in infants with CHD could be considered a prognostic indicator of future adverse outcomes in this vulnerable cohort.

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Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of Children's Health Ireland at Crumlin.

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