Cardiology in the Young

cambridge.org/cty

Increased interstage morbidity and mortality following stage 1 palliation in patients with genetic abnormalities

Alyson R. Pierick[1], Trudy A. Pierick[2], Thomas D. Scholz[2], M. Bridget Zimmerman[2] and Benjamin E. Reinking[2]

[1]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA and [2]Department of Pediatrics, University of Iowa Stead Family, Iowa City, IA, USA

Original Article

Cite this article: Pierick AR, Pierick TA, Scholz TD, Zimmerman MB, and Reinking BE (2022) Increased interstage morbidity and mortality following stage 1 palliation in patients with genetic abnormalities. *Cardiology in the Young* **32**: 1999–2004. doi: 10.1017/S1047951122000166

Received: 25 May 2021
Revised: 19 December 2021
Accepted: 1 January 2022
First published online: 9 February 2022

Keywords:
Hypoplastic left heart syndrome; genetic abnormalities; interstage period; mortality; feeding and growth

Author for correspondence:
Benjamin Reinking, Department of Pediatrics, University of Iowa Stead Family, 200 Hawkins Drive, BT 1020, Iowa City, IA 52242, USA.
Tel: +319-356-3537; Fax: +319-356-4693.
E-mail: benjamin-reinking@uiowa.edu

Abstract

Background: Hypoplastic left heart syndrome and single ventricle variants with aortic hypoplasia are commonly classified as severe forms of CHD. We hypothesised patients with these severe defects and reported genetic abnormalities have increased morbidity and mortality during the interstage period.

Methods and Results: This was a retrospective review of the National Pediatric Cardiology Quality Improvement Collaborative Phase I registry. Three patient groups were identified: major syndromes, other genetic abnormalities, and no reported genetic abnormality. Tukey post hoc test was applied for pairwise group comparisons of length of stay, death, and combined outcome of death, not a candidate for stage 2 palliation, and heart transplant. Participating centres received a survey to establish genetic testing and reporting practices. Of the 2182 patients, 110 (5%) had major genetic syndromes, 126 (6%) had other genetic abnormalities, and 1946 (89%) had no genetic abnormality. Those with major genetic syndromes weighed less at birth and stage 1 palliation. Patients with no reported genetic abnormalities reached full oral feeds sooner and discharged earlier. The combined outcome of death, not a candidate for stage 2 palliation, and heart transplant was more common in those with major syndromes. Survey response was low (n = 23, 38%) with only 14 (61%) routinely performing and reporting genetic testing.

Conclusions: Patients with genetic abnormalities experienced greater morbidity and mortality during the interstage period than those with no reported genetic abnormalities. Genetic testing and reporting practices vary significantly between participating centres.

Patients with hypoplastic left heart syndrome and other single ventricle variants with aortic arch hypoplasia are palliated with three staged procedures. The first procedure, most commonly a variation of the Norwood, is typically performed during the first week of life and is one of the highest risk congenital heart procedures, with mortality ranging between 7 and 19%.[1] Similarly, the interstage period, the time between stage 1 palliation discharge and admission for stage 2 palliation, is high-risk with a mortality of 4–15%.[1] Risk factors for mortality during the interstage period include lower birth weight, younger gestational age, confirmed or suspected genetic abnormality, race, and longer length of stay following stage 1 palliation.[2] Due to these risk factors, most cardiac programs have implemented Home Monitoring Programs to follow feeding, growth, oxygen saturations, and other clinical parameters more closely during the interstage period.

Genetic abnormalities can be identified in 20–30% of patients with CHD. Identification of a genetic defect in a patient with CHD can help determine prognosis, guide evaluation for extracardiac anomalies, and assess risk for neurodevelopmental delay.[3] The combination of CHD and genetic abnormalities is more likely to lead to pregnancy termination and postnatal comfort care[4] and patients with all forms of CHD and genetic defects experience greater morbidity and mortality following neonatal surgery.[5] Despite this, genetic testing practices vary among surgical centres and is reported to occur in as few as 25% of infants undergoing cardiac surgery.[6] How genetic testing is utilised in patients who will be palliated with a variation of the Norwood procedure and the impact genetic abnormalities have on morbidity and mortality in this population during the interstage period is not well described.

The major aim of this study is to investigate the association between genetic abnormalities and interstage survival using data from phase I of the National Pediatric Cardiology Quality Improvement Collaborative registry database. The secondary aim is to compare comorbidities during the interstage period in those with and without reported genetic abnormalities. Finally, we aim to establish genetic testing and reporting practices of participating centres.

Materials and methods

Study group

This study was a multicentre retrospective chart review of infants with hypoplastic left heart syndrome and other single ventricle lesions with systemic outflow obstruction following a variation of the Norwood or stage 1 hybrid procedure. Data were gathered from the National Pediatric Cardiology Quality Improvement Collaborative registry database. This registry is a secure, web-based system (REDCap, Vanderbilt University) with a standard data set with data definitions, online web-based data entry, and data quality checks. The data are housed in a secure server at Cincinnati Children's Hospital Medical Center. Local Institutional Review Board approval was obtained for data entry and centre participation in the collaborative. This study was determined to be exempt from review by the Institutional Review Board of the University of Iowa as it did not fit definition of human patients' research.

The National Pediatric Cardiology Quality Improvement Collaborative is a voluntary registry that receives data from over 60 paediatric cardiac centres across the United States whose stated mission is to "decrease mortality and improve quality of life for infants with single ventricle CHD and their families." Phase 1 of the collaborative was singularly focused on the interstage period. Since initial patient enrolment began in 2009, the collaborative has expanded its focus and grown in participation. All patients from phase 1 of the collaborative, who underwent stage 1 palliation and survived to hospital discharge between 2013 and 2017 were included in this analysis.

Demographic data, cardiac diagnosis, type of stage 1 palliation, nutrition and feeding information, and genetic testing results were evaluated. Patients were divided into three groups based on reported genetic testing results: major genetic syndrome, other genetic abnormalities, and no reported genetic abnormality. Major genetic syndromes were defined in the NPCQIC database as Trisomy 21, Turner syndrome, CHARGE syndrome, DiGeorge syndrome, Jacobsen syndrome, VATER syndrome, and heterotaxy syndrome. Other genetic testing abnormalities was defined as any abnormal genetic testing results not included in the major genetic syndromes group. No reported genetic abnormality was defined as either no reported genetic testing result or normal genetic testing. In addition, a brief survey was distributed through email by the collaborative to participating centres to establish testing and reporting practices for genetic abnormalities in the database.

Statistics

Demographic and clinical variables were compared among groups of infants with major genetic syndromes, other genetic abnormalities and no genetic abnormalities using Pearson Chi-square test for the categorical variables, and one-way ANOVA or Kruskal–Wallis test for continuous variables. Tukey post hoc test was applied to adjust p-values for the pairwise group comparisons. The outcome of days to discharge (length of stay) was analysed using survival analysis methods to identify covariates, specifically log-rank test for association with categorical variables and Cox proportional hazard regression for association with continuous variables. Cox proportional hazard regression was used to compare days to discharge among the genetic abnormality groups adjusted for covariates. For the outcome of death (or combined outcome of death/not a candidate for stage 2 palliation/heart transplant), test of association to identify covariates used Pearson Chi-square test for categorical variables, and t-test or Wilcoxon rank-sum test for continuous variables. Logistic regression analysis was used to compare mortality outcome among the genetic abnormality groups adjusted for covariates. Variables selected for regression analysis were thought to be clinically relevant or have been previously associated with interstage morbidity and mortality.[2] All the statistical analyses were performed using SAS (version 9.4; SAS/STAT 14.3).

Results

Patient demographics and characteristics

A total of 2182 patients were identified from the National Pediatric Cardiology Quality Improvement Collaborative Phase 1 database from 2013 to 2017. Female patients accounted for 37.8% (825 total). Major genetic syndromes were identified in 110 patients, and 126 patients had reported other genetic abnormalities. The remaining 1946 patients either had normal genetic testing or no comment was made about genetic testing in the NPCQIC database. Characteristics of the three groups can be found in Table 1. There was a significantly greater proportion of females ($p < 0.001$) with major genetic syndromes compared to the other two groups. Mean birthweight of those with major genetic syndromes was significantly lower than those with no genetic abnormality. While hypoplastic left heart syndrome was the most common primary cardiac in all three groups, the diagnosis of unbalanced AV canal was significantly more common in the major syndrome group. In addition, when evaluated as the combined outcome of "other secondary cardiac diagnosis," the presence of moderate to severe atrioventricular valve regurgitation, moderate to severe ventricular dysfunction, or arrhythmia requiring therapy was more common in those with major genetic syndromes or other genetic abnormalities than those with no genetic abnormality.

Infants with any genetic abnormality had a higher rate of major anomalies of other organ systems compared to those with no genetic abnormality (Table 1). Major gastrointestinal abnormalities were the most common non-cardiac diagnoses and were significantly more common among those with major genetic syndromes (19%) compared to those with other genetic abnormalities (2%), or no genetic abnormality (1.1%). Major anomalies of other organ systems (genitourinary, central nervous system, ear-nose-throat, musculoskeletal, endocrine, or pulmonary) were relatively infrequent overall.

Nutrition, feeding, and hospital course

A significantly higher percent of patients with no genetic abnormality were on full oral feeds at discharge than either the major genetic syndrome or other genetic abnormality groups (75% versus 59% and 62%, respectively) and were also discharged following stage 1 palliation at a younger age (median age of 35 days of life versus 45 and 43 days, respectively). Those with no genetic abnormality also reached full enteral feeds following stage 1 palliation significantly faster compared to those with other genetic abnormalities (19 days versus 24 days), shown in Table 2. Comparison of age at discharge among the three groups, adjusted for covariates, showed a significantly longer length of stay in those

https://doi.org/10.1017/S1047951122000166 Published online by Cambridge University Press

Table 1. Patient demographics and characteristics.

Variable	Major syndrome (n = 110)	Other genetics (n = 126)	Normal genetics (n = 1946)	p-value	Pairwise comparison		
					Major versus Normal	Other versus Normal	Major versus Other
Sex (Female)	67 (61%)	47 (37%)	711 (37%)	<0.0001	<0.0001	0.985	0.001
Birthweight (kg)	(n = 108) 3.04 (0.49)	(n = 125) 3.13 (0.56)	(n = 1929) 3.22 (0.54)	0.0007	0.002	0.170	0.374
Gestational age (weeks)	(n = 109) 38.3 (1.5)	38.3 (1.6)	(n = 1937) 38.5 (1.5)	0.223			
Primary cardiac dx	(n = 109)	(n = 125)	(n = 1939)	<0.0001	<0.0001	0.122	<0.0001
HLHS	39 (36%)	82 (66%)	1363 (70%)				
Double inlet LV	5 (5%)	2 (2%)	90 (5%)				
Unbalanced AV canal	31 (28%)	8 (6%)	82 (4%)				
Other cardiac dx	34 (31%)	33 (26%)	404 (21%)				
Secondary cardiac dx							
Restrictive atrial septum	7 (6%)	21 (17%)	329 (17%)	0.015	0.015	0.997	0.048
Other cardiac	48 (44%)	42 (33%)	402 (21%)	<0.0001	<0.0001	0.003	0.236
Major anomalies other organs							
GI	21 (19%)	3 (2%)	21 (1.1%)	<0.0001	<0.0001	0.401	0.001
Any major, other than GI	30 (27%)	37 (29%)	144 (7%)	<0.0001	<0.0001	<0.0001	0.933
Fetal cardiac diagnosis	84 (76%)	93 (74%)	(n = 1943) 1558 (80%)	0.155			
Age initial discharge after newborn admission (days)	45 [28–62]	43 [31–70]	(n = 1945) 35 [24–52]	<0.0001	0.001	<0.0001	>0.99
Last weight prior to discharge (kg)	3.66 (0.80)	3.81 (0.96)	(n = 1937) 3.70 (0.69)	0.179			
Length at discharge (cm)	(n = 68) 50.8 (7.1)	(n = 89) 52.9 (4.8)	(n = 1327) 52.2 (4.5)	–			

Patients categorised based on presence of a major genetic syndrome, other genetic abnormality or no genetic abnormality with comparisons of different patient characteristics
AV = atrioventricular; GI = gastrointestinal; HLHS = hypoplastic left heart syndrome; LV = left ventricle

with major genetic syndromes compared to those with no genetic abnormality, with hazard ratio of 0.78 (95% CI: 0.63, 0.97; p = 0.026).

Transplant free survival to stage 2

The covariates in the Cox proportional hazard regression model included birthweight, secondary cardiac diagnosis, other major organ anomalies, age and weight at Norwood surgery, and age at initial full enteral feeds (Table 3). For the outcome of death only, there was no significant difference among the groups, even after adjusting for covariates (OR 1.55). However, the combined outcome of death, not a candidate for stage 2 palliation, and heart transplant was more likely in those with a major syndrome after adjusting for covariates, (odds ratio 1.77, 95% CI 1.03, 3.03; p = 0.039). Other risk factors for the combined outcome included female sex, younger gestational age, and major anomalies of other organ systems other than gastrointestinal. Those who underwent stage 1 hybrid were more likely to experience the combined outcome compared to those who had Norwood with Blalock Taussig shunt (odds ratio 0.55, 95% CI 0.37, 0.81; p = 0.003) or Norwood with Sano (odds ratio 0.34, 95% CI 0.23, 0.5; p = 0.0001).

Survey results

Twenty-three of 60 centres responded to the questionnaire about genetic testing and reporting practices. There was significant variation between responding centres with 61% (n = 14) routinely performing genetic testing on all single ventricle infants. The type of genetic testing performed also varied with 84% (n = 19) of centres doing a chromosomal microarray, 47% (n = 11) doing fluorescence in situ hybridisation, 42% (n = 9) doing Karyotype, and 10% (n = 2) reporting other. The reporting of genetic testing results in the REDCap database also varied by centre. Most centres responding to the survey (65%, n = 15) only reported abnormal genetic testing results if one of the major syndromes listed in REDCap was detected, 25% (n = 5) documented all abnormal tests (including copy number variants), and 10% (n = 2) had variable reporting practices.

Discussion

This large multicentre study utilising the National Pediatric Cardiology Quality Improvement Collaborative database sought to identify how genetic abnormalities affect morbidity and

https://doi.org/10.1017/S1047951122000166 Published online by Cambridge University Press

Table 2. Nutrition and feeding comparison.

Variable	Major syndrome (n = 110)	Other genetics (n = 126)	Normal genetics (n = 1946)	p-value	Pairwise comparison		
					Major versus Normal	Other versus Normal	Major versus Other
Age initial full enteral feeds (days)	(n = 109) 21 [15–32]	24 [17–37]	(n = 1945) 19 [14–28]	<0.0001	0.293	<0.0001	0.150
Route of nutrition, discharge plan	(n = 109)		(n = 1938)				
Oral (only/with NG/NJ or G-Tube)	64 (59%)	78 (62%)	1449 (75%)	<0.0001	0.0008	0.005	0.872
NG/NJ (only/with Oral)	38 (35%)	46 (37%)	788 (41%)	0.337			
G-Tube (only/with Oral)	41 (38%)	45 (36%)	450 (23%)	<0.0001	0.002	0.005	0.951
Type of nutrition, discharge plan		(n = 125)	(n = 1937)	0.499			
Breastmilk	12 (11%)	12 (10%)	259 (13%)				
Formula	52 (47%)	55 (44%)	790 (41%)				
Breastmilk and Formula	46 (42%)	58 (46%)	888 (46%)				

Patients categorised based on presence of a major genetic syndrome, other genetic abnormality or no genetic abnormality with comparisons of initiation of feeds following stage 1 palliation and type/route of nutrition at discharge
G-tube = gastrostomy tube; NG = nasogastric; NJ = nasojejunal

Table 3. Cox proportional hazard regression model.

Variable	Odds ratio (95% CI)	p-value
Sex (F)	1.38 (1.04, 1.83)	0.025
Gestational age (weeks) per +1 week	0.90 (0.83, 0.98)	0.017
Secondary cardiac diagnoses		
Restrictive atrial septum	1.36 (0.95, 1.95)	0.09
Other cardiac	1.29 (0.94, 1.77)	0.123
Major anomalies other organs		
GI	0.34 (0.10, 1.17)	0.086
Any major, other than GI	1.67 (1.10, 2.54)	0.016
Type of Norwood procedure		<0.0001
Norwood/DKS BT shunt	0.55 (0.37, 0.81)	0.003
Norwood RV-PA conduit	0.34 (0.23, 0.50)	<0.0001
Hybrid Norwood/Other	-ref-	
Major syndrome		0.051
Major	1.77 (1.03, 3.03)	0.039
Other genetics	0.69 (0.36, 1.34)	0.275
Normal genetics	-ref-	

Cox proportional hazard regression model for a combined outcome of death, not a candidate for S2P or heart transplant. Other cardiac diagnoses included the presence of moderate to severe AV valve regurgitation, moderate to severe ventricular dysfunction or arrhythmia requiring therapy
BT = Blalock–Taussig; DKS = Damus–Kaye–Stansel; GI = gastrointestinal; RV-PA = right ventricle-pulmonary artery

mortality during the interstage period. We identified differences in the demographics, feeding, hospital course and outcomes when genetic abnormalities are present in this population. In addition, we identified variation in the genetic testing and reporting practices of participating centres.

Patient demographics and characteristics

In this cohort of patients, those with any genetic abnormality weighed less at birth, had delayed oral feeding, and were more likely to have non-cardiac abnormalities than those with no reported genetic abnormality. Many of our findings in infants with major genetic syndromes agree with previous studies. Others have reported lower birth weights in infants with hypoplastic left heart syndrome and major genetic syndromes.[7–11] The female preponderance is likely due to the association between Turner syndrome and hypoplastic left heart syndrome and the increased incidence of CHD in females with Trisomy 21.[12,13] Finally, the diagnosis of unbalanced atrioventricular canal defect is known to be more common in patients with Trisomy 21 and heterotaxy syndrome than in non-syndromic patients.[14,15]

We have shown an increased rate of gastrointestinal abnormalities in patients with major genetic syndromes. This finding is not surprising when one considers the common non-cardiac malformations seen in the major genetic syndromes as defined in this study. Children with Trisomy 21 have increased risk of duodenal and anal atresia,[15] those with Turner syndrome have increased risk of gastrointestinal vascular abnormalities,[16] and heterotaxy syndrome is associated with a diverse array of gastrointestinal malformations. Not surprisingly, any infant with abnormal genetic testing also had higher rates of non-cardiac malformations.

Nutrition, feeding, and hospital course

Infants with single ventricle heart disease and aortic hypoplasia are at risk for oral feeding problems early in life. Factors that contribute to poor oral feeding in this population include delay in initiation of oral feeds, vocal cord dysfunction, prolonged intubation, gastroesophageal reflux, and non-cardiac abnormalities.[17] Initiation of feeding prior to the first procedure has been an area of contention due to concerns for reduced splanchnic blood flow and potential risk of necrotising enterocolitis. In contrast, initiation of early trophic feeds has been associated with shorter length

https://doi.org/10.1017/S1047951122000166 Published online by Cambridge University Press

of intubation and earlier feeding tolerance after stage 1 palliation.[18] Our findings suggest that infants with any genetic abnormality are slower to reach full enteral feeds and less likely to be on full oral feeds at discharge. These findings are multifactorial in nature. As shown, infants with a major genetic syndrome were more likely to have gastrointestinal anomalies than the other two groups. Many of these anomalies, such as duodenal atresia, are independently linked to a delay in feeds and need for gastric feeds.[19] In addition, infants with genetic abnormalities have increased risk of other major anomalies, such as ear, nose, and throat or nervous system anomalies that may also interfere with initiation of enteral feeds and delay oral feeding opportunities.

Prior to nutrition and growth interventions made by the National Pediatric Cardiology Quality Improvement Collaborative, growth in infants during the interstage period was suboptimal and varied widely between institutions.[20] Following the implementation of a nutrition algorithm from the collaborative's feeding work group, there was improvement in change in weight-for-age z-scores consistent with all participating centres having a positive change. These algorithms involved specific guidelines for the initiation of feeding following stage 1 palliation, sequential advancements to goal feedings, and ongoing evaluations of growth during the interstage period.[21] A follow-up study performed by Slicker et al revealed that although most institutions did not use these exact feeding guidelines, a majority used modified guidelines written by their institutions.[22] During the postoperative period, most centres participating in the National Pediatric Cardiology Quality Improvement Collaborative recommend a consistent weight gain goal of 20 g/day for these infants, regardless of genetic abnormality. This growth parameter may explain why this cohort had no statistical difference in weight at hospital discharge between the three groups.

Transplant free survival to stage 2

The combined outcome of death, not a candidate for stage 2 palliation, and heart transplant was more likely in those with a major syndrome after adjusting for covariates. Others have defined long-term outcomes in this patient cohort similarly due to low numbers of patients in each category.[23,24] The reason for poorer outcomes in those with major genetic syndromes is likely multi-factorial. Those with major genetic syndromes in our cohort were more likely to have previously described risk factors for death during the interstage period including lower birth weight, supplemental tube feeds, and non-cardiac abnormalities.[25,26]

Other risk factors for death, not a candidate for stage 2 palliation, and heart transplant in this cohort included female sex, major non-cardiac anomalies (other than gastrointestinal), and younger gestational age. This combined outcome was significant in female infants, OR 1.38 (1.04, 1.83), which may be related to both increased incidence of CHD in females with Trisomy 21 and the high-risk nature of stage 1 palliation in infants with Turner syndrome.[12,27] These two syndromes, and other major genetic syndromes, lead to increased risk of the combined outcome, with an OR of 1.77 (1.03, 3.03).

Stage 1 palliation is typically a Norwood with a Blalock–Taussig shunt or a right ventricle to pulmonary artery conduit (Sano shunt), but a hybrid procedure for stage 1 palliation is performed routinely at some centres with practice variation among centres and individual surgeons. Our data show decreased odds of this combined outcome of death, not a candidate for stage 1 palliation, and heart transplant in patients treated with a Blalock–Taussig or Sano shunt in comparison to a hybrid procedure, in agreement with prior studies showing decreased survival following the hybrid procedure.[28–30]

Limitations of our current study are multifold. First, inherent in this study are the limitations present in all retrospective chart reviews. Second, as seen in our survey results, there was significant variation in the type of genetic testing performed and in how the results of the testing were entered into the collaborative database. Survey response rate was also low at 38%. As a result, it is likely that the number of patients with abnormal genetics was included in the normal genetics cohort, and therefore overall underreported. Lastly, some patients with a major genetic syndrome or abnormal genetic testing may not have been entered into the National Pediatric Cardiology Quality Improvement Collaborative phase 1 database due to a primary heart transplant, palliative care pathway, or not discharged prior to stage 2 palliation due to complications or increased risks for discharge.

The care of patients during the interstage period continues to evolve. Our finding that the combined outcome of death, not a candidate for stage 2 palliation, and transplant is more likely in those with a major syndrome may impact how this group is cared for in the future. This finding also supports the use of routine genetic testing for this population. Based upon survey results, there is significant practice variation between centres in what genetic testing is performed and reported in the NPCQIC collaborative database. Standardisation of genetic data collection and reporting will be important for future evaluations of this cohort.

Acknowledgements. None.

Financial support. Current funding sources for the National Pediatric Cardiology Quality Improvement Collaborative include (1) participation fees from enrolled centres; (2) a grant from the Children's Heart Association of Cincinnati; and (3) a federal grant to the paediatric Center for Education and Research in Therapeutics at Cincinnati Children's Hospital Medical Center, funded by the federal Agency for Healthcare, Research and Quality (#U19HS021114 AHRQ). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Conflicts of interest. None.

References

1. Ohye RG, Sleeper LA, Mahony L, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med 2010; 362: 1980–1992.
2. Kaplinski M, Ittenbach RF, Hunt ML, et al. Decreasing interstage mortality after the Norwood procedure: a 30-year experience. J Am Heart Assoc 2020; 9: e016889.
3. Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. Circulation 2018; 138: e653–e711.
4. De Groote K, Vanhie E, Roets E, et al. Outcome after prenatal and postnatal diagnosis of complex congenital heart defects and the influence of genetic anomalies. Prenat Diagn 2017; 37: 983–991.
5. Morales-Demori R. Congenital heart disease and cardiac procedural outcomes in patients with Trisomy 21 and Turner syndrome. Congenit Heart Dis 2017; 12: 820–827.
6. Connor JA, Hinton RB, Miller EM, Sund KL, Ruschman JG, Ware SM. Genetic testing practices in infants with congenital heart disease. Congenit Heart Dis 2013; 9: 158–167.
7. Ergaz-Shaltiel Z, Engel O, Erlichman I, Naveh Y, Schimmel MS, Tenenbaum A. Neonatal characteristics and perinatal complications in neonates with Down syndrome. Am J Med Genet 2017; 173: 1279–1286.

https://doi.org/10.1017/S1047951122000166 Published online by Cambridge University Press

8. McAndrew S, Acharya K, Nghiem-Rao TH, Leuthner S, Clark R, Lagatta J. NICU management and outcomes of infants with Trisomy 21 without major anomalies. J Perinatol 2018; 38: 1068–1073.
9. Yao D, Ji C, Chen W, Li M, Zhao ZY. Physical growth and development characteristics of children with Williams syndrome aged 0-24 months in Zhejiang Province. J Pediatr Endocrinol Metab 2019; 32: 233–237.
10. Bernasconi S, Larizza D, Benso L, et al. Turner's syndrome in Italy: familial characteristics, neonatal data, standards for birth weight and for height and weight from infancy to adulthood. Acta Paediatr 1994; 83: 292–298.
11. Wisniewski A, Milde K, Stupnicki R, Szufladowicz-Wozniak J. Weight deficit at birth and Turner's syndrome. J Pediatr Endocrinol Metab 2007; 20: 607–613.
12. Diogenes TCP, Mourato FA, de Lima Filho JL, Mattos SDS. Gender differences in the prevalence of congenital heart disease in Down's syndrome: a brief meta-analysis. BMC Med Genet 2017; 18: 111.
13. Samanek M. Boy: girl ratio in children born with different forms of cardiac malformations: a population-based study. Pediatr Cardiol 1994; 15: 53–57.
14. Umapathi KK, Agasthi P. Atrioventricular Canal Defects. StatPearls Publishing, USA, 2020.
15. Stoll C, Dott B, Alembik Y, Roth MP. Associated congenital anomalies among cases with Down syndrome. Eur J Med Genet 2015; 58: 674–680.
16. Kucharska A, Józefczuk P, Książyk M, Labochka D, Banaszkiewicz A. Gastrointestinal vascular malformations in patients with Turner's syndrome: a systemic review of case reports. Horm Res Paediatr 2018; 90: 39–43.
17. Hehir DA, Cooper DS, Walters EM, Ghanayem NS. Feeding, growth, nutrition, and optimal interstage surveillance for infants with hypoplastic left heart syndrome. Cardiol Young 2011; 21: 59–64.
18. Toms R, Jackson KW, Dabal RJ, Reebals CH, Alten JA. Preoperative trophic feeds in neonates with hypoplastic left heart syndrome. Congenit Heart Dis 2015; 10: 36–42.
19. Smith MD, Landman MP. Feeding outcomes in neonates with Trisomy 21 and duodenal atresia. J Surg Res 2019; 244: 91–95.
20. Anderson JB, Iyer SB, Schidlow DN, Williams R, Varadarajan K. Variation in growth of infants with a single ventricle. J Pediatr 2012; 161: 16–21.
21. Slicker J, Hehir DA, Horsley M, et al. Nutrition algorithms for infants with hypoplastic left heart syndrome; birth through the first interstage period. Congenit Heart Dis 2013; 8: 89–102.
22. Slicker J, Sables-Baus S, Lambert LM, Peterson LE, Woodard FK, Ocampo EC. Perioperative feeding approaches in single ventricle infants: a survey of 46 center. Congenit Heart Dis 2016; 11: 707–715.
23. Tabbutt S, Ghanayem N, Ravishankar C, et al. Risk factors for hospital morbidity and mortality after the Norwood procedure: a report from the Pediatric Heart Network Single Ventricle Reconstruction Trial. J Thorac Cardiovasc Surg 2012; 144: 882–895.
24. Evans CF, Sorkin JD, Abraham DS, Wehman B, Kaushal S, Rosenthal GL. Interstage weight gain is associated with survival after first-stage single-ventricle palliation. Ann Thorac Surg 2017; 104: 674–680.
25. Ono M, Kido T, Wallner M, et al. Preoperative risk factors influencing inter-stage mortality after the Norwood procedure. Interact Cardiovasc Thorac Surg 2021; 33: 218–226.
26. Cross RR, Harahsheh A, McCarter RJ, Martin G. Identified mortality risk factors associated with presentation, initial hospitalization, and interstage period for the Norwood operation in a multi-centre registry: a report from the national pediatric cardiology-quality improvement collaborative. Cardiol Young 2014; 24: 253–262.
27. Lara DA, Ethen MK, Canfield MA, Nembhard WN, Morris SA. A population-based analysis of mortality in patients with Turner syndrome and hypoplastic left heart syndrome using the Texas birth defects registry. Congenit Heart Dis 2017; 12: 105–112.
28. Sower CT, Romano JC, Yu S, Lowery R, Pasquali SK, Zampi JD. Early and midterm outcomes in high-risk single-ventricle patients: Hybrid vs Norwood palliation. Ann Thorac Surg 2019; 108: 1849–1855.
29. Simsic JM, Phelps C, Kirchner K, et al. Interstage outcomes in single ventricle patients undergoing hybrid stage 1 palliation. Congenit Heart Dis 2018; 13: 757–763.
30. Wilder TJ, McCrindle BW, Hickey EJ, Ziemer G, Tchervenkov CI. Is a hybrid strategy a lower-risk alternative to stage 1 Norwood operation? J Thorac Cardiovasc Surg 2017; 153: 163–172.

https://doi.org/10.1017/S1047951122000166 Published online by Cambridge University Press