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ORIGINAL ARTICLE

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Differences in midterm outcomes in infants with hypoplastic left heart syndrome diagnosed with necrotizing enterocolitis: NPCQIC database analysis

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Abstract

Introduction: Neonates with hypoplastic left heart syndrome (HLHS) are at increased risk for necrotizing enterocolitis (NEC). Initial hospital outcomes are well described, but minimal midterm data exist. Goal of this study was to compare outcomes of HLHS infants with NEC (HLHS-NEC) to HLHS without NEC (HLHS-nNEC) during the interstage period.

Methods: Data were reviewed from 55 centers using the NPC-QIC database. Case-control study with one HLHS-NEC matched to HLHS-nNEC neonates in a 1:3 ratio based on institutional site, type of surgical repair, and gestational age ±1 week was performed. Baseline demographics as well as outcome data were recorded. The *t* tests or chi-square tests were performed as appropriate.

Results: There were 57 neonates in the HLHS-NEC (14 Norwood-BT, 37 Norwood-RVPA, and 6 hybrid) and 171 neonates in the HLHS-nNEC group. There were significant differences between the HLHS-NEC versus HLHS-nNEC for presence of atrioventricular valve regurgitation (7% vs 2%), use of extracorporeal membrane oxygenation (11% vs 2%), hospital stay (60.4 ± 30.0 vs 36.3 ± 33.6 days), Z-score weight at discharge (−2.1 vs −1.6), incidence of no oral intake (33% vs 14%), and use of formula only nutrition at discharge (61% vs 29%), respectively. There were no significant differences between groups in readmission rates due to adverse gastrointestinal events, use of gastrointestinal medications, interstage deaths, or Z-score weight at time of second surgery. HLHS-NEC continued to be more likely to be entirely tube dependent for enteral intake at time prior to the second procedure (39% vs 15%).

Conclusions: Despite similar baseline characteristics, HLHS-NEC infants had significant differences in hospital course compared with HLHS-nNEC neonates. In addition, HLHS-NEC infants were less likely to be fed orally during the entire interstage period. Future studies are needed minimize NEC in this high risk population to possibly improve oral feeds.

KEYWORDS
hypoplastic left heart syndrome, necrotizing enterocolitis, outcomes

1 | INTRODUCTION

The incidence of necrotizing enterocolitis (NEC) is higher in neonates with congenital heart disease (CHD) when compared with healthy term infants. In particular, neonates with single ventricle physiology are at increased risk for NEC during their initial hospitalization when they undergo the first stage of congenital heart repair.[1–5] NEC is associated with substantial morbidity and mortality in these patients.[3,6,7] Potential short-term consequences for any neonate that develops NEC include an increased risk of infectious and hematologic complications, the need for ostomy and/or prolonged total parental nutrition, and death.[1,2,8–10]

While immediate outcomes have been described for neonates with single ventricle physiology that develop NEC during their initial hospitalization, data on more long-term outcomes, including nutritional health, are lacking. Among infants without CHD, NEC has been associated with short bowel syndrome, need for G-tube feeds, electrolyte imbalances, and poor growth in the months posthospitalization.[11,12] For patients with single ventricle physiology, the interstage period, defined as the time from initial hospital discharge to subsequent second stage surgery, is also a high-risk period for poor weight gain and death.[13–17] The added sequelae of having had NEC on disease-related morbidity during the interstage period are unknown.

The goal of this study was to compare the midterm outcomes during the interstage period for infants with hypoplastic left heart syndrome who had survived to hospital discharge that developed NEC (HLHS-NEC) versus those that did not develop NEC (HLHS-nNEC) during their initial hospitalization.

2 | METHODS

This study was a retrospective, case-control analysis of data on infants with hypoplastic left heart syndrome using data from the National Pediatric Cardiology Quality Improvement Collaborative (NPCQIC) from July 2008 to September 2014. This study was deemed exempt from review by the Institutional Review Board of Nationwide Children's Hospital because it did not fit the definition of human subjects research under 45 CFR46.102(f).

The NPCQIC is a multicenter clinical network of 58 hospitals in 33 states and the District of Columbia. The stated goal of this organization is "to reduce mortality and improve the quality of life of infants with hypoplastic left heart syndrome during the interstage period between discharge from the first stage palliation and readmission for the second stage palliation."[18] To that end, NPCQIC created a clinical database. In the first phase of this collaborative, which this data was derived from, patients were included in the database if they meet all four of the following criteria: (1) participants must have a diagnosis of univentricular congenital heart disease that required a Norwood or Norwood variant procedure for palliation (eg, Damus–Kaye–Stansel anastomosis, aortic arch reconstruction, and modified Blalock–Taussig (BT) shunt; Norwood procedure with either a modified BT shunt or right ventricle-to-pulmonary artery conduit; or hybrid stage I palliation; (2) patients must have survived the initial palliative procedure; (3) the patient must have been discharged alive to home following their initial admission for palliation; and (4) parental consent was acquired for participation.[19]

HLHS-NEC : HLHS-nNEC patients were matched in a 1:3 ratio based on surgical center, gestational age ± 1 week, and type of primary palliative surgery. Participants were matched on all three variables for study inclusion in order to account for variation in clinical practices across institutions and clinical factors independently associated with prematurity and to address impact of variable physiologies created by different stage I procedures. Patients with CHD diagnoses other than HLHS were excluded. Antenatal, perinatal, and postnatal demographic data were recorded. Additional data collected included subsequent medical diagnoses, complications, and procedural variables throughout the initial hospitalization during which the first stage of palliative surgery was performed. Inter-stage data was collected as well as data just prior to the patients' second stage palliative surgery.

Differences in patient characteristics between HLHS-NEC and HLHS-nNEC infants were assessed using chi-square tests for categorical data and continuous *t* tests or Wilcoxon rank-sum tests for continuous data, as appropriate. We determined the proportions of patients with lack of oral intake at second stage palliation between the two groups. To evaluate if development of NEC was associated with lack of oral intake at time of second stage palliation, univariable and multivariable conditional logistic regression analyses were performed to calculate unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Demographic and clinical variables were evaluated as potential risk factors and retained in the multivariable model if found to be statistically significant in univariable analyses (P value $\leq .10$) or if were considered a priori to be clinically important. Conditional logistic regression analyses were performed to account for the 1:3 matching of HLHS- NEC to HLHS-nNEC infants. All analyses were performed using STATA 12.1 (StataCorp LP, College Station, Texas).

3 | RESULTS

Over the study period, 1595 neonates were enrolled in the NPC-QIC database, of which 1163 had HLHS. The incidence of NEC in the total cohort was 5.8% (68/1163). Among neonates with a gestational age less than 37 weeks, the incidence of NEC was 18.3% (11/60), compared with an incidence of 5.2% (57/1103) among neonates with a gestational age greater than 37 weeks.

Although 68 patients were diagnosed with HLHS-NEC, 11 patients could not be matched in an 1:3 ratio. All of these excluded patients had a gestational age less than 37 weeks. The final study sample was thus composed of 57 neonates with HLHS-NEC that were matched 1:3 ratio with 171 neonates with HLHS-nNEC. The initial stage I palliative surgical procedure for the HLHS-NEC patients was a Norwood with modified Blalock–Taussig shunt in 14 patients, Norwood with a right ventricle to pulmonary artery conduit in 37 patients, and a hybrid procedure in 6 patients.

There were no significant differences in baseline characteristics between the HLHS-NEC versus the HLHS-nNEC groups (Table 1). There were also no significant differences in operative characteristics between the two groups (Table 2). The incidence of extracorporeal membrane use was higher and length of hospitalization was longer in the HLHS-NEC patients. HLHS-NEC patients were more likely to have moderate to severe atrioventricular valve regurgitation on echocardiographic analysis at time of discharge. Weight for Z-score was lower for HLHS-NEC patients at time of discharge. In addition, HLHS-NEC patients were more likely to be fed purely via nasogastric or gastrostomy tube and fed only formula versus HLHS-nNEC patients upon hospital discharge (Table 3).

TABLE 1 Demographics

Characteristic	HLHS-NEC (n = 57)	HLH-nNEC (n = 171)	*P* value
Male sex, n (%)	39 (68%)	111 (65%)	.62
Race			
White	44 (77%)	142 (83%)	.61
African American	7 (12%)	15 (9%)	
Other	6 (11%)	14 (9%)	
Hispanic ethnicity	15 (26%)	36 (21%)	.41
Median gestational age (weeks), IQR	39 (38–39)	39 (38–39)	.94
Median birth weight (kg), IQR	3.2 (2.9-3.5)	3.3 (3.0–3.6)	.32
Presence of restrictive atrial septum, n (%)	7 (12%)	30 (18%)	.35

Abbreviation: IQR, interquartile range.

At the time of stage II procedure, HLHS-NEC patients were less likely to be taking oral feeds (Table 4) compared with HLHS-nNEC patients. Other clinical characteristics evaluated at that time were similar between the two groups. After adjustment, no oral intake at time of discharge (adjusted OR 11.0; 95% CI: 2.02–60.4) was a significant risk factor for lack of oral intake at time of stage II procedure, as was increasing length of stay of initial hospitalization in days (adjusted OR 1.02 per day; 95% CI: 1.00–1.03) (Table 5). There were no significant variables, including the presence of NEC during initial hospitalization, which predicted increased odds of readmission during the interstage period due to gastrointestinal issues or the use of gastrointestinal medications.

4 | DISCUSSION

The incidence of NEC is high in neonates with congenital heart disease, especially in those patients with single ventricle physiology.[1–3,5,7] The immediate short-term outcomes have been described, but less is known about mid-term outcomes in this population. In this study, there were differences in hospital variables between HLHS-NEC versus HLHS-nNEC patients. Furthermore, HLHS-NEC patients were less likely to be orally feeding by their stage II procedure compared with HLHS-nNEC patients. However, the development of NEC by itself did not increase the odds of not feeding orally at the time of the stage II procedure.

Baseline demographic risk factors for NEC have been well described and include, but are not limited to, prematurity/low birth weight and congenital heart disease.[5,7,20] In this study, no baseline demographic variable was different between the two groups. Since HLHS-NEC patients were matched according to gestational age, it was expected that gestational age and birth weight were not significantly different between groups. However, the incidence of NEC in neonates born less than 37 weeks gestation was higher than those born after 37 weeks, consistent with prematurity being a risk factor for NEC. Despite the overall worse prognosis for HLHS patients with a restrictive atrial septum, the incidence of this variable in the HLHS-NEC patients was not higher than the HLHS-nNEC patients.[21,22]

Correspondingly, operative characteristics such as weight and bypass times during surgery also were not different between the two groups. Though imperfect, bypass times could be used as a possible surrogate for the technical difficulty of the procedure. Since bypass times were not different between groups, this would suggest that at least some of the technical aspects of the surgery were not major contributing factors in the development of NEC. It must also be added that since NEC occurs in patients undergoing the hybrid procedure as well, which does not require cardiopulmonary bypass, it may be the overall underlying physiology of a circuit in parallel versus series that places these patients at increased risk for NEC and not just the fact of undergoing cardiopulmonary bypass.[1] The ability to accurately determine the presence of residual lesions after the surgical procedure and decisions to intervene or not intervene were difficult to ascertain from the database, so no comment was made on those issues to determine if there were differences in those variables.

The higher incidence of significant atrioventricular valve regurgitation or use of extracorporeal membrane oxygenation and longer length of hospital stay in HLHS-NEC infants may reflect a more ill population that is at risk for developing NEC. In addition, once NEC has been diagnosed in an infant, there is likely a period of no intestinal feeding as well as a slow escalation to full feeds that contributes to overall hospital stay. We are unsure why the presence of ventricular dysfunction was not also higher in the HLHS-NEC patients. Both function and regurgitation were qualitatively graded, but it may be that more quantitative measures of function are needed to better differentiate between these two groups.[23,24]

When analyzing nutritional outcomes, HLHS-NEC patients had a lower weight for age Z-score and were more likely to be fed entirely via artificial means at time of initial hospital discharge. Although feeding via artificial means is not ideal, in many cases this is likely needed to optimize nutrition in these patients. Patients with congenital heart disease are already known to have feeding abnormalities regardless of any other issues.[25,26] The presence of NEC probably exacerbates these issues leading to the poorer weight gain and lack of oral motor skills at time of discharge. An unexpected finding was the fact that the HLHS-NEC patients were more likely to be fed formula only versus the

TABLE 2 Operative data

Characteristic	HLHS-NEC (n = 57)	HLHS-nNEC (n = 171)	*P* value
Mean weight-for-age Z-score at time of stage I, SD[a]	−0.31 (1.01)	−0.16 (0.92)	.29
Median cardiopulmonary bypass time (min), IQR	153 (116–183)	146 (110–180)	.67
Median circulatory arrest time (min), IQR	62 (48–85)	60 (44–78)	.36

[a]Weight-for-age Z-scores calculated using 2006 World Health Organization's sex-specific weight-for-age charts. Abbreviation: IQR = interquartile range.

TABLE 3 Hospitalization data

Characteristic	HLHS-NEC (n = 57)	HLHS-nNEC (n = 171)	*P* value
Presence of moderate-to-severe atrioventricular valve regurgitation	**4 (7%)**	**3 (2%)**	**<.05**
Presence of ventricular dysfunction	3 (5%)	5 (3%)	.41
Presence of arrhythmia requiring treatment	1 (2%)	1 (0.6%)	.41
Use of extracorporeal membrane oxygenation	**6 (11%)**	**4 (2%)**	**.01**
Median length of hospital stay after first stage palliation, days (IQR)	**55 (39–74)**	**28 (21–42)**	**<.01**
Mean weight-for-age Z-score at time of discharge after first stage palliation, SD[a]	**−2.1 (1.11)**	**−1.64 (1.17)**	**<.01**
Route of nutrition at time of discharge after first stage palliation, n (%)			
No oral intake	**19 (33%)**	**24 (14%)**	**<.01**
Some oral intake	**38 (67%)**	**147 (86%)**	
Type of nutrition at time of discharge after first stage palliation, n (%)			
Breast milk only	**10 (18%)**	**24 (14%)**	**<.01**
Formula only	**35 (61%)**	**39 (29%)**	
Breast milk and formula	**12 (21%)**	**98 (57%)**	
Mean recommended caloric intake, kcal/ounce (SD)	24.8 (4.02)	24.3 (2.65)	.44
Median oxygen saturation at time of stage I procedure hospitalization discharge, % (IQR)	82 (80–85)	83 (80–87)	.30

[a]Weight-for-age Z-scores calculated using 2006 World Health Organization's sex-specific weight-for-age charts.
Abbreviations: IQR, interquartile range; SD, standard deviation.

HLHS-nNEC patients. The benefits of breast milk over formula are well known, so encouraging breast milk in the HLHS-NEC patients would seem to be intuitive.[27] The reason for this difference in type of nutrition at time of discharge between these groups cannot be easily explained unless there is concern for milk protein allergy. This data may make caregivers more cognizant of this discrepancy. This difference does offer a possible intervention to encourage caregivers of HLHS-NEC patients to provide breast milk for their children to optimize care if there are no concerns for milk protein allergy.

Despite the differences observed between groups in initial hospital course, it was reassuring that number of readmissions for gastrointestinal issues and use of gastrointestinal medications were not different between

TABLE 4 Interstage and stage II data

Characteristic	HLHS-NEC (n = 57)	HLHS-nNEC (n = 171)	*P* value
Median age at time of second stage palliation, days (IQR)	160 (133–181)	142 (128–167)	.14
Mean weight-for-age Z-score at time of second stage palliation, SD[a]	−1.71 (1.12)	−1.50 (1.08)	.23
Mean rate of change in weight-for-age Z-score from discharge after first stage palliation to time of second stage palliation, Z-score/day (SD)	0.003 (0.01)	0.002 (0.01)	.33
Median oxygen saturation at time of second stage palliation, % (IQR)	80 (77–82)	79 (75–83)	.89
Type of nutrition at time of second stage palliation, n (%)			
Breast milk only	5 (8.8%)	23 (14%)	.52
Formula only	40 (70%)	106 (62%)	
Breast milk and formula	5 (8.8%)	24 (14%)	
Missing	7 (12%)	18 (11%)	
No oral intake at stage II	**22 (39%)**	**26 (15%)**	**<.01**
Missing data on oral intake	**8 (14%)**	**20 (12%)**	
Use of gastrointestinal medications	13 (28%)	34 (20%)	.64
>1 readmission for poor feeding after hospital discharge following stage I procedure	24 (42%)	59 (35%)	.30

[a]Weight-for-age Z-scores calculated using 2006 World Health Organization's sex-specific weight-for-age charts.

TABLE 5 Risk of no oral intake at time of stage II in HLHS-NEC patients

Characteristic	Unadjusted OR (95% CI) for nutritional route at Glenn	*P* value	Adjusted OR (95% I) for nutritional route at Glenn	*P* value
Presence of NEC during Norwood hospitalization	4.98 (2.14, 11.6)	<.01	2.17 (0.63, 7.09)	.22
Route of nutrition at time of Norwood hosp. discharge				
Some or all oral intake	**Reference**		**Reference**	
No oral intake	**20.9 (4.82, 90.5)**	**<.01**	**11.0 (2.02, 60.4)**	**<.01**
Type of nutrition at time of Norwood hosp. discharge				
Breast milk	Reference		Ref	
Formula	7.51 (1.50, 37.7)	.01	4.63 (0.44, 49.0)	.20
Breast milk and formula	1.98 (0.38, 10.4)	.42	2.44 (0.22, 26.7)	.47
Sex				
Female	Reference			
Male	0.99 (0.45, 2.20)	.98		
Race				
White	Reference			
African American	1.48 (0.35, 6.33)	.60		
Other	0.74 (0.16, 3.46)	.70		
Ethnicity				
Hispanic	Reference			
Non-Hispanic	0.84 (0.24, 2.88)	.780		
Length of hospital stay after Norwood procedure (days)	**1.03 (1.01, 1.05)**	**<.01**	**1.02 (1.00, 1.03)**	**.02**
Presence of restrictive atrial septum	1.24 (0.44, 3.52)	.68		
Presence of moderate-to-severe atrio-ventricular valve regurgitation	5.12 (0.45, 58.2)	.19		
Presence of ventricular dysfunction	6.00 (0.54, 66.2)	.14		
Use of extracorporeal membrane oxygenation (ECMO)	4.37 (0.44, 43.1)	.21		

them. Also, Z-score weight at time of the second surgical procedure was not different between groups. This would suggest that the HLHS-NEC infants were able to catch up in growth compared with the HLHS-nNEC infants. Previous studies have documented poorer weight gain in those HLHS patients who are not orally fed, however, other studies have shown good weight gain in institutions that have a instituted a home monitoring program.[15,28–33] Most of the institutions participating in NPC-QIC have instituted some form of home monitoring program with nutritional assistance, and this potentially explains the improved weight gain even in those patients not orally fed. There was no difference in type of nutrition that these two groups were fed at time of their second surgery in comparison to the differences found at initial discharge. Unfortunately, this was not because of an increase in breast milk use in the HLHS-NEC infants, but rather a decrease in the HLHS-nNEC group from feeding both breast milk and formula to feeding formula alone.

There continued to be a significant difference in the ability to orally feed in the HLHS-NEC infants compared with the HLHS-nNEC infants at time of their second surgery. This is consistent with data in noncongenital heart disease patients that documented route of feeding at time of initial hospital discharge predicting long-term feeding difficulties.[34] As stated before, infants with congenital heart disease have underlying issues that place them at increased risk for feeding issues, but the inability to orally feed may have cognitive, communication, and motor implications in these patients.[25,26,34] Though presence of NEC was associated with increased unadjusted odds of not being fed orally, adjusted odds ratio found that NEC was not necessarily a significant risk factor. Though it is reassuring that NEC does not seem to affect mid-term outcomes after hospital discharge, methods to reduce the incidence of NEC in this high risk population should be investigated to possibly improve the incidence of oral feeding in this patient population.[4,35–37]

There are several limitations to this study. This was a retrospective study of a registry database, so we could not independently verify registry data and were unable to collect any missing data points. NEC diagnosis was based on individual institution's definition and not necessarily on a uniform grading scale for diagnosing NEC.[38] Further, results could be affected by uncontrolled confounding issues due to variables not routinely collected by the NPCQIC. We were unable to match 11 patients due to their premature gestational age. More quantitative data such as nutritional laboratory values, echocardiographic data, catheterization data, and specific surgical techniques (shunt size, conduit size, stent diameter, and pulmonary artery diameter width) were not available. Finally, the registry cohort is limited to patients who were discharged home after stage I procedure and whose caregivers gave consent for them to participate in the study, so risk factors for NEC could not be fully ascertained. Those patients with the most severe cases of NEC are less likely to be included in this database as they may not have survived or been stable for discharge prior to their second stage palliation. Despite these limitations, this study is the largest to describe intermediate, postdischarge outcomes for HLHS patients who developed NEC during their initial hospitalization in a matched fashion.

In conclusion, despite similar baseline characteristics, HLHS-NEC infants had significant differences in hospital course compared with HLHS-nNEC infants. However, patients who developed NEC were able to overcome more complicated hospital courses to have comparable nutritional outcomes to their counterparts without NEC. Future studies are needed to explore if there are long-term consequences of a lack of oral feeding among those patients who developed NEC.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study to release data via the respective institutions in the NPC-QIC collaborative.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Concept/design: Lopez, Backes, and Cua
Data analysis/interpretation: Gowda and Nandi
Drafting article: Lopez and Cua
Data collection: Miller-Tate, Fichtner, Allen, and Stewart
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REFERENCES

[1] Luce WA, Schwartz RM, Beauseau W. Necrotizing enterocolitis in neonates undergoing the hybrid approach to complex congenital heart disease. *Pediatr Crit Care Med*. 2011;12(1):46–51.

[2] Leung MP, Chau KT, Hui PW, et al. Necrotizing enterocolitis in neonates with symptomatic congenital heart disease. *J Pediatr*. 1988;113(6):1044–1046.

[3] Jeffries HE, Wells WJ, Starnes VA, Wetzel RC, Moromisato DY. Gastrointestinal morbidity after Norwood palliation for hypoplastic left heart syndrome. *Ann Thorac Surg*. 2006;81(3):982–987.

[4] Braudis NJ, Curley MA, Beaupre K, et al. Enteral feeding algorithm for infants with hypoplastic left heart syndrome poststage I palliation. *Pediatr Crit Care Med*. 2009;10(4):460–466.

[5] McElhinney DB, Hedrick HL, Bush DM, et al. Necrotizing enterocolitis in neonates with congenital heart disease: risk factors and outcomes. *Pediatrics*. 2000;106(5):1080–1087.

[6] Cozzi C, Aldrink J, Nicol K, Nicholson L, Cua C. Intestinal location of necrotizing enterocolitis among infants with congenital heart disease. *J Perinatol*. 2013;33(10):783–785.

[7] ElHassan NO, Tang X, Gossett J, et al. Necrotizing enterocolitis in infants with hypoplastic left heart syndrome following stage 1 palliation or heart transplant. *Pediatr Cardiol*. 2018 Feb 1 [Epub ahead of print].

[8] Kelleher J, Mallick H, Soltau TD, Harmon CM, Dimmitt RA. Mortality and intestinal failure in surgical necrotizing enterocolitis. *J Pediatr Surg*. 2013;48(3):568–572.

[9] Müller MJ, Paul T, Seeliger S. Necrotizing enterocolitis in premature infants and newborns. *J Neonatal-Perinatal Med*. 2016;9(3):233–242.

[10] Short SS, Papillon S, Berel D, Ford HR, Frykman PK, Kawaguchi A. Late onset of necrotizing enterocolitis in the full-term infant is associated with increased mortality: results from a two-center analysis. *J Pediatr Surg*. 2014;49(6):950–953.

[11] Raphael BP, Mitchell PD, Finkton D, Jiang H, Jaksic T, Duggan C. Necrotizing Enterocolitis and central line associated blood stream infection are predictors of growth outcomes in infants with short bowel syndrome. *J Pediatr*. 2015;167(1):35–40.

[12] Yeh TC, Chang JH, Kao HA, Hsu CH, Hung HY, Peng CC. Necrotizing enterocolitis in infants: clinical outcome and influence on growth and neurodevelopment. *J Formos Med Assoc*. 2004;103:761–766.

[13] Anderson JB, Beekman RH, Eghtesady P, et al. Predictors of poor weight gain in infants with a single ventricle. *J Pediatr*. 2010;157(3):407–413.

[14] Patel MD, Uzark K, Yu S, et al. Site of interstage outpatient care and growth after the Norwood operation. *Cardiol Young*. 2015;25(07):1340–1347.

[15] Miller-Tate H, Stewart J, Allen R, et al. Interstage weight gain for patients with hypoplastic left heart syndrome undergoing the hybrid procedure. *Congenit Heart Dis*. 2013;8(3):228–233.

[16] Cua CL, Thiagarajan RR, Taeed R, et al. Improved interstage mortality with the modified Norwood procedure: a meta-analysis. *Ann Thorac Surg*. 2005;80(1):44–49.

[17] Ghanayem NS, Allen KR, Tabbutt S, et al. Interstage mortality after the Norwood procedure: results of the multicenter single ventricle reconstruction trial. *J Thorac Cardiovasc Surg*. 2012;144(4):896–906.

[18] Kugler JD, Beekman Iii RH, Rosenthal GL, et al. Development of a pediatric cardiology quality improvement collaborative: from inception to implementation. From the Joint Council on Congenital Heart Disease Quality Improvement Task Force. *Congenit Heart Dis*. 2009;4(5):318–328.

[19] Baker-Smith CM, Goldberg SW, Rosenthal GL. Predictors of prolonged hospital length of stay following stage ii palliation of hypoplastic left heart syndrome (and variants): analysis of the national pediatric cardiology quality improvement collaborative (NPC-QIC) database. *Pediatr Cardiol*. 2015;36(8):1630–1641.

[20] Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. *J Perinatol*. 2003;23(4):278–285.

[21] Alsoufi B, Mori M, Gillespie S, et al. Impact of patient characteristics and anatomy on results of Norwood operation for hypoplastic left heart syndrome. *Ann Thorac Surg*. 2015;100(2):591–598.

[22] Vlahos AP, Lock JE, McElhinney DB, van der Velde ME. Hypoplastic left heart syndrome with intact or highly restrictive atrial septum: outcome after neonatal transcatheter atrial septostomy. *Circulation*. 2004;109(19):2326–2330.

[23] Bellsham-Revell HR, Simpson JM, Miller OI, Bell AJ. Subjective evaluation of right ventricular systolic function in hypoplastic left heart syndrome: how accurate is it?. *J Am Soc Echocardiogr*. 2013;26(1):52–56.

[24] Nadorlik H, Fleishman C, Brown DW, et al. Survey of how pediatric cardiologists noninvasively evaluate patients with hypoplastic left heart syndrome. *Congenit Heart Dis*. 2015;10(2):E73–E82.

[25] Jadcherla SR, Vijayapal AS, Leuthner S. Feeding abilities in neonates with congenital heart disease: a retrospective study. *J Perinatol.* 2009;29(2):112–118.

[26] Malkar MB, Jadcherla S. Neuromotor mechanisms of pharyngoesophageal motility in dysphagic infants with congenital heart disease. *Pediatr Res.* 2014;76(2):190–196.

[27] Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet.* 1990;336(8730):1519–1523.

[28] Anderson JB, Iyer SB, Schidlow DN, et al. Variation in growth of infants with a single ventricle. *J Pediatr.* 2012;161(1):16–21.

[29] 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(S2):59–64.

[30] Hehir DA, Ghanayem NS. Single-ventricle infant home monitoring programs: outcomes and impact. *Curr Opin Cardiol.* 2013;28(2):97–102.

[31] Hehir DA, Rudd N, Slicker J, et al. Normal interstage growth after the norwood operation associated with interstage home monitoring. *Pediatr Cardiol.* 2012;33(8):1315–1322.

[32] Oster ME, Ehrlich A, King E, et al. Association of interstage home monitoring with mortality, readmissions, and weight gain: a multicenter study from the national pediatric cardiology quality improvement collaborative. *Circulation.* 2015;132(6):502–508.

[33] Williams RV, Zak V, Ravishankar C, et al. Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network Infant Single Ventricle Trial. *J Pediatr.* 2011;159(6):1017–1022.

[34] Jadcherla SR, Khot T, Moore R, Malkar M, Gulati IK, Slaughter JL. Feeding methods at discharge predict long-term feeding and neurodevelopmental outcomes in preterm infants referred for gastrostomy evaluation. *J Pediatr.* 2017;181:125–130.

[35] del Castillo SL, McCulley ME, Khemani RG, et al. Reducing the incidence of necrotizing enterocolitis in neonates with hypoplastic left heart syndrome with the introduction of an enteral feed protocol. *Pediatr Crit Care Med.* 2010;11:373–377.

[36] Manuri L, Morelli S, Agati S, et al. Early hybrid approach and enteral feeding algorithm could reduce the incidence of necrotising enterocolitis in neonates with ductus-dependent systemic circulation. *Cardiol Young.* 2017;27(01):154–160.

[37] Carpenito KR, Prusinski R, Kirchner K, et al. Results of a feeding protocol in patients undergoing the hybrid procedure. *Pediatr Cardiol.* 2016;37(5):852–859.

[38] Bell MJ. Neonatal necrotizing enterocolitis. *N Engl J Med.* 1978;298(5):281–282.

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