ORIGINAL RESEARCH

Impact of Palliation Strategy on Interstage Feeding and Somatic Growth for Infants With Ductal-Dependent Pulmonary Blood Flow: Results from the Congenital Catheterization Research Collaborative

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***Background*—**In infants with ductal-dependent pulmonary blood flow, the impact of palliation strategy on interstage growth and feeding regimen is unknown.

***Methods and Results*—**This was a retrospective multicenter study of infants with ductal-dependent pulmonary blood flow palliated with patent ductus arteriosus (PDA) stent or Blalock-Taussig shunt (BTS) from 2008 to 2015. Subjects with a defined interstage, the time between initial palliation and subsequent palliation or repair, were included. Primary outcome was change in weight-for-age *Z*-score. Secondary outcomes included % of patients on: all oral feeds, feeding-related medications, higher calorie feeds, and feeding-related readmission. Propensity score was used to account for baseline differences. Subgroup analysis was performed in 1- (1V) and 2-ventricle (2V) groups. The cohort included 66 PDA stent (43.9% 1V) and 195 BTS (54.4% 1V) subjects. Prematurity was more common in the PDA stent group (P=0.051). After adjustment, change in weight-for-age *Z*-score did not differ between groups over the entire interstage. However, change in weight-for-age *Z*-score favored PDA stent during the inpatient interstage (P=0.005) and BTS during the outpatient interstage (P=0.032). At initial hospital discharge, PDA stent treatment was associated with all oral feeds (P<0.001) and absence of feeding-related medications (P=0.002). Subgroup analysis revealed that 2V but not 1V patients demonstrated significant increase in weight-for-age *Z*-score. In the 2V cohort, feeding-related readmissions were more common in the BTS group (P=0.008).

***Conclusions*—**In infants with ductal-dependent pulmonary blood flow who underwent palliation with PDA stent or BTS, there was no difference in interstage growth. PDA stent was associated with a simpler feeding regimen and fewer feeding-related readmissions. **(*J Am Heart Assoc*. 2020;9:e013807. DOI: 10.1161/JAHA.119.013807.)**

Key Words: congenital heart disease • outcomes research • surgery

Infants with congenital heart disease (CHD) face challenges to normal somatic growth and development.[1–3] Malnutrition and poor weight gain are often multifactorial in cause.[4–7] Patients with palliated CHD demonstrate substantial variability in growth during the interstage (the time period between initial palliation and definitive repair or subsequent staged palliation). This time period has become a focus of nationwide quality improvement efforts, in part because of a demonstrated capacity to modify growth trajectory with targeted intervention bundles.[8,9] Optimizing early growth is paramount because poor nutritional status may portend worse clinical outcomes, including mortality.[10–15] Furthermore, early

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013807

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Clinical Perspective

What is New?

- In this comparison of infants with ductal-dependent pulmonary blood flow who underwent palliation with patent ductus arteriosus stent or BT shunt, equivalent interstage growth was achieved between groups.
- Patent ductus arteriosus stent patients experienced a simpler feeding regimen and fewer feeding-related hospital readmissions.

What Are the Clinical Implications?

- In infants with ductal-dependent pulmonary blood flow, initial palliation strategy does not impact overall interstage growth, which remains less than adequate across the population.
- Initial palliation with patent ductus arteriosus stent may reduce feeding-related care complexity and costs, primarily through use of a simpler feeding regimen and fewer feeding-related hospital readmissions.

interstage growth trajectory may impact late growth trajectory following further palliation or definitive repair.[16,17]

In the setting of cyanotic CHD and ductal-dependent pulmonary blood flow (PBF), infants require early intervention for survival. Initial palliation may be undertaken with either a modified Blalock-Taussig shunt (BTS) or patent ductus arteriosus (PDA) stent. Recently, it has been demonstrated that initial palliation with PDA stent, compared with BTS, results in comparable-to-superior mortality and perioperative morbidity profiles.[18,19] In patients with cyanotic CHD and ductal-dependent PBF, the impact of palliation strategy on somatic growth has not been evaluated. Therefore, we sought to assess the impact of management strategy on interstage somatic growth, feeding regimen complexity, and feeding-related readmissions in infants with ductal-dependent PBF palliated with either a PDA stent or BTS, adjusted for baseline differences.

Patients and Methods

A retrospective cohort study was performed that included all infants with ductal-dependent PBF and confluent pulmonary arteries palliated at <1 year of age with either a BTS (from January 1, 2012) or PDA stent (from January 1, 2008) through November 1, 2015 at 4 participating centers of the Congenital Catheterization Research Collaborative. The data that support the findings of this study are available from the corresponding author upon reasonable request. Primary results of this study have been published previously.[18] PDA stenting was adopted at each of the centers in the Congenital Catheterization Research Collaborative over different dates. The different ranges of study period for the 2 strategies were chosen to (1) capture all PDA stent subjects at all 4 centers; and (2) generate a contemporaneous cohort of BTS subjects with a goal ratio of ≈2 BTS cases for each PDA stent case. All subjects included in the prior analysis were eligible for inclusion in this study. Subjects without a discrete interstage period, defined as the time interval between initial palliation and stage II palliation or definitive repair, were excluded. Thus, patients with interstage mortality, or without subsequent cardiac surgery (either staged palliation or definitive repair) during the study period, were excluded from the analysis. Follow-up data were collected through December 24, 2015. The Congenital Catheterization Research Collaborative, as previously described, is a multicenter research collaborative comprising investigators (at the time of this study) from the Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Children's Healthcare of Atlanta, and Texas Children's Hospital.[20,21] Data collection was performed by individual centers under the direction of site principal investigators using common data collection tools and definitions. Data were collected, cleaned, and analyzed at 1 center (Children's Healthcare of Atlanta), which serves as the data-coordinating center for the Congenital Catheterization Research Collaborative. This study was approved by the Institutional Review Board at each participating center with a waiver of the need for informed consent.

Subject eligibility was established by direct review of patient charts. In eligible subjects, demographic, clinical, and procedural characteristics were extracted by further chart review as previously described.[18] The primary outcome was the change in weight-for-age *Z*-score (WAZ) across the interstage, which was defined as the time period from initial palliation to admission for stage II palliation or complete repair (entire interstage). Change in WAZ was also assessed across discrete components of the interstage, including the time from initial palliation to initial hospital discharge (inpatient interstage) and from initial hospital discharge to admission for stage II palliation or complete repair (outpatient interstage). Secondary outcomes included change in weight-for-length *Z*-score (WLZ), method of feeding (bolus, continuous, or combination), mode of feeding (oral [PO], nasogastric tube, gastrostomy tube), caloric content of feeds and daily caloric intake, use of feeding-related medications, and the incidence of feeding-related readmission during the interstage period. The analysis was conducted for the entire eligible cohort, and in subgroups stratified by single- (1V or 1.5V) or 2-ventricle (2V) circulation status. WAZ and WLZ were calculated using World Health Organization Child Growth Standards for children between 0 and 2 years of age.[22]

Descriptive statistics are presented as counts and percentages for categorical variables and median (25th–75th percentile) for continuous data. Continuous data were compared between groups with the use of Wilcoxon rank-sum

tests, and comparisons between categorical variables were performed with χ^2 tests or Fisher exact tests, as appropriate.

In order to account for baseline difference between groups, inverse probability of treatment weighting with propensity scores was used to control for potential confounders and baseline differences between groups. A propensity score is mostly intended for observational studies, in which some of the covariates might predict which treatment to receive. Therefore, the propensity score was estimated with a logistic regression model in which treatment assignment (PDA stent versus BTS, with BTS as the reference) was regressed on 5 variables: prematurity, history of necrotizing enterocolitis before initial palliation, genetic syndrome, extracardiac anomalies (including gastrointestinal anomalies), and intrauterine growth restriction. These 5 variables were selected a priori because they might be expected to influence both assignment to treatment strategy and subsequent outcomes. To stabilize the weights, inverted propensity scores were truncated at the first and 99th percentiles and were normalized by dividing each individual propensity score by the mean propensity score of its respective treatment assignment. All adjusted models included the main effect of treatment and were weighted by the inverse probability of treatment weighting to achieve balance between groups.

To compare the effect of treatment on dichotomous outcomes, χ^2 tests, weighted by the propensity score, were used to evaluate differences in outcome between treatment groups. Results are presented as weighted percentages. For continuous outcomes, residual errors were gauged for normality via histograms and quantile-quantile plots. Failing to meet the normality assumption, continuous outcomes were ranked before analysis and modeling was carried out on the rank-transformed data. Unadjusted and adjusted estimates are presented as unweighted and weighted medians (25th–75th percentile) and adjusted *P* values were derived from propensity score weighted 2-sample *t* test on the ranked data.

Because of the extreme imbalance between groups, center was not included in the propensity score. A sensitivity analysis was performed to control for the effect of center in our inverse probability of treatment weighting adjusted analyses. For continuous outcomes, linear regression, including the inverse probability of treatment weighting as a weight, was performed on the ranked data with treatment strategy and center included as a fixed effect. In an additional sensitivity analysis to control for the effect of time between initial palliation and stage II surgery, interstage time (days) was also included as a fixed effect. For binary outcomes, logistic regression was used to obtain the adjusted effect of treatment using a similar model as described above. *P* values from these models are presented for comparative purposes.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), and statistical significance was assessed at the 0.05 level.

Results

Of the 357 patients in the primary study, 261 patients had a defined interstage period and thus met inclusion criteria for this study cohort, including 66 (25%) treated with PDA stent and 195 (75%) treated with BTS. Ninety-six patients in the primary study were excluded from this analysis, including 44 who did not undergo subsequent cardiac surgery (n=21 BTS, n=23 PDA stent) during the study period (but remained alive), 34 who experienced interstage mortality (n=27 BTS, n=7 PDA stent), 15 who did not have somatic growth data available, and 3 who were not discharged during the interstage.

Baseline characteristics are summarized in Table 1. Birth weight and length were not different but prematurity was more common in the PDA stent group. There were some differences in frequency of cardiac anatomic diagnoses between the groups. There were no significant differences in other baseline characteristics between the groups, including the proportion of patients with expected 2V physiology, genetic syndrome, congenital gastrointestinal anomalies, or preoperative gastrointestinal pathology. The WAZ did not differ between groups at birth or at initial intervention. In the subgroup analysis stratified by expected ultimate physiology, WAZ at initial palliation did not differ between groups within the 1V or 2V circulation cohorts.

Initial Hospital Course

Feeding and growth characteristics at the time of hospital discharge, following initial palliation, are presented in Table 2. In the cohort overall, PDA stent patients had a greater WLZ (P=0.036), were more significantly associated with feeding exclusively PO (P<0.001), and were less frequently receiving feeding-related medications (P=0.002), when compared with the BTS group. These differences remained significant following propensity score adjustment. WAZ did not differ by palliation strategy at initial hospital discharge (Figure 1). In the subgroup of patients with 2V circulation, in addition to the differences noted above, the PDA stent group demonstrated a greater WAZ (P=0.014) and lower caloric content of feeds (P=0.031) at hospital discharge. In the subgroup with 1V circulation, no significant differences were found based on palliation strategy.

Hospital Admission for Repair or Stage II Palliation

Data derived from the time of admission for definitive repair or stage II palliation are presented in Table 3. Compared with BTS, PDA stent patients were older at admission (P=0.011), experienced a longer interstage period (P=0.007), and were more likely to feed exclusively PO (P<0.001). Feeding-related medications remained more prevalent in the BTS group

Table 1. Baseline Characteristics

Characteristic	N	PDA Stent (N=66, 25.3%)	BT Shunt (N=195, 74.7%)	*P* Value
Male	261	43 (65.1%)	109 (55.9%)	0.188
Genetic syndrome	261	9 (13.6%)	34 (17.4%)	0.472
Birth weight (kg)	260	2.8 (2.4 to 3.4)	3.0 (2.5 to 3.3)	0.261
WAZ at birth	260	−1.06 (−2.12 to 0.13)	−0.75 (−2.10 to 0.10)	0.381
Birth length (cm)	260	48 (45 to 50)	49 (46 to 50)	0.110
Prematurity (<37 wks)	258	22 (33.9%)	42 (21.8%)	0.051
Gestational age (wks)	256	38 (36 to 39)	38 (37 to 39)	0.221
Other comorbid medical conditions	259	9 (13.9%)	38 (19.6%)	0.299
Anatomic diagnosis				
VSD/PS	261	22 (33.3%)	55 (28.2%)	<0.001
VSD/PA		13 (19.7%)	76 (39.0%)	
TA with PA or PS		5 (7.6%)	33 (16.9%)	
PA/IVS		24 (36.4%)	31 (15.9%)	
Isolated PS		2 (3.0%)	0 (0.0%)	
Expected 2-ventricle physiology	261	37 (56.1%)	89 (45.6%)	0.143
Age at intervention (d)	261	8 (5 to 16)	7 (4 to 19)	0.349
Weight at intervention (kg)	261	3.1 (2.6 to 3.7)	3.1 (2.6 to 3.6)	0.595
WAZ at intervention	261	−1.31 (−2.77 to 0.06)	−0.99 (−2.13 to [−0.04])	0.458
1V circulation	135	−1.44 (−3.05 to 0.06)	−0.77 (−1.77 to [−0.02])	0.104
2V circulation	126	−0.95 (−2.25 to 0.02)	−1.17 (−2.72 to [−0.23])	0.476
WLZ at intervention	211	−0.06 (−1.25 to 1.09)	−0.51 (−1.36 to 0.58)	0.134
NEC before initial palliation	261	2 (3.0%)	3 (1.5%)	0.603
Gastrointestinal anatomic anomalies	20	5 (7.6%)	15 (7.7%)	0.976
TEF		2	0	
Esophageal atresia w/o TEF		0	0	
Duodenal atresia		1	0	
Malrotation		1	12	
Omphalocele		0	1	
Gastroschisis		1	0	
Imperforate anus/anal atresia		1	2	
Other		0	3	

Values reported as N (%) or median (25th–75th percentiles). BT indicates Blalock-Taussig; 1V, single-ventricle; 2V, 2-ventricle; IVS, intact ventricular septum; NEC, necrotizing enterocolitis; PA, pulmonary atresia; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TA, tricuspid atresia; TEF, tracheoesophageal fistula; VSD, ventricular septal defect; WAZ, weight-for-age *Z*-score; WLZ, weight-for-length *Z*-score.

(*P*=0.025). WAZ and WLZ, in the overall cohort as well as in the 1V and 2V subgroups, were not different between palliation groups (Figure 1). In the subgroup with 2V circulation, BTS patients were more likely to encounter feeding-related hospital readmission (*P*=0.008) and receive a higher caloric content of feeds (*P*=0.029). Following propensity score adjustment, use of feeding-related medications remained more common in BTS patients (*P*=0.025); however, after adjusting for center, the result was no longer statistically significant. Feeding-related readmission remained more common in the 2V BTS subgroup after propensity score adjustment (*P*=0.007) and adjustment for center (*P*=0.029).

Unadjusted Comparisons of Interstage Growth

Comparisons of unadjusted (observed) differences in growth outcomes between groups are summarized in Table S1. The primary outcome, change in WAZ, was not significantly different between treatment groups when evaluated across the entire interstage period. Notably, the change in WAZ was

Table 2. Unadjusted Feeding and Growth Characteristics at Hospital Discharge Following Initial Palliation

	Overall (N=261)				Single Ventricle (N=135, 51.7%)				Two Ventricle (N=126, 48.3%)			
	N	PDA Stent (N=66, 25.3%)	BT Shunt (N=195, 74.7%)	*P* Value	N	PDA Stent (N=29, 21.5%)	BT Shunt (N=106, 78.5%)	*P* Value	N	PDA Stent (N=37, 29.4%)	BT Shunt (N=89, 70.6%)	*P* Value
Age at discharge (d)	261	20 (14 to 40)	23 (15 to 43)	0.350	135	24 (16 to 63)	24 (15 to 39)	0.556	126	19 (12 to 29)	22 (15 to 52)	0.079
Weight at discharge (kg)	261	3.3 (3.0 to 4.1)	3.3 (2.9 to 3.7)	0.239	135	3.3 (2.9 to 4.1)	3.3 (3.0 to 3.7)	0.730	126	3.3 (3.1 to 3.9)	3.2 (2.7 to 3.6)	0.127
WAZ	261	−1.51 (−2.67 to (−0.45))	−1.66 (−2.80 to (−0.77))	0.450	135	−1.79 (−3.32 to (−0.88))	−1.37 (−2.40 to (−0.67))	0.170	126	−1.27 (−2.23 to (−0.41))	−2.20 (−2.86 to (−1.16))	0.014
WLZ	250	−0.02 (−1.17 to 0.90)	−0.60 (−1.56 to 0.40)	0.036	132	0.03 (−1.21 to 1.38)	−0.57 (−1.37 to 0.44)	0.188	118	−0.02 (−1.16 to 0.68)	−0.71 (−1.73 to 0.32)	0.104
Method of feeding												
Bolus	261	61 (92.4%)	169 (86.7%)	0.234	135	27 (93.1%)	97 (91.5%)	0.698	126	34 (91.9%)	72 (80.9%)	0.188
Continuous		3 (4.5%)	22 (11.3%)			1 (3.4%)	7 (6.6%)			2 (5.4%)	2 (5.4%)	
Combination of bolus and continuous		2 (3.0%)	4 (2.1%)			1 (3.4%)	2 (1.9%)			1 (2.7%)	2 (5.4%)2 (2.3%)	
Mode of feeding, detailed												
PO	261	45 (68.2%)	87 (44.6%)	0.005	135	17 (58.6%)	58 (54.7%)	0.096	126	28 (75.7%)	29 (32.6%)	<0.001
PO/NGT		12 (18.2%)	53 (27.2%)			7 (24.1%)	29 (27.4%)			5 (13.5%)	24 (27.0%)	
NGT solely		4 (6.1%)	41 (21.0%)			1 (3.4%)	14 (13.2%)			3 (8.1%)	27 (30.3%)	
GT/JT/NJT		5 (7.6%)	14 (7.1%)			4 (13.8%)	5 (4.7%)			1 (2.7%)	9 (10.1%)	
Mode of feeding, collapsed												
PO alone	261	45 (68.2%)	87 (44.6%)	<0.001*	135	17 (58.6%)	58 (54.7%)	0.708		28 (75.7%)	29 (32.6%)	<0.001*
All others		21 (31.8%)	108 (55.4%)			12 (41.4%)	48 (45.3%)		126	9 (24.3%)	60 (67.4%)	
Caloric Content of feeds (kcal/oz)	258	22 (20 to 24)	24 (22 to 24)	0.307	133	24 (22 to 27)	24 (21 to 24)	0.373	125	22 (20 to 24)	24 (22 to 24)	0.031
Feeding-related medications	261	28 (42.4%)	125 (64.1%)	0.002*	135	15 (51.7%)	63 (59.4%)	0.456†	126	13 (35.1%)	62 (69.7%)	<0.001*
Feeding-related medications												
H2RA	153	17	76		78	8	37		75	9	39	
PPI		13	43			8	23			5	20	
Other		0	36			0	22			0	14	

Values reported as N (%) or median (25th–75th percentile). GT indicates gastrostomy tube; H2RA, histamine H2-receptor antagonist; JT, jejunostomy tube; NGT, nasogastric tube; NJT, nasojejunal tube; PDA, patent ductus arteriosus; PO, per os (oral); PPI, proton pump inhibitor; WAZ, weight-for-age *Z*-score; WLZ, weight-for-length *Z*-score.

**P* value remains significant after adjustment using the propensity score.

†Treating center as fixed effect, adjusted *P* value becomes significant ($P<0.05$).

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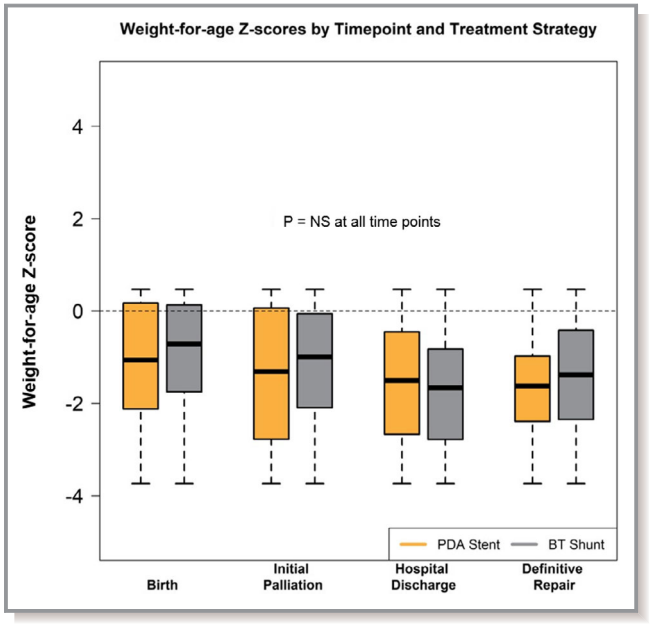

Figure 1. Weight-for-age *Z*-score by timepoint and treatment strategy. Paired box-and-whisker plots presented by timepoint. The median is marked by the horizontal line and the boxes span the interquartile range. Whiskers extend to 1.5 times the interquartile range or the maximum observation, whichever is smaller. There were no differences in the weight-for-age *Z*-score among the palliation strategies. BT indicates Blalock-Taussig; NS, not significant; PDA, patent ductus arteriosus.

negative overall for both groups. Change in WAZ remained nonsignificant in stratified analyses of 1V and 2V circulation subgroups. Change in WLZ was also not different by palliation group. Daily weight gain was not different between palliation groups for the cohort overall, but in patients with 1V circulation, BTS patients demonstrated greater daily weight gain (P=0.043). This analysis was also performed for the discrete inpatient and outpatient components of the interstage period. During the inpatient interstage, PDA stent patients demonstrated a significantly smaller decline in WAZ than the BTS group, both in the overall cohort (P=0.005) and in the subgroup of patients with 2V circulation (P=0.027). Daily weight gain favored the BTS group in 1V subanalysis only (P=0.015). During the outpatient interstage period, there were no differences in change in WAZ or WLZ by treatment group.

Propensity Score Adjusted Comparisons of Interstage Growth

Following propensity score adjustment of growth outcomes (Table 4), there remained no difference in the primary outcome of change in WAZ across the interstage period, for the entire cohort. However, when assessed by interstage component, change in WAZ was less negative in the PDA stent group during the inpatient interstage (−0.33 versus −0.63, P=0.005), whereas change in WAZ was more positive in the BTS group during the outpatient interstage period (0.37 versus −0.14, P=0.032) (Figure 2). These findings appeared to have been driven by significant differences present in the 2V but not the 1V circulation subgroup. After inclusion of center and interstage duration as a fixed effect in the adjusted analysis, change in WAZ significantly favored the PDA stent group during the inpatient interstage period in both the 1V (Figure 3) and 2V (Figure 4) cohorts. Adjusted daily weight gain was greater in the BTS group during the outpatient interstage (P=0.004), but not during the entire interstage (Table S2).

Discussion

In this multicenter report, we present comparisons of growth- and feeding-related outcomes in infants with cyanotic CHD and ductal-dependent PBF who underwent initial palliation with either PDA stent or BTS. After adjustment for baseline factors, no difference in overall interstage somatic growth was evident. However, PDA stent was associated with better early growth during the inpatient interstage, while BTS was associated with superior growth during the outpatient interstage. The achievement of equivalent somatic growth across the interstage relied upon a more complex feeding regimen in the BTS cohort, including greater use of supplemental tube feedings and feeding-related medications. Furthermore, among patients with 2V circulation, BTS palliated patients received higher caloric density feeds and more commonly experienced feeding-related hospital readmission. To our knowledge, this is the first multicenter report to describe interstage growth- and feeding-related outcomes in infants palliated with PDA stent. The overall size of the cohort and variability in practice patterns across participating centers allowed for comparison of the 2 treatment strategies after adjustment with propensity score methods, to mitigate potential bias related to confounding by indication. This balanced approach facilitated an ideal comparison of treatment groups, despite the absence of randomization in treatment assignment.

WAZ was chosen as the primary outcome measure in this study based upon its broad reflection of nutritional status and somatic growth.[23,24] It is generally recognized that the use of WAZ offers the most reliable single metric for analysis and reporting of anthropometric data for both population- and individual-based assessment.[25] In this study, we report the change in WAZ to account for both baseline and interstage duration differences between treatment groups. We found an overall negative trend in change in WAZ across the interstage, regardless of palliation strategy. This finding is consistent with previous reports demonstrating that infants with CHD exhibit

Table 3. Unadjusted Feeding and Growth Characteristics at Admission for Subsequent Staged Palliation or Definitive Repair

	Overall (N=261)				Single Ventricle (N=135, 51.7%)				Two Ventricle (N=126, 48.3%)			
	N	PDA Stent (N=66, 25.3%)	BT Shunt (N=195, 74.7%)	*P* Value	N	PDA Stent (N=29, 21.5%)	BT Shunt (N=106, 78.5%)	*P* Value	N	PDA Stent (N=37, 29.4%)	BT Shunt (N=89, 70.6%)	*P* Value
Age at Admission (d)	261	208 (150 to 294)	167 (132 to 218)	0.011	135	182 (160 to 259)	155 (128 to 196)	0.002	126	210 (143 to 294)	180 (149 to 241)	0.473
Time between initial palliation and definitive repair (d)	261	179 (143 to 276)	150 (117 to 206)	0.007	135	176 (150 to 242)	142 (112 to 182)	<0.001	126	181 (122 to 288)	167 (128 to 227)	0.464
Weight at admission (kg)	261	6.5 (5.9 to 7.8)	6.3 (5.5 to 7.3)	0.191	135	6.3 (5.9 to 7.1)	6.3 (5.5 to 7.0)	0.754	126	6.6 (5.9 to 7.9)	6.2 (5.5 to 7.4)	0.186
WAZ	258	−1.62 (−2.39 to (−0.98))	−1.38 (−2.35 to (−0.42))	0.324	134	−1.65 (−2.35 to (−1.21))	−1.20 (−2.11 to (−0.40))	0.061	124	−1.52 (−2.56 to (−0.72))	−1.69 (−2.57 to (−0.64))	0.674
WLZ	258	−0.84 (−1.95 to 0.17)	−0.80 (−1.87 to 0.17)	0.980	134	−0.80 (−2.07 to 0.51)	−0.77 (−1.48 to 0.12)	0.842	124	−0.95 (−1.82 to 0.10)	−1.01 (−2.38 to 0.20)	0.639
Method of feeding												
Bolus	260	60 (90.9%)	168 (86.6%)	0.586	134	24 (82.8%)	98 (93.3%)	0.073	126	36 (97.3%)	70 (78.7%)	0.029
Continuous		4 (6.1%)4 (6.1%)	20 (10.3%)			3 (10.3%)	6 (5.7%)			1 (2.7%)		
Combination of bolus and continuous		2 (3.0%)	6 (3.1%)			2 (6.9%)	1 (1.0%)			0 (0%)	14 (15.7%)5 (5.62%)	
Mode of feeding, detailed												
PO	260	50 (75.8%)	133 (68.6%)	0.383	134	21 (72.4%)	75 (71.4%)	0.091	126	29 (78.4%)	58 (65.2%)	0.129
PO/NGT		7 (10.6%)	19 (9.8%)			2 (6.9%)	13 (12.54)			5 (13.5%)	6 (6.7%)	
NGT solely		2 (3.0%)	21 (10.8%)			1 (3.4%)	11 (10.5%)			1 (2.7%)	10 (11.2%)	
GT/JT/NJT		7 (10.6%)	21 (10.8%)			5 (17.2%)	6 (5.8%)			2 (5.4%)	15 (16.8%)	
Mode of feeding, collapsed												
PO alone	252	(70.1%)	(44.0%)	<0.001*	133	(61.9%)	(54.9%)	0.501	119	28 (75.7%)	29 (32.6%)	<0.001†
All others		(29.9%)	(56.0%)			(38.1%)	(45.1%)			0 (0.0%)	0 (0.0%)	
Caloric content of feeds (kcal/oz)	239	22(20 to 24)	24(20 to 24)	0.399	122	24(20 to 27)	24(20 to 24)	0.207	117	20(20 to 24)	24(20 to 24)	0.029‡
Feeding-related medications	261	32 (48.5%)	125 (64.1%)	0.025†,‡	135	14 (48.3%)	67 (63.2%)	0.146§	126	18 (48.6%)	58 (65.2%)	0.084
Feeding-related medications												
H2RA	157	16	76		81	8	48		76	8	28	
PPI		17	53			7	23			10	30	
Other		2	21			1	14			1	7	
% of patients with ≥1 feeding-related readmission	261	11 (16.7%)	46 (23.6%)	0.239	135	8 (27.6%)	19 (17.9%)	0.249	126	3 (8.1%)	27 (30.3%)	0.008†

Values reported as N (%) or median (25th–75th percentiles). BT indicates Blalock-Taussig; GT, gastrostomy tube; H2RA, histamine H2-receptor antagonist; JT, jejunostomy tube; NGT, nasogastric tube; NJT, nasojejunal tube; PDA, patent ductus arteriosus; PO, per os (oral); PPI, proton pump inhibitor; WAZ, weight-for-age *Z*-score; WLZ, weight-for-length *Z*-score.

**P* value no longer significant after adjustment using the propensity score.

†*P* value remains significant after adjustment using the propensity score.

‡Treating center as fixed effect, adjusted *P* value no longer significant ($P>0.05$).

§Treating center as fixed effect, adjusted *P* value becomes significant ($P<0.05$).

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Table 4. Adjusted Change in WAZ Based on Treatment Strategy

Time Interval	Overall (N=252)				Single Ventricle (N=133)				Two Ventricle (N=119)			
	N	PDA Stent (N=64, 25.4%)	BT Shunt (N=188, 74.6%)	*P* Value	N	PDA Stent (N=29, 21.5%)	BT Shunt (N=106, 78.5%)	*P* Value	N	PDA Stent (N=35, 29.4%	BT Shunt (N=84, 70.6%)	*P* Value
Entire Interstage	250	−0.44 (−1.23 to 0.41)	−0.31 (−1.10 to 0.69)	0.545	132	−0.26 (−1.39 to 0.39)	−0.36 (−0.97 to 0.38)	0.798	118	−0.60 (−1.15 to 0.48)	−0.17 (−1.26 to 0.98)	0.430
Inpatient Interstage	252	−0.33 (−0.75 to 0.04)	−0.63 (−1.15 to (−0.14))	0.005	133	−0.29 (−0.79 to 0.04)	−0.63 (−1.15 to (−0.19))	0.101*	119	−0.33 (−0.75 to (−0.04))	−0.63 (−1.19 to (−0.08))	0.025
Outpatient Interstage	250	−0.14 (−0.72 to 0.67)	0.37 (−0.41 to 1.14)	0.032	132	−0.02 (−0.66 to 0.68)	0.25 (−0.39 to 1.00)	0.613	118	−0.21 (−0.92 to 0.52)	0.46 (−0.48 to 1.46)	0.012

Values reported as N (%) or median (25th–75th percentiles). Adjusted for prematurity, necrotizing enterocolitis, genetic syndrome, extracardiac anomalies, and intrauterine growth restriction. BT indicates Blalock-Taussig; PDA, patent ductus arteriosus; WAZ, weight-for-age *Z*-score.
*Treating center and interstage duration as fixed effects, adjusted *P* value becomes significant ($P<0.05$).

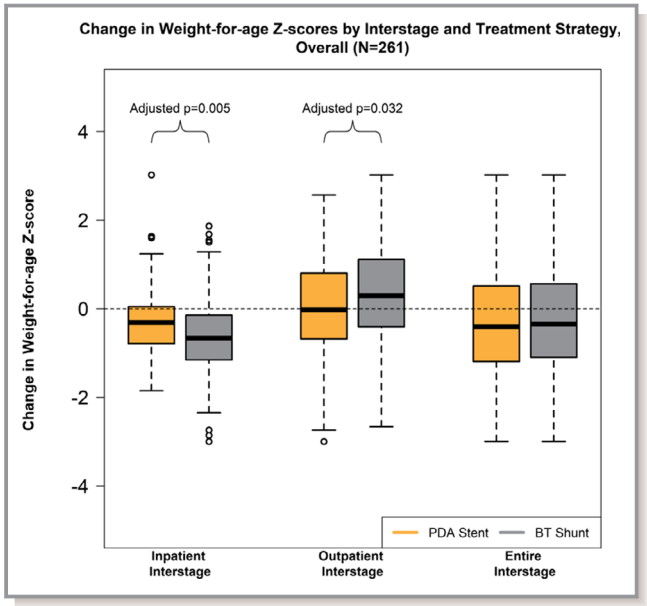

Figure 2. Change in weight-for-age *Z*-score by interstage period for the overall cohort. Comparisons were performed on the adjusted data, while the figure displays the unadjusted data. The PDA stent group exhibited significantly better growth during the inpatient interstage, while the Blalock-Taussig shunt group exhibited superior growth during the outpatient interstage. Across the entire interstage, there was no difference in change in weight-for-age *Z*-score. BT indicates Blalock-Taussig; PDA, patent ductus arteriosus. The circles represent outliers beyond the whiskers.

significant deficits in somatic growth in comparison to healthy controls.[1,23,24,26–28]

Our findings emphasize the need for serial monitoring and targeted nutritional interventions during the interstage period, in light of prior investigations suggesting potential benefit to an interstage monitoring program, particularly in those with 1V circulation.[29,30] Given the increasing national focus on interstage care delivery, including feeding and growth, the data presented herein suggest that 2V patients palliated with PDA stent and BTS may benefit similarly from clinical programs that routinely monitor 1V interstage infants. In this study, we evaluated not just somatic growth, but also the nutritional measures put in place in an effort to achieve ideal growth potential. Although measures of feeding and nutritional complexity favored the PDA stent group, patients in both groups encountered some of these factors during the interstage, and thus faced the added burdens associated with these care requirements. Thus, we hypothesize that participation in a dedicated interstage monitoring program, including rigorous nutrition-focused evaluation, therapy, and supports, could contribute to a positive change in WAZ during this critical time period.

Although BTS and PDA stent palliation both generate a similar circulatory pattern, the 2 strategies may not be physiologically identical. As previously reported, BTS patients were more likely to be discharged from the hospital on

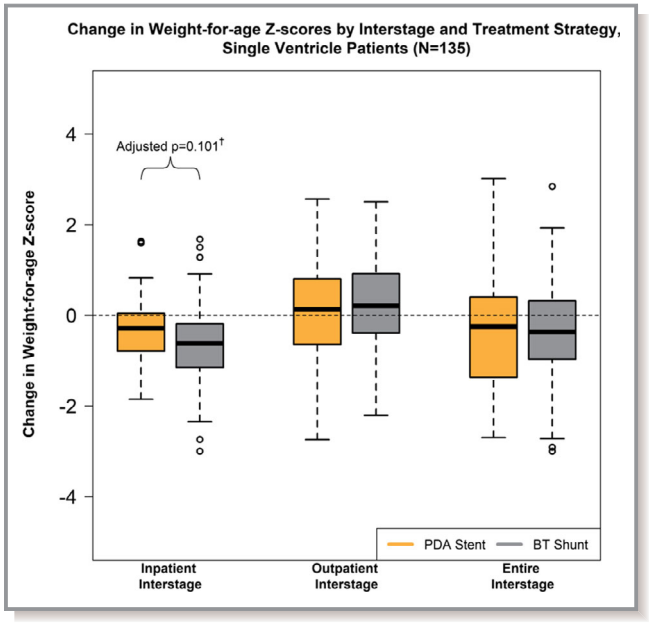

Figure 3. Change in weight-for-age *Z*-score by interstage period for the single ventricle (1V) cohort. In an analysis limited to the 1V cohort, when treating center was included as a fixed effect in the propensity score, the PDA stent group exhibited a superior change in weight-for-age *Z*-score across the inpatient interstage period (†$P<0.05$). BT indicates Blalock-Taussig; PDA, patent ductus arteriosus. The circles represent outliers beyond the whiskers.

diuretic therapy.[18] This difference may suggest that the BTS group was exposed to relatively excessive pulmonary blood flow (a higher ratio of pulmonary-to-systemic blood flow) early in the interstage course. In contrast to the fixed diameter of the BTS, the PDA stent environment is more dynamic, with the onset of in-stent stenosis frequently prompting elective reintervention during the interstage, in the setting of declining saturations. This "acquired stenosis" and other differences between palliation types may account for relatively reduced pulmonary overcirculation in the PDA stent group, thus possibly accounting for reduced burden of diuretic therapy.

There are other important potential contributors to differences in somatic growth between groups, particularly during the inpatient interstage. As previously reported, PDA stent patients encountered a lower risk of procedural complications, shorter intensive care unit length of stay, and a shorter duration of mechanical ventilation and inotrope use.[18] Moreover, periprocedural complications in the BTS cohort tended to be more serious in nature. Taken in combination, these in-hospital morbidities could contribute to delays in initiation of enteral feeding, negatively impact gastrointestinal motility, further increase caloric requirements, and impair the ability to tolerate an adequate feeding volume. Delays in delivering goal nutrition would be expected to result in poor somatic growth.[6] In contrast, the most common complication encountered in the PDA stent group was access-related vascular injury, which would not be anticipated to impact feeding initiation, feeding route, or metabolic demands.

Importantly, following a greater early decrease in WAZ during the inpatient interstage, the BTS group demonstrated a superior change in WAZ during the outpatient interstage period. This may reflect a recovery from the early morbidities detailed above, and resultant "catch up" growth, following physiologic stabilization and mitigation of early health challenges. Additionally, early somatic growth would serve to reduce the pulmonary-to-systemic blood flow ratio of a fixed-diameter shunt, thereby reducing relative pulmonary overcirculation and facilitating improved growth during the outpatient interstage. Notably, though, this improvement in WAZ in the BTS cohort came at the cost of a more complex feeding regimen (especially in the 2V group), which may reflect a more complicated in-hospital course or greater ongoing metabolic demands in the BTS cohort.

When infants are primarily fed by tube supplementation and deprived of PO feedings, they are at risk for developing oral aversion, increasing the likelihood of prolonged reliance on tube supplementation. Nonstandard feeding strategies increase the risk of feeding and respiratory complications. Gastrostomy tube placement improves feeding stability but is an invasive procedure with associated procedural, anesthetic,

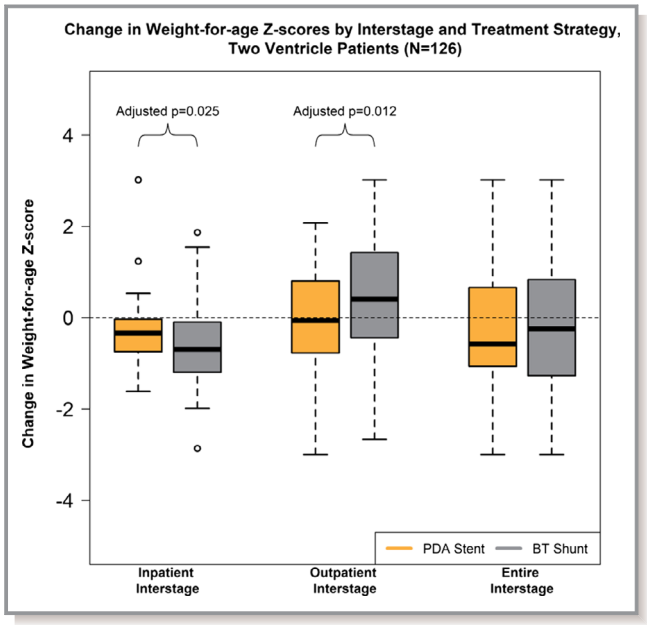

Figure 4. Change in weight-for-age *Z*-score by interstage period for the 2-ventricle (2V) cohort. In an analysis of the 2V cohort, patients who received a PDA stent demonstrated better growth during the inpatient interstage, while those who underwent BT shunt placement exhibited superior growth during the outpatient interstage. Across the entire interstage, there was no difference in change in weight-for-age *Z*-score between groups. BT indicates Blalock-Taussig; PDA, patent ductus arteriosus. The circles represent outliers beyond the whiskers.

and infectious risks.[31] It has been shown that infants discharged with a tube feeding regimen demonstrate an increased incidence of emergency department visits, hospitalizations, and mortality because of tube-related complications.[32] In addition to the increased societal and personal healthcare utilization costs, tube feeding at hospital discharge, regardless of gestational age and clinical risk factors, has been associated with impaired cognitive, motor, and communicative neurodevelopmental outcomes.[33]

There are several limitations to the present study. Although we attempted to adjust for potentially relevant confounding variables, the retrospective nature of this study allows the possibility of unmeasured confounders. Specifically, we were unable to account fully for in- and between-center differences in postpalliation inpatient and outpatient nutritional practices. While most of the outcome measures were readily obtainable from all subjects (eg, weight or length), feeding-related hospital readmissions and emergency department visits might be underrepresented if admissions occurred at a nonstudy center, without associated transfer to a study center. Nevertheless, we have no reason to suspect that this happened with significant frequency, nor that it occurred in a disproportionate fashion between treatment groups. Although exclusive breast milk feeding was rare in this study population, we were unable to precisely determine caloric intake in that cohort, since it was not easily measurable. Data related to postpalliation gastrointestinal complications (including necrotizing enterocolitis), apart from readmissions following initial hospital discharge, were not collected, and thus we are unable to provide insight into these potentially relevant complications. There was a difference in the length of the interstage period between the 2 treatment groups, which could impact the primary outcome, although this variable was included in a sensitivity analysis in an effort to account for this inequality between groups. Exclusion of patients with interstage mortality or without a defined interstage period was necessary for purposes of study design but could have excluded outlier patients, which may have impacted results of the analysis. Finally, in the setting of distinct interstage durations between the 2 groups, and the absence of serial anthropometric measurements obtained at set time intervals across the interstage period, we are unable to describe accurately the trajectory of somatic growth across the outpatient interstage period.

Conclusions

In this comparison of infants with ductal-dependent PBF who underwent initial palliation with either PDA stent or BTS, adjusted for baseline differences, there was no difference in overall interstage somatic growth. Equivalence in somatic growth between the groups was achieved with a simpler feeding regimen and lower incidence of feeding-related medications in the PDA stent patients. Among patients with 2V circulation, BTS palliation was associated with a higher incidence of feeding-related hospital readmission during the interstage.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Unadjusted Growth Outcomes Based on Treatment Strategy.

		Overall (N=261)				Single Ventricle (N=135)				Two Ventricle (N=126)			
Time Interval	**Variable**	**N**	**PDA Stent N=66 25.3%**	**BT Shunt N=195 74.7%**	**P**	**N**	**PDA Stent N=29 21.5%**	**BT Shunt N=106 78.5%**	**P**	**N**	**PDA Stent N=37 29.4%**	**BT Shunt N=89 70.6%**	**P**
Entire Interstage	Daily weight gain (grams/d)	261	18.7 (14.4 – 23.5)	19.5 (15.3 – 24.2)	0.287	135	17.7 (14.4 – 20.9)	20.9 (15.3 – 25.7)	0.043	126	19.8 (15.5 – 24.7)	18.7 (15.7 – 21.9)	0.491
	Change in WAZ	258	-0.40 (-1.19 – 0.51)	-0.35 (-1.1 – 0.56)	0.978	134	-0.25 (-1.37 – 0.40)	-0.37 (-0.97 – 0.32)	0.704	124	-0.58 (-1.07 – 0.66)	-0.25 (-1.27 – 0.83)	0.915
	Change in WLZ	208	-0.73 (-2.07 – 0.42)	-0.46 (-1.75 – 0.85)	0.389	108	-0.54 (-1.68 – 0.76)	-0.33 (-1.70 – 0.72)	0.972	100	-1.30 (-2.30 – 0.40)	-0.48 (-2.06 – 0.89)	0.420
Inpatient Interstage	Daily weight gain (grams/d)	258	12.2 (0.0 – 28.5)	9.3 (-6.5 – 20.0)	0.124	134	18.1 (15.9 – 22.2)	22.7 (17.5 – 28.1)	0.015	124	7.4 (0.0 – 26.1)	10.1 (-11.0 – 22.5)	0.508
	Change in WAZ	261	-0.31 (-0.79 – 0.04)	-0.66 (-1.16 – (-0.15))	0.005	135	-0.29 (-0.79 – 0.04)	-0.62 (-1.15 – (-0.19))	0.096	126	-0.34 (-0.75 – (-0.04))	-0.70 (-1.19 – (-0.10))	0.027
	Change in WLZ	209	-0.17 (-0.79 – 0.58)	-0.08 (-1.26 – 0.69)	0.679	109	-0.47 (-0.92 – 0.64)	-0.09 (-1.22 – 0.48)	0.762	100	-0.13 (-0.73 – 0.46)	-0.07 (-1.28 – 0.75)	0.828
Outpatient Interstage	Daily weight gain (grams/d)	258	18.6 (14.8 – 23.7)	21.0 (16.7 – 27.2)	0.027	134	18.1 (15.9 – 22.2)	22.7 (17.5 – 28.1)	0.015	124	18.8 (13.9 – 25.0)	20.4 (15.4 – 24.4)	0.510
	Change in WAZ	258	-0.03 (-0.68 – 0.80)	0.30 (-0.41 – 1.11)	0.146	134	0.13 (-0.64 – 0.80)	0.21 (-0.39 – 0.92)	0.816	124	-0.06 (-0.77 – 0.80)	0.41 (-0.44 – 1.42)	0.068
	Change in WLZ	247	-0.66 (-2.13 – (-0.45))	-0.24 (-1.59 – 0.87)	0.118	131	-0.20 (-2.25 – 0.45)	-0.15 (-1.37 – 0.85)	0.283	116	-1.13 (-2.12 – 0.43)	-0.35 (-2.11 – 1.11)	0.361

Values are reported as N (%) or median (25^{th} – 75^{th} percentiles)
WAZ = Weight-for-Age Z-score; WLZ = Weight-for-Length Z-Score

Table S2. Adjusted Growth Outcomes Based on Treatment Strategy.

		Overall (N=252)					Single Ventricle (N=133)					Two Ventricle (N=119)			
Time Interval	**Variable**	**N**	**PDA Stent N=64 25.4%**	**BT Shunt N=188 74.6%**	**P**		**N**	**PDA Stent N=29 21.5%**	**BT Shunt N=106 78.5%**	**P**		**N**	**PDA Stent N=35 29.4%**	**BT Shunt N=84 70.6%**	**P**
Entire Interstage	Daily weight gain (grams/d)	252	18.4 (14.3 – 21.5)	19.5 (15.6 – 24.2)	0.071		133	17.7 (14.4 – 20.9)	21.1 (15.1 – 25.7)	0.036†		119	18.9 (13.7 – 22.1)	18.9 (15.8 – 22.0)	0.760
	Change in WLZ	200	-0.90 (-2.31 – 0.50)	-0.45 (-1.74 – 0.89)	0.267		106	-0.43 (-1.41 – 1.04)	-0.36 (-1.67 – 0.80)	0.919		94	-1.48 (-2.68 – 0.41)	-0.47 (-2.03 – 1.02)	0.212
Inpatient Interstage	Daily weight gain (grams/d)	249	12.2 (0.0 – 26.1)	8.9 (-4.0 – 20.0)	0.145		132	13.6 (0.0 – 37.0)	8.7 (-4.0 – 18.8)	0.124‡		117	7.9 (0.0 – 26.1)	10.9 (-4.3 – 23.0)	0.577
	Change in WLZ	200	-0.19 (-0.80 – 0.58)	-0.10 (-1.23 – 0.70)	0.899		107	-0.47 (-0.92 – 0.64)	-0.11 (-1.21 – 0.47)	0.850		93	-0.17 (-0.75 – 0.43)	-0.04 (-1.28 – 0.78)	0.936
Outpatient Interstage	Daily weight gain (grams/d)	249	18.5 (14.8 – 23.0)	21.2 (17.0 – 27.2)	0.004		132	18.5 (16.2 – 22.4)	22.9 (17.5 – 28.1)	0.013†		117	17.3 (13.8 – 24.0)	20.7 (16.7 – 24.5)	0.103
	Change in WLZ	239	-0.76 (-2.13 – 0.45)	-0.23 (-1.59 – 1.06)	0.097		129	-0.18 (-1.43 – 0.45)	-0.09 (-1.37 – 1.01)	0.335		110	-1.21 (-2.13 – 0.43)	-0.34 (-2.11 – 1.35)	0.245

Values reported as N (%) or median (25^{th} – 75^{th} percentiles). WLZ = Weight-for-Length Z-Score. Adjusted for prematurity, NEC, genetic syndrome, extracardiac anomalies and intrauterine growth restriction.

* P-valve remains significant after adjustment using the propensity score
¢ P-value no longer significant after adjustment using the propensity score
† Treating center as fixed effect, adjusted p-value no longer significant ($p>0.05$)
‡ Treating center as fixed effect, adjusted p-value becomes significant ($p<0.05$)