Poor Weight Recovery Between Stage 1 Palliation and Hospital Discharge for Infants with Single Ventricle Physiology: An Analysis of the National Pediatric Cardiology Quality Improvement Collaborative Phase II Dataset

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Objective To investigate change in weight-for-age z-scores (WAZ) and risk factors for impaired weight gain between stage 1 palliation (S1P) for single ventricle physiology and discharge.

Study design This was a secondary analysis of the National Pediatric Cardiology Quality Improvement Collaborative Phase II database. The primary outcome was change in WAZ between S1P and discharge. Risk factors were selected using multivariable mixed effects regression constructed by step-wise model selection, with adjustment for WAZ at S1P and a random effect for center.

Results Of 730 infants who were discharged after S1P, WAZ decreased in 98.6% (-1.5 ± 0.7). WAZ at discharge was <-1 but >-2 (at risk) in 40% and <-2 (failure to thrive) in 35% of participants. Males, higher WAZ at S1P, non-S1P procedures (mostly noncardiac), increased length of stay, necrotizing enterocolitis, and angiotensin-converting enzyme inhibitor use at discharge were associated with a greater decrease in WAZ. Preoperative enteral feeding and respiratory medications were associated with a lesser decrease in the WAZ.

Conclusions Nearly all infants lose weight after S1P with little recovery by hospital discharge. At discharge, three-quarters of the infants in the cohort were at risk for impaired weight gain or had failure to thrive. Most risk factors associated with change in WAZ were unmodifiable or surrogates of disease severity. Novel interventions are needed to minimize the early catabolic effects and promote anabolic recovery after S1P. *(J Pediatr 2021;234:20-6)*.

Failure to gain adequate weight after cardiac surgery is associated with an increased risk of postoperative morbidity and predicts need for transplant or death for infants with single ventricle physiology during the interstage period (discharge from stage 1 palliation [S1P] to stage 2 procedure).[1] Recent efforts focused on weight gain during the interstage have proven successful, but the interstage may not be the most vulnerable period.[2-4] These infants are at high risk for weight loss in the immediate postoperative period for several reasons, including the catabolic effects of major surgery, increase in energy expenditure, insufficient caloric intake, alterations in serum growth hormone, genetic influences, chronic cyanosis, and unfavorable hemodynamics associated with atrioventricular valve regurgitation and abnormal ventricular function.[5-11] We sought to evaluate change in weight-for-age z-score (WAZ) during the early postoperative period after S1P and to identify factors associated with change in weight and weight recovery.

Methods

We performed a secondary analysis of the data collected for infants enrolled in the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC), a voluntary registry that receives data from >60 pediatric cardiac programs. There is a standard dataset 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. We analyzed data across 57 centers on infants or fetuses presenting at the individual sites with a clinical diagnosis of hypoplastic left heart syndrome and other univentricular variants who underwent S1P, including the Norwood procedure with a Blalock Taussig shunt or right ventricle to pulmonary artery conduit and a hybrid procedure with ductal stent

S1P	Stage 1 palliation
NEC	Necrotizing enterocolitis
NPC-QIC	National Pediatric Cardiology Quality Improvement Collaborative
WAZ	Weight-for-age z-score

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and pulmonary artery banding. The registry began enrollment in June 2016 and continues to enroll all eligible infants at participating centers. All participants who survived to hospital discharge after S1P were identified. We excluded participants for prematurity (<37 weeks of gestation), associated major noncardiac congenital anomalies or syndromes, undergoing the S1P at >21 days of age, remaining hospitalized between the S1P and stage 2 procedure, and having no discharge weight recorded. The NPC-QIC registry was approved by the institutional review board at each participating center, and written informed consent was obtained from a parent or guardian before enrollment. The University of Utah Institutional Review Board approved this secondary analysis under an exemption.

Z-scores were obtained from age-adjusted weights using a SAS macro from the World Health Organization. To allow comparison with previous investigators' assessment of the severity of impaired weight gain, we used WAZ of <−1 but >−2 to identify a potentially at-risk population and WAZ of <−2 for those with failure to thrive.[11]

The **Appendix** (available at www.jpeds.com) summarizes the data extraction elements used for this analysis. Briefly, we collected fetal diagnosis and intervention, postnatal diagnosis, and birth demographics, as well as preoperative catheterization, echocardiographic data, nutrition, and discharge data. Surgical data included type of surgical palliation, cardiopulmonary bypass times, postoperative complications (including extracorporeal membrane oxygenation, catheterization or reintervention, duration of vasoactive medication use, and duration of intubation). Echocardiographic data were collected preoperatively and at discharge, including systemic atrioventricular valve regurgitation and ventricular function. Discharge data included medications as well as feeding regimen, mode of feeding, and target daily caloric intake. Variables were analyzed across 3 phases—preoperative, intraoperative, and postoperative—where appropriate.

Continuous variables were summarized using range, mean and SD, or median and IQR, depending on distribution skew. Categorical variables were summarized using count and percentage. Descriptive plots (boxplots, scatter plots) were used to assess pair-wise relationships among all on-study variables and to examine distributions for outliers. The primary outcome was the absolute difference between discharge WAZ and S1P WAZ.

The magnitude of the change in WAZ as related to each variable during the 3 phases (**Appendix**) was considered using both univariable and multivariable linear mixed effects modeling. A random effect for center was included in all models to account for center variability. S1P WAZ was also included in all models because a patient's starting weight has a direct influence on change in WAZ. Forward and backward step-wise model selection by Akaike information criterion was implemented to construct multivariable models for each set of predictors (preoperative, intraoperative, and postoperative). We constructed a combined model with the variables selected from each of the separate set of predictors, and again implemented step-wise model selection to create a parsimonious model. In each model we checked for multicollinearity among the potential predictors using the generalized variance inflation factor, adjusted for degrees of freedom. Variables with an adjusted generalized variance inflation factor of >2.24 or equivalently variance inflation factor of >5 were dropped from the multivariable model. We reported regression coefficients, their 95% CIs, and P values. Owing to the notable number of variables available for our analysis, we excluded those that were not associated with the outcome ($P > .1$) and also had >20% missingness from multivariable analysis. Regression coefficients were interpreted as the mean change in WAZ (discharge WAZ–S1P WAZ) expected for a 1-unit increase in a continuous predictor, or for a given level of a categorical predictor relative to the reference level for that predictor. Statistical significance was assessed at the .05 level using 2-tailed tests. The statistical analyses were implemented in R v. 3.6.0.[12]

Results

Of the 1235 participants enrolled in the NPC-QIC Phase II between June 2016 and August 2019, 733 infants from 51 centers met our study criteria. Extensive data filtering was performed to determine outliers. In addition, the NPC-QIC did begin a formal data audit process in January 2020. We excluded 3 outliers with increases in weight from birth to surgical intervention that were nonphysiologic and likely from erroneous data entry of weight in pounds rather than kilograms, leaving 730 infants in the cohort (**Figure 1**; available at www.jpeds.com). Participants were 64% male, 85% had single right ventricle morphology, and 94% had S1P consisting of a Norwood procedure (right ventricle to pulmonary artery conduit 66%, Blalock Taussig shunt 28%) with the remaining having a hybrid procedure (**Table I**).

At birth, the majority of infants (83%) had weight appropriate for gestational age with only 5% large (>90th percentile) and 12% small (<10th percentile) for gestational age. S1P was performed at a median age of 5 days (IQR, 4-7 days; range, 0-21 days). At the time of surgery, the median WAZ was −0.2 (IQR, −0.8 to 0.4; range, −5.0 to 2.3). The median hospital length of stay (**Figure 2**; available at www.jpeds.com) was 29 days (IQR, 20-42 days; range, 8-210 days). Between S1P and hospital discharge, 98.6% infants had a decrease in WAZ with a mean group decrease of -1.5 ± 0.7 (**Figure 3**) with 40% (n = 293) being at risk and 35% (n = 256) having failure to thrive at discharge.

Factors in the final combined multivariable mixed regression model obtained from step-wise selection are listed in **Table II**. The majority of participants (98.6%) had a decrease in the WAZ between S1P and discharge. A negative coefficient indicated a more negative change in WAZ, and although a positive coefficient indicated a more positive change in WAZ, overall patients generally still

Table I. Cohort characteristics (n = 730)

Demographics	
Male	
Female	464 (64)
Small for gestational age	266 (36)
Appropriate for gestational age	90 (12)
Large for gestational age	602 (83)
Birth weight (kg)	38 (5)
Gestational age at birth (weeks)	3.2 (3.0-3.5)
Age at S1P (days)	39 (38-39)
Single ventricle morphology and type of palliation	5 (4-7)
Single left ventricle	
Single right ventricle	59 (8)
Mixed morphology	622 (85)
Norwood with Blalock Taussig shunt	49 (7)
Norwood with RVPA conduit	203 (28)
Hybrid procedure	485 (66)
Feeding	42 (6)
Target nutrition recommended at discharge (kcal/kg/d)	120 (112-126)
Time from surgery to starting enteral feeds, including trophic feeds (days)	4 (3-6)
Echocardiography data	
Ventricular function at discharge	
Normal/low normal	655 (90)
Mild dysfunction	42 (6)
Moderate dysfunction	18 (2)
Severe dysfunction	3 (<1)
Unspecified	11 (1)
Atrioventricular valve regurgitation at discharge	
None/trivial	334 (46)
Mild	259 (36)
Moderate	119 (16)
Severe	6 (1)
Unspecified	9 (1)

RVPA, right ventricle to pulmonary artery.
Values are number (%) or median (IQR).

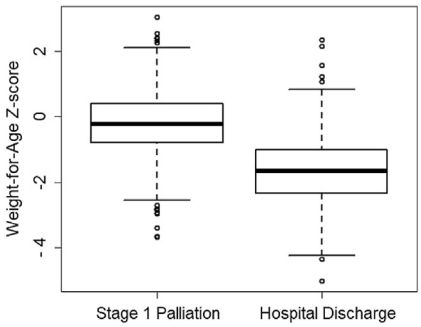

Figure 3. WAZ at surgery and discharge. WAZ decreased in 98.6% (−1.5 ± 0.7) of participants from S1P to discharge.

experienced a decrease between S1P and discharge. The absolute birth and surgical weights were strongly collinear with surgical WAZ, so they were removed as candidate factors in the combined multivariable model. The last weight before discharge was similarly excluded owing to a strong collinearity with length of stay.

The number of postoperative complications and medications were significant in the univariable analyses and individual complications and medications were part of the final multivariable model. Each additional postoperative complication (≤3) was associated with a negative change in WAZ in univariable analysis. Compared with participants who had fewer complications, those who had ≥3 complications had a 0.31 more negative change in WAZ (95% CI, −0.46 to −0.17; multiple comparison adjusted $P < .001$). There was no added impact with ≥4 complications. Arrhythmia, respiratory complications, and vocal cord dysfunction were the most frequent postoperative complications, but had no individual association with change in WAZ. Necrotizing enterocolitis (NEC) occurred in 11.2% of participants (n = 82) and remained in the multivariable model with an associated 0.30 more negative change in WAZ (95% CI, −0.45 to −0.14; $P < .001$) compared with those without this complication. The NPC-QIC did not have a specific definition for NEC, but it was coded based on clinical presentation and definitions at participating sites, including nil per os status, antibiotic use, and radiographic evidence. Medical and surgical NEC were clearly delineated as categories in the database, with only 2 cases of surgical NEC. Additional procedures in the postoperative period (mostly noncardiac) were also in the multivariable model and associated with a 0.23 more negative change in WAZ (95% CI, −0.34 to −0.12; $P < .001$). The most common procedures (**Table III**; available at www.jpeds.com) included bedside laryngoscopy to assess vocal cords (n = 211 [28.9%]) and gastrostomy tube placement (n = 138 [18.9%]).

A univariable analysis did not show a significant impact on WAZ for patients who were on ≤2 or fewer medications, but each additional medication prescribed, ≤5, was associated with a stepwise decrease in the WAZ. The most frequently prescribed medications at discharge were antiplatelet drugs, diuretics, digoxin, and gastrointestinal medications. Compared with participants who were prescribed fewer medications at discharge, those prescribed ≥3 medications had a 0.30 more negative change in WAZ (95% CI, −0.48 to −0.12; multiple comparison adjusted $P = .001$) (**Figure 4**). On multivariable analysis angiotensin-converting enzyme inhibitors were associated with a 0.11 more negative change in WAZ (95% CI, −0.21 to 0; $P = .044$) and respiratory medications were associated with a 0.53 more positive change in WAZ (95% CI, 0.14 to 0.93; $P = .008$, **Table II**). The 11 infants on respiratory medications had a mean change in WAZ of −1.3 ± 1.0 and about twice the duration of mechanical ventilation; 8 of the 11 were treated with inhaled steroids and 5 failed extubation and required postoperative extracorporeal membrane oxygenation.

Overall, while controlling for other variables in the multivariable model, participants had a 0.26 more negative change in WAZ at discharge for each unit increase in WAZ at S1P (95% CI, −0.31 to −0.21; $P < .001$). The change in WAZ for participants receiving any enteral feedings preoperatively was 0.11 more positive compared with those with no preoperative enteral feeding (95% CI, 0.01 to 0.22; $P = .039$). The change in WAZ was 0.19 more negative in males (95% CI, −0.29 to −0.09; $P < .001$) and 0.09 more negative for each

Table II. Continuous and categorical variables in the final model: Associations with change in WAZ using stepwise multivariable analysis

Variables	Coefficient (95% CI)	*P* value
NEC	−0.30 (−0.45 to −0.14)	<.001
Higher WAZ at S1P	−0.26 (−0.31 to −0.21)	<.001
Postoperative procedures (yes)	−0.23 (−0.34 to −0.12)	<.001
Male vs female	−0.19 (−0.29 to −0.09)	<.001
Angiotensin-converting enzyme inhibitor at discharge (yes)	−0.11 (−0.21 to 0)	.044
Increased length of stay (months)	−0.09 (−0.16 to −0.01)	.024
Enteral feedings before S1P (yes)	0.11 (0.01 to 0.22)	.039
Respiratory medications at discharge (yes)	0.53 (0.14 to 0.93)	.008
Gastrointestinal medications at discharge (yes)	−0.1 (−0.21 to 0.01)	.08
Echocardiogram performed within 72 hours of S1P (yes)	−0.06 (−0.16 to 0.04)	.27
Longer cardiopulmonary bypass time	−0.02 (−0.07 to 0.04)	.59
Older age at S1P (days)	0 (−0.02 to 0.01)	.70
Postoperative arrhythmia on medication	−0.01 (−0.12 to 0.09)	.81

The model R^2 is 0.32 with a coefficient and 95% CI of the model intercept of −0.99 (−1.14 to −0.85). After mean-centering the model, the intercept is defined as the average change in WAZ when all risk factors equal the null value (mean or reference level).

additional month of length of stay (95% CI, −0.16 to −0.01; $P = .024$).

Of note, the type of surgical palliation, postoperative days of intubation, weaning of vasoactive medications within 5 days of S1P, delayed sternal closure, diaphragm paralysis, ventricular function, atrioventricular valve regurgitation, oxygen saturation at discharge, postoperative day that feeds were initiated, tube feeding, use of breastmilk vs formula, or caloric density of feeds were not associated with change in WAZ between S1P and hospital discharge.

Discussion

Our findings support prior reports that the highest risk for precipitous weight loss remains the immediate postoperative period after S1P.[8,9,11] The implementation of preoperative enteral feeding and prevention of NEC were protective and associated with a more positive change in WAZ. Infants who did not undergo major noncardiac procedures also had a more positive change in WAZ. However, many risk factors were unmodifiable or seemed to be surrogates of disease severity.

We found that weight recovery is worse in male infants, which is consistent with prior reports.[11] The NPC-QIC database did not allow us to investigate the potential reasons for poor weight gain among males with single ventricles. Other investigators also found that males were more vulnerable in other areas as well. For example, males who had a Fontan palliation had more cardiac and hemorrhagic complications and higher mortality.[13-15]

Age at S1P was part of the final model, but was not associated significantly with weight recovery in our study. Prior reports suggest a prolonged period of ductal-dependent physiology or preoperative factors that delay surgery, such as postnatal or delayed diagnosis, hemodynamic instability, or infection, may impair somatic growth.[16,17] Our finding that a higher WAZ at S1P was associated with a more negative change in WAZ is similar to other reports of higher absolute birth weight independently associated with a more negative change in WAZ.[11] Because change in WAZ is an absolute measurement, it may simply be those who start higher have more to lose.

An increased length of stay is negatively associated with weight recovery, and we confirmed that relationship.[10] Infants who struggle with weight gain and require exclusive tube feeding have prolonged hospitalizations with more morbidities and medications.[18]

More postoperative procedures, such as laryngoscopy to assess vocal cords and gastrostomy tube placement, were associated with a more negative change in WAZ. These procedures likely represent surrogates for difficulties with oral feeding.[19,20] Gastrostomy tubes have been associated with prolonged lengths of stay and complications without an increased in-hospital mortality risk.[21] However, avoiding these procedures may not be possible, because the need for them likely reflects disease severity.

Poor ventricular function and higher oxygen saturations were associated with poor growth in the early postoperative period in other studies, but this finding was not demonstrated in our cohort.[4,22] This difference may partially be explained by the small number of infants with moderate or severe ventricular dysfunction (n = 21) in the NPC-QIC database. Angiotensin-converting enzyme inhibitors did not improve interstage weight gain in prior studies, including a randomized clinical trial.[23,24] We found that angiotensin-converting enzyme inhibitors had a negative association with weight recovery in the immediate postoperative period, but indications for this therapy were not recorded in the database and their use may reflect hemodynamic instability. We also found that a small proportion of infants (1.5%) who were prescribed respiratory medications at discharge, largely inhaled corticosteroids, had a positive association with weight recovery. This small subgroup was not representative of the cohort owing to the disproportionate use of extracorporeal membrane oxygenation, failed extubation, and prolonged mechanical ventilation. This subgroup may have received systemic steroids during their hospitalization, but the use of these medications were not collected.

Any preoperative enteral feeding, regardless of volume, had a favorable effect on change in WAZ, and was the only potentially modifiable factor identified in our study. Because preoperative enteral feeding is not standardized and there are no established guidelines for enteral feeds, practice varies widely among centers.[25] However, preoperative enteral feeding can be done safely in ductal-dependent cardiac lesions, and withholding preoperative enteral feeds often has a negative effect.[26,27] Preoperative feeding volumes of <100 mL/kg/day and the use of unfortified human milk are associated with a lower risk of preoperative NEC, and delayed enteral feeds are associated with enteric cell atrophy, abnormal increases in gut permeability, and delayed intestinal maturation and dysmotility.[28-30] Thus, our finding that

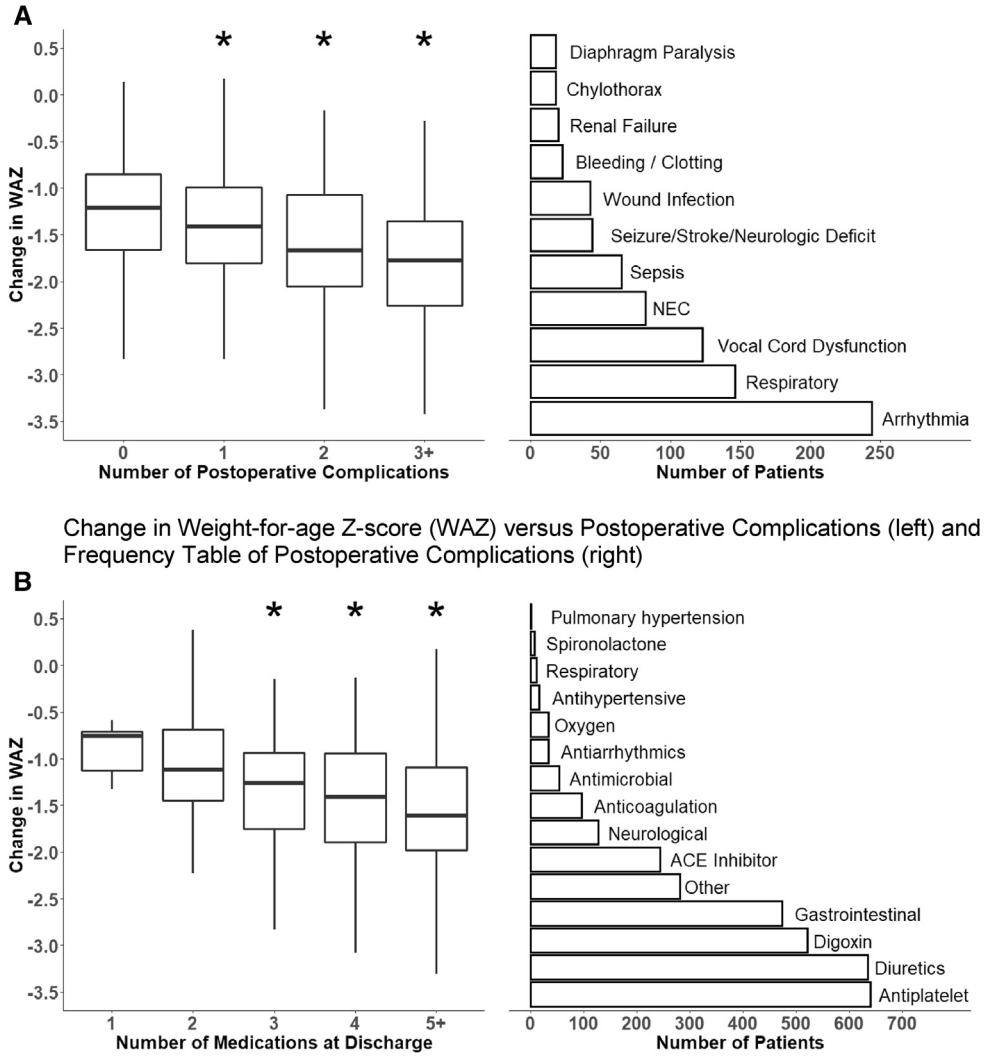

Figure 4. Univariable analysis of change in WAZ vs **A,** Complications and **B,** Medications. Asterisks indicates a significant difference between groups split by a given number of complications or medications. More complications and medications negatively impact WAZ.

NEC was associated with poor weight recovery is not surprising; these infants are less likely to feed orally and often have inadequate caloric intake.[31] Although there may be hemodynamic factors that delay preoperative feeding, the routine avoidance of enteral nutrition in the preoperative period may be unwarranted.

In contrast with the preoperative period, early resumption of postoperative enteral feeds and increased caloric intake were not associated with change in WAZ postoperatively in the NPC-QIC cohort. This finding suggests that the postoperative optimization of enteral nutrition is insufficient to promote early postoperative weight gain.[32] Medications that promote anabolism may have a role in promoting weight recovery in this population. A small, open-label trial of oxandrolone in medium chain triglyceride oil has shown potential for growth benefit and reversal of the postoperative catabolic state in patients after a Norwood procedure.[33]

Although infants who were discharged after S1P with oral feeding have better average daily weight gain than infants with tube-assisted enteral feeding, nutrition protocols in the interstage often use enteral tube feeding to promote weight gain.[2,11,18,34-36] There was no association between enteral tube feeding and change in WAZ in the early postoperative period in our cohort. Previous studies have shown that proton pump inhibitors had no benefit on interstage weight gain.[23,37] Similarly, our model included gastrointestinal medications (largely antireflux) and showed no association between their use and weight recovery after S1P. It is unclear if symptoms attributed to reflux have a gastrointestinal etiology or if they are indicative of more severe cardiac disease and impaired gut perfusion.

There were limitations to our analysis. The NPC-QIC dataset contains retrospective, observational data that are submitted voluntarily from programs participating in the improvement collaborative. Therefore, limitations in the data may relate to patient selection bias, partial datasets for some patients, inaccurate data entry, and/or the heterogeneous composition of participating programs of different sizes and geographic locations. We acknowledge that hemodynamic factors have reported associations with poor outcomes, and we were surprised that the analysis did not support this finding. We recognize that there are limitations of having 2 data points at surgery and discharge for weight in terms of mapping a specific trajectory. However, it is likely that centers would be discharging patients when they are euvolemic without any respiratory distress. If that is in fact the case, the change in weight from surgery to discharge should be reflective of nutritive changes in weight. Operative and postoperative variables were intermediate on the causal pathway between preoperative variables and the primary change in WAZ outcome, which can result in overadjustment bias.[38]

Infants undergoing S1P are at high risk for weight loss and impaired weight recovery in the immediate postoperative period before discharge. Increased caloric intake and enteral tube feeding were not associated with postoperative weight recovery. Incorporating preoperative feeding may mitigate this decrease. More studies are needed to evaluate novel interventions to improve nutrition and decrease postoperative complications as well as minimize the early catabolic effects of S1P and promote recovery of an anabolic state and weight gain in this vulnerable population. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Curious Cases of Cutaneous Fistulas from Mucosal Sites of Trauma and Infection

Christen AG. Persistent cutaneous fistulas of dental origin in children: report of two cases. J Pediatr 1971;79:51-4.

Arden G. Christen, DDS, MSD, the Base Dental Surgeon at Zaragoza Air Base in Spain, reported 2 cases of cutaneous fistulas (one to the face and the other to the neck) from dental origins to alert pediatricians to these frequently misdiagnosed infections. When purulent drainage is seen near a gumline or the patient has a toothache, consideration of a dental source of infection is obvious. Tooth or gum trauma, dental caries, periapical abscess, or rarely maxillary or mandibular osteomyelitis are the initiating events. When oral commensal microbial flora, especially anaerobic bacteria, and especially *Actinomyces* species, get stuck in a wrong place infection ensues, becomes purulent, and expands along fascial plains in search of egress, creating a fistulous tract that can end mucosally, cutaneously, or sometimes intracranially. This usually occurs without rubor, dolor, or tumor at the dental site. *Actinomyces*, abetted by its microaerophilic colleague *Aggregatibacter actinomycetemcomitans*, can take on the pathologic personality of traveling from the primary sites of infection in the mouth, lung, or gastrointestinal tract (where they are contiguous commensals) along fascial plains or burrowing through bones in a bizarre odyssey to make their appearance distantly as a purplish dermal nodule (eg, from a primary focus in the lung to the thigh, from a maxillary tooth to the face infraorbitally [as in one of Christen's cases], or from the gastrointestinal tract through the diaphragm and lung to the lower back). We infectious diseases subspecialists all have our own remarkable cases. During this writer's fellowship, Dr Bennett Lorber from Temple Hospital presented his memorable case of a seamstress who habitually held pins in her mouth while travelling on Philadelphia streetcars. Unbeknownst to her a lurch must have led to her swallowing a pin that ended up in her appendix—the story unravelling only after development of a cutaneous fistula tracking back to the pin. Usually, intervention at the source site cures the problem. Absent a source, a long course (eg, 1 year) of penicillin orally usually is curative. Surgical removal of the fistulous tract is not necessary. In the rare case of chronic osteomyelitis of the maxilla or mandible, aggressive surgical debridement can be necessary to prevent relapses.

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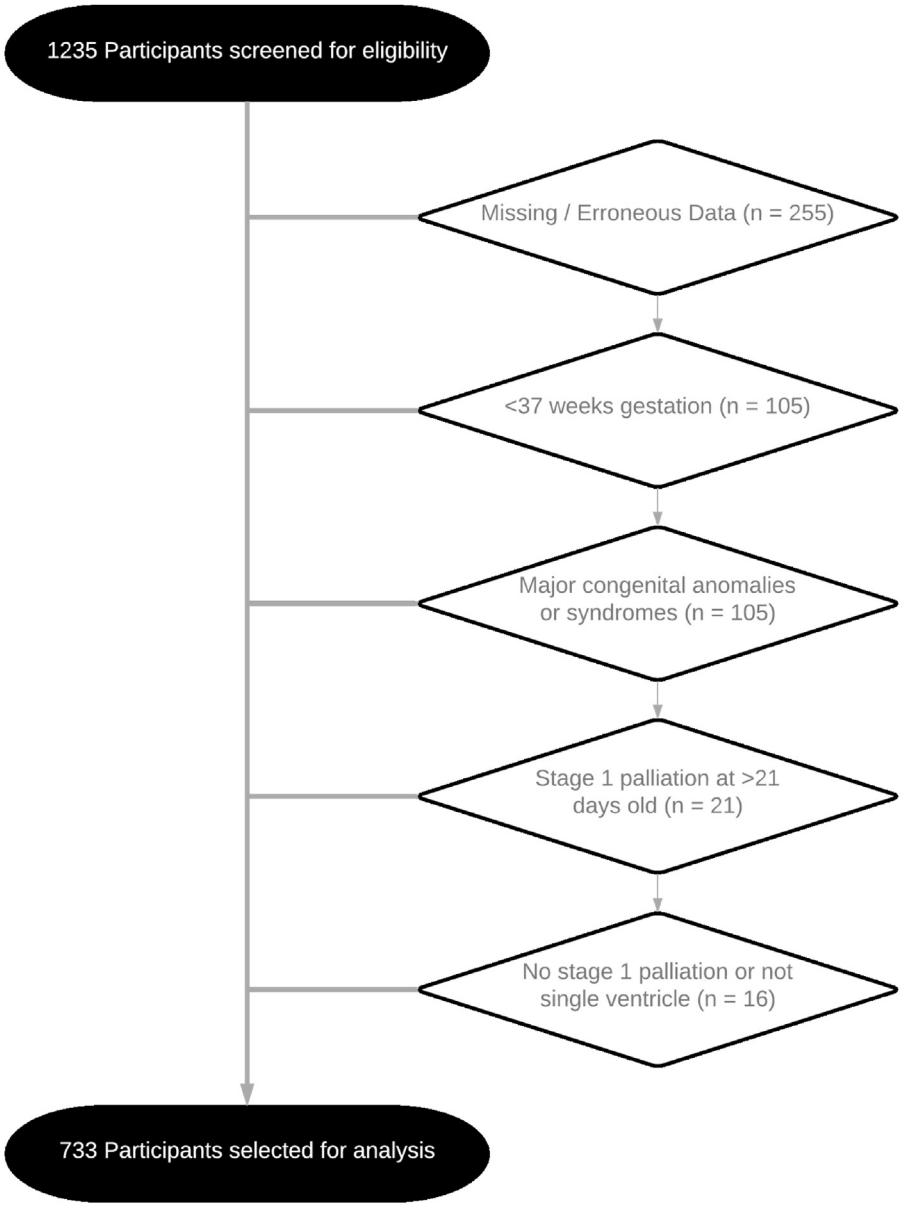

Figure 1. Flowchart of participant selection. Participants who were excluded from the total number enrolled to form the cohort for this study.

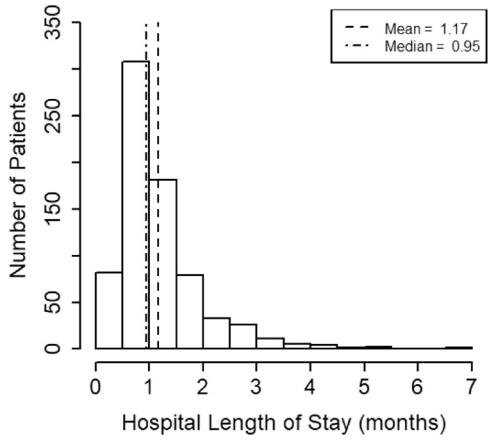

Figure 2. Hospital length of stay histogram. The median length of stay was just under 1 month.

Table III. Non-S1P procedures

Procedures	No. performed
Bedside laryngoscopy to assess vocal cords	211
Gastrostomy tube placement	138
Bronchoscopy	29
Fundoplication	26
Diaphragm plication	15
Exploratory laparotomy	14
Dialysis	9
Pericardiocentesis	8
Cardioversion	6
Chest exploration or complex closure	7
Cerebral shunts	6
Supraglottoplasty	3
Thoracic duct ligation	3
Lung biopsy	2
Genitourinary repair	2
Liver biopsy	1
Rectal biopsy	1
Tracheoesophageal fistula/esophageal atresia repair	1