Title

Impact of pharmacotherapy on interstage mortality and weight gain in children with single ventricle

Short title:

Interstage pharmacotherapy in single ventricles

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Funding sources: None

Conflict of Interest Disclosure: None

Abstract

Objective: Infants with single ventricle physiology have a high mortality and poor somatic growth during the interstage period. We retrospectively assessed the impact of pharmacotherapy in this population using a multicenter database.

Design and results: Records for 395 patients (63.5% boys) with single ventricle were obtained from the National Pediatric Cardiology Quality Improvement Collaborative registry. Median of 5 medications were prescribed per patient at discharge after stage 1 palliation (interquartile range 3 to 6); the most common medications being aspirin (95.7%), diuretics (90.4%), angiotensin convertase enzyme inhibitors (37.7%), proton-pump inhibitors (33.4%), H2 receptor blockers (30.6%), and digoxin (27.6%). Interstage mortality was 9.4%. Digoxin use was associated with lower risk of death ($p = 0.03$) on univariable analysis, however no single medication was an independent predictor on regression analysis. Change in weight-for-age Z score was studied as outcome of somatic growth with 36.3% patients showing a decrease during the interstage period. Total number of medications prescribed to a patient showed a negative correlation with the interstage change in Z score ($r = -0.19$, $p = 0.002$). On univariable comparisons, use of metoclopramide and lansoprazole were associated with decreased Z-score ($p = 0.004$ and 0.041 respectively) although linear regression failed to identify any agent as independent predictor.

Conclusions: Children with single ventricle have high mortality and a profound medication burden. No individual medication is independently associated with better survival or weight gain during interstage period. Despite widespread use, proton-pump inhibitors and prokinetic agents are not associated with better outcomes and may be associated with poor growth.

Key words: Pharmacotherapy, Single ventricle, Quality improvement

Introduction

Staged surgical palliation has significantly improved survival for patients with hypoplastic left heart syndrome (HLHS) and other complex heart defects with single ventricle physiology.(1) The palliation typically has three stages. First stage (S1P) is commonly a Norwood procedure or its variant performed in the first few days of life; second stage (S2P) is a bidirectional cavopulmonary anastomosis performed at 4-6 months of age; and the final stage is a Fontan type circulation or its variant in which all systemic venous return is directed to the lungs before passing to the heart. The interstage period between S1P and S2P is extremely crucial with well documented high mortality and poor somatic growth.(2–4) Although survival to discharge after S1P has improved, mortality in the interstage period, defined as death after S1P discharge but prior to hospitalization for S2P has remained around 10-15% over the last decade.(5–10) Hence, with improvements in surgical technique, perfusion strategies, and post-operative intensive care in the recent years, interstage death accounts for an even larger proportion of overall mortality.

In published literature, the type of S1P shunt, residual anatomic lesions, poor myocardial function, high systemic vascular resistance, arrhythmia, older age at S1P, and extra-cardiac complications have all been associated with increased risk of interstage mortality.(5–7,9,11–15) Outcomes are worse in those with associated non-cardiac malformations and genetic syndromes.(16) Children who successfully undergo S2P have reasonably good catch up growth after the surgery, however lower weight at the time of S2P has been shown to prolong post-operative hospitalization.(17,18) Close monitoring, calorie rich formula, feeding algorithms and standardization of care have been shown to improve interstage weight gain and outcomes.(19–21) Single ventricle patients in the interstage period have a high burden of medications including cardiac and non-cardiac drugs. Weight gain is a good indicator of a patient's overall well being and cardiac status. Hence all medications used in this population have the potential

to directly or indirectly influence interstage weight gain. Despite numerous published studies that have evaluated the association of surgical and other clinical variables with interstage outcomes, only a few have analyzed the impact of pharmacotherapy.(22,23) Authors of a recent report from a single large pediatric center concluded that despite this burden, pharmacotherapeutic regimens appear to have little effect on interstage weight gain.(24)

In the present study, we sought to describe medications used during the interstage period and study their impact on somatic growth and mortality retrospectively using a multicenter database. Results of such a description and analysis may be useful in designing better pharmacological regimens for this vulnerable population and may also lay a foundation for future prospective drug trials.

Methods

Data for the study were obtained from the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) which is a quality improvement initiative of the Joint Council on Congenital Heart Disease (JCCHD), an alliance of pediatric cardiology leaders representing multiple organizations invested in the care of children with heart diseases. The objective of the initial QI project of the NPC-QIC is to reduce mortality and to improve the quality of life of children with HLHS and other complex single-ventricle lesions during the interstage period. Data in the NPC-QIC registry are entered into a central online data repository using a secure web-based interface by participating centers.(25) The criterion for registry enrollment is an infant with HLHS or other complex single ventricle who underwent a Norwood or a Norwood-variant procedure and was discharged to home. Hence patients with intraoperative or immediate post-operative deaths are excluded from the database. The registry captures information regarding patient demographics, clinical care processes, and outcomes. For the current study we included all patients enrolled in the registry between June 2008 and December 2011. Patients with associated major organ system malformations and those with identified genetic syndromes were intentionally excluded. By excluding them we were able to create a relatively homogenous study population as these patients are likely to have a higher medication burden and have been shown to have worse outcomes.(16) Specific data regarding patient demographics, gestational ages, cardiac diagnoses, S1P surgical procedure, weight at discharge from S1P, weight at S2P, medications at discharge from S1P, and outcome were extracted. For each weight measurement, weight for age Z scores (WAZ) were computed using the current CDC data files.(26) Each participating center has obtained approval from their respective institutional review boards. Additionally the institutional review board at Children's National Medical Center approved this study.

Statistical analysis

Aims of our analysis were as follows: 1) provide a description of pharmaceutical agents prescribed at discharge from S1P, 2) identify medications that may be associated with higher risk of interstage death, and 3) identify medications that may be associated with higher or lower change in WAZ during the interstage period. Descriptive statistics were used to characterize the study population and medication profiles. Data are expressed as percentages, means with standard deviations (when parametric) and medians with interquartile ranges (IQR) when non parametric. Central tendencies for parametric variables were compared using t tests while those of non-parametric variables were compared using Mann Whitney U test. Normality of continuous variables was assessed using Shapiro-Wilk test and visual inspection of histograms. Association between demographic and pharmacological data and death were initially assessed using univariable comparisons with Fisher's exact test. Subsequently, a multivariable Cox regression analysis was performed to predict death using variables that had a probability of < 0.1 on univariable analysis. To assess weight gain, patients were classified into 2 groups; those that showed an increase in WAZ during the interstage period (iWAZ) and those who either showed a decrease or no change in the WAZ during interstage period (dWAZ). Association between medications and interstage change in WAZ was initially assessed using univariable comparisons with Fisher's exact test. Pearson correlation was used to assess correlation between number of medications prescribed and interstage change in WAZ score. Subsequently a linear regression analysis was performed including all medications that showed a probability <0.1 as nominal variables and the total number of medications prescribed as an ordinal variable. Type I error was set at 0.05. All calculations were performed using SPSS Statistics 17 for Windows (IBM Corporation, USA) or Open Office Calc (openoffice.org v3.3.0 Oracle Inc, USA).

Results

Study population

Four hundred and eighty nine patients were enrolled in the NPC-QIC database from June 2008 to December 2011. Of these, 395 met study inclusion criteria. Among those that were excluded, 28 had genetic syndromes without identified major malformations, 40 had major organ system malformations without identified genetic syndrome, and 26 had identified genetic syndromes with associated major malformations. Data for the 395 included patients were contributed by a total of 41 participating centers and the number of patients per center ranged from 1 to 46.

Boys accounted for 63.5% of the patient population. White race accounted for 71.4%, African American 16.2%, Asian 0.8% and others/unknown for 9.1% of the study cohort. Ethnicity of 21% was Hispanic, 69.9% Non-Hispanic and 9.1% were unknown. Median gestational age of the population was 39 weeks (IQR 38-39 weeks) and 8.6% of the patients were born prematurely (<37 weeks). Primary cardiac diagnosis and the type of S1P surgery are presented in Table 1. Median age at S1P was 5 days (IQR 4 to 8 days) and median duration of hospitalization after surgery was 33 days (IQR 23 to 49 days).

Medications

Median number of medications prescribed at discharge from S1P surgery was 5 (IQR 3 to 6, range 1 to 15). Overall prescription rates for medications are presented in Table 2. Data from 24 participating centers that had contributed a minimum of 5 cases to the database each were further analyzed to see if certain centers prescribed specific medications to all or majority of their S1P discharges. Aspirin and diuretics stood out as being almost universally used. Aspirin was prescribed >89% of S1P discharges by 23 of these 24 centers (given to 100% patients by 15 centers). Diuretics were prescribed to >83% of

S1P discharges by 22 of the 24 centers (given to 100% patients by 11 centers). Among other medications, digoxin was prescribed to 100% of discharges at 2 participating centers; the remaining centers ranged from 0-67%. ACE inhibitors were prescribed to 80% of discharges at one center; the remaining centers ranged from 0-73%. Multivitamins and iron were prescribed to 96% and 92% of discharges respectively by a single center; the remaining centers prescribed these to <75% of their discharges. None of the other medications showed an indication of being used as a part of a universal protocol by any center.

Pharmacotherapy and interstage mortality

Two hundred and eighty one (71.1%) of the 395 patients had undergone S2P within the study period. Of the 114 that had not made it to S2P, 36 were withdrawn from the study (29 died, 3 were not considered candidates for Glenn and 4 had heart transplantation), and 78 were awaiting surgery. Excluding those who were still awaiting surgery, death rate during the interstage period was 9.4%. Median duration between S1P and death was 67 days (IQR 46.5 to 117 days) and that between S1P and S2P was 142 days (IQR 115 to 166 days). Associations between demographics and medications and death are shown in Table 3. As seen in the table, use of digoxin was significantly associated with survival on univariable analysis, however multivariable Cox regression analysis failed to identify any independent predictor for survival to S2P.

Pharmacotherapy and interstage weight gain

Median birth weight of our study population was 3185 grams (IQR 2863 to 3500 gram) with median WAZ score of -0.59 (IQR -1.1 to 0.02). Median weight at S1P discharge was 3470 grams (IQR 3158 to 3900) and median WAZ score was lower than that at birth (-1.63, IQR -2.16 to -1.12, $p < 0.01$). Changes in WAZ scores for individual patients are depicted in Fig 1. WAZ score was highest at birth for 72.2% patients and at S2P for 21.7% of patients. Of the 281 patients that underwent S2P, weight at

S1P as well as S2P was available for 278 patients. Among these 278 patients, 177 (63.7%) showed an increase in the WAZ score (iWAZ) and 101 (36.3%) showed either a decrease or no change in the WAZ score (dWAZ) during the interstage period. Interstage WAZ change showed statistically significant negative correlation with S1P discharge WAZ ($r = -0.37$, $p < 0.01$, Fig 2.)

Total number of medications prescribed to a patient showed a weak but statistically significant negative correlation with the interstage change in WAZ score ($r = -0.19$, $p = 0.002$). Further analysis was conducted to identify individual medications that might be associated with increase or decrease in WAZ during the interstage period. On univariable comparisons, use of metoclopramide and lansoprazole were associated with dWAZ. Of the 47 children who received metoclopramide, 26 (55.3%) showed dWAZ as compared to 75 of 231 (32.5%) children that did not get the drug ($p = 0.004$). Of the 81 children who received lansoprazole, 37 (45.7%) showed dWAZ as compared to 64 of 197 (32.5%) children that did not get the drug ($p = 0.041$). Multivariate linear regression did not identify any individual medication to be independently associated with increase or decrease in WAZ during the interstage period.

Clinically the most concerning patients are those who are comparatively small at S1P discharge and continue to have a decrease in WAZ during the interstage period. Hence we further analyzed patients with WAZ less than -2 at S1P discharge ($n = 88$). Twenty of these 88 (22.7%) patients showed dWAZ while 68 (77.3%) showed iWAZ over the interstage period. The negative correlation between number of medications and interstage WAZ change was statistically significant, and in fact stronger than that for the entire study population ($r = -.328$, $p = 0.002$). In these patients metoclopramide, lansoprazole and iron were associated with dWAZ while H2 receptor antagonists were associated with iWAZ. Eight of the 18 (44.4%) patients receiving metoclopramide showed dWAZ as compared to 12 of the 70 (17.1%) that did not get the medication ($p = 0.024$). Nine of the 16 (56.3%) patients receiving iron

showed dWAZ as compared to 11 of the 72 (15.3%) that did not get the medication (p = 0.001). Ten of the 24 (41.7%) patients receiving lansoprazole showed dWAZ as compared to 10 of the 64 (15.6%) that did not get the medication (p = 0.020). Twenty five of the 27 (92.6%) patients receiving H2 receptor antagonists showed iWAZ as compared to 43 of the 61 (70.5%) that did not get the medication (p 0.027). Similar to the entire study population, linear regression failed to identify any individual medication to be independently associated with interstage WAZ change.

Discussion

This study presents a comprehensive review of pharmaceutical agents used in the care of children with single ventricle during the interstage period. We found that these children have a very high medication burden with some receiving as many as 15 different medications per day. When translated into number of medication doses, this amounts to an immense burden on the caretakers of this fragile population. Mortality during interstage period is 9.4%, and no individual medication is independently associated with better survival. About one third of children show a decrease in WAZ during the interstage period and those receiving more medications tend to fare worse.

Usefulness or lack thereof is convincingly established for certain medications in management of single ventricle physiology. Aspirin, which was used in greater than 95% of our study population, reduced shunt thrombosis and death in a large prospective study of cyanotic heart disease patients, including 346 infants with HLHS.(23) Conversely, administration of enalapril to children in the period after S2P did not improve somatic growth, ventricular function, or heart failure severity in a recent multicenter prospective randomized trial.(22) The rationale behind use of ACE inhibitors, digoxin and diuretics is to aid the volume overloaded right ventricle and prevent maladaptive ventricular modeling, although convincing evidence of their benefit in single ventricle patients is lacking.(27) In the present study, significantly higher proportion of patients receiving digoxin survived to S2P although it was not identified as an independent predictor of survival. Use of digoxin varied widely across participating centers and 2 centers prescribed it to 100% of their discharges, possibly related to a standard discharge protocol. There is a notable paucity of published literature with regards to digoxin administration in this population despite its widespread use.

Birth WAZ of our study population was well below normal which is in accordance with previously

published literature.(28) The rate of prematurity in our cohort (8.6%) is lower than that reported by Williams et al. (16%) based on analysis of 1245 newborns with single ventricle.(28) Our exclusion of patients with genetic syndromes and major system malformations, and automatic exclusion of infants who do not survive to S1P discharge in the NPC-QIC database likely accounts for this difference. Growth failure in single ventricle patients is evident by the fact that less than 25% of children in the present study reach birth WAZ score at the time of S2P. However it is encouraging to note that children who are smaller at S1P discharge are more likely to show catch up growth. This perhaps reflects the efforts of care teams of these smaller patients towards nutritional rehabilitation. Using the same NPC-QIC database, it was shown that centers that use nutritional practices that allow early identification of feeding difficulties and very close monitoring for early signs of growth problems demonstrate better growth performance.(29)

Metoclopramide and lansoprazole are widely used medications for gastroesophageal reflux disease (GERD) in patients with cardiac and non-cardiac diagnoses. Despite the absence of a Food and Drug Administration approved indication for the use of any proton pump inhibitors (PPI) in children under age 1 year, PPI use in infants is estimated to have increased up to 7-fold between 1999 and 2004.(30) In the present study both metoclopramide and lansoprazole were associated with poor interstage weight gain in the entire population as well as in the subgroup of patients with S1P WAZ < -2. The utility of both these agents in treatment of GERD was seriously questioned in recent pediatric studies.(31,32) While patients with single ventricle have a very high gastrointestinal morbidity(33), in light of above findings, benefits of these medications should be thoughtfully considered before they are prescribed. In the subgroup of patients with S1P WAZ < -2, two additional medications showed significant associations. Iron was associated with decrease in WAZ while H2 receptor antagonists were associated with increase in WAZ. Iron therapy might indicate presence of anemia which can result from a number of factors including frequent hospitalizations and blood draws. Hence poor weight gain in these

children is understandable. However, the reasons behind positive association between increase in WAZ and H2 receptor blockers in this subgroup of patients are not clear. Nevertheless, similar to findings reported by Moffett et al., no individual medication in the present study was independently shown to be beneficial and a higher overall medication burden correlated with lower WAZ gain.(24)

Higher medication burden also increases the chances of non-adherence to prescribed regimen.(34) After S1P surgery, children with single ventricle exhibit a delicate balance between systemic and pulmonary circulations. Adherence to prescribed pharmacotherapy is of paramount importance as a minor imbalance can lead to catastrophic results. Each additional medication dose can add significantly to the already tremendous burden of the caretakers. In addition, formulations suitable for infants are often not readily available for many commonly used medications making the caretakers' job even more challenging.(35,36) Hence limiting the number of medications and simplifying dosing regimens may go a long way in ensuring adherence.

Although the present study was able to analyze data from a large number of patients with single ventricle physiology from a relatively homogenous group, it has inherent limitations due to a non-randomized, retrospective design. There is a notable absence of care guidelines for children with single ventricle, resulting in variation in preoperative care, operative technique, medication use and nutritional management between participating centers. The participating centers voluntarily submit data leading to a possibility of reporting bias. Additionally, only patients who were eligible and consented were enrolled in the NPC-QIC registry. Some patients remain hospitalized during the interstage period and would thus not be eligible for inclusion in the registry. Clinical differences may exist between patients enrolled and those who were not enrolled in the registry. We only analyzed medications prescribed at discharge from S1P hence our results do not account for therapy changes made on follow up visits and hospital readmissions. Doses and formulations of individual medications are not available in the

registry and were not analyzed. Based on the nature of the data, the present study could only derive associations between medications and outcomes but not prove causality. Lastly, there is a possibility that practice protocols in certain individual centers may have unequally impacted some of the data. However, the size of the dataset, relatively small number of patients per center, and the need to maintain anonymity of individual centers precluded 'center level' analysis.

In conclusion, children with single ventricle have high mortality and a profound medication burden. No individual medication is independently associated with better survival or weight gain during interstage period. Despite widespread use, proton-pump inhibitors and prokinetic agents are not associated with better outcomes and may be associated with poor growth. Further prospective studies are recommended to convincingly establish roles of various medications in single ventricle physiology, especially with respect to use of digoxin and gastrointestinal medications.

This study was made possible because of the cooperation among participating centers involved in the NPC-QIC. As is true with many rare pediatric disorders, it is difficult to determine best practices by any individual practice or center. Along with other researchers who have contributed to the knowledge of managing children with single ventricle physiology using NPC-QIC database, we hope that findings of our study help in moving towards a more uniform management of infants with single ventricle as well as provide direction for future clinical trials.(29,37–39) Collaboratives such as NPC-QIC have a potential to make a real impact on the lives of children with congenital heart disease. We hope that such collaborative efforts only grow with time making it possible to answer even more difficult clinical questions in a shorter period of time.

Acknowledgments

We would like to acknowledge the Leadership Taskforce of the NPC-QIC for their vision in creation and support of this collaborative. The Leadership Taskforce includes Robert H. Beekman III, MD, Kathy J. Jenkins, MD, MPH, John D. Kugler, MD, Thomas S. Klitzner, MD, PhD, Gerard R. Martin, MD, R. Steven Neish, MD, and Geoffrey L. Rosenthal, MD. We also wish to thank Lynn Darbie, MS of the Division of Biostatistics and Epidemiology at Cincinnati Children's Hospital for her assistance in obtaining the required data fields from the database and for calculation of weight for age Z-scores.

Author contributions

Sunil J. Ghelani: Study design, data procurement, data analysis, data interpretation, statistical analysis and drafting the article.

Christopher F. Spurney: Study design, data analysis, data interpretation, critical review and final approval of the manuscript.

Gerard R. Martin: Data interpretation, critical review and final approval of the manuscript.

Russell R. Cross: Study design, data procurement, data analysis, data interpretation, critical review and final approval of the manuscript.

References

1. Karamlou T, Diggs BS, Ungerleider RM, Welke KF. Evolution of treatment options and outcomes for hypoplastic left heart syndrome over an 18-year period. *J. Thorac. Cardiovasc. Surg.* 2010; 139:119–126; discussion 126–127.

2. Kelleher DK, Laussen P, Teixeira-Pinto A, Duggan C. Growth and correlates of nutritional status among infants with hypoplastic left heart syndrome (HLHS) after stage 1 Norwood procedure. *Nutrition*. 2006; 22:237–244.

3. Davis D, Davis S, Cotman K, Worley S, Londrico D, Kenny D, Harrison AM. Feeding difficulties and growth delay in children with hypoplastic left heart syndrome versus d-transposition of the great arteries. *Pediatr Cardiol*. 2008; 29:328–333.

4. Lee JR, Choi JS, Kang CH, Bae EJ, Kim YJ, Rho JR. Surgical results of patients with a functional single ventricle. *Eur J Cardiothorac Surg*. 2003; 24:716–722.

5. Hehir DA, Dominguez TE, Ballweg JA, Ravishankar C, Marino BS, Bird GL, Nicolson SC, Spray TL, Gaynor JW, Tabbutt S. Risk factors for interstage death after stage 1 reconstruction of hypoplastic left heart syndrome and variants. *J. Thorac. Cardiovasc. Surg*. 2008; 136:94–99, 99.e1–3.

6. Ghanayem NS, Hoffman GM, Mussatto KA, Cava JR, Frommelt PC, Rudd NA, Steltzer MM, Bevandic SM, Frisbee SS, Jaquiss RDB, Litwin SB, Tweddell JS. Home surveillance program prevents interstage mortality after the Norwood procedure. *J. Thorac. Cardiovasc. Surg.* 2003; 126:1367–1377.

7. Fenton KN, Siewers RD, Rebovich B, Pigula FA. Interim mortality in infants with systemic-to-pulmonary artery shunts. *Ann. Thorac. Surg.* 2003; 76:152–156; discussion 156–157.

8. Azakie A, Martinez D, Sapru A, Fineman J, Teitel D, Karl TR. Impact of right ventricle to pulmonary artery conduit on outcome of the modified Norwood procedure. *Ann. Thorac. Surg.* 2004; 77:1727–1733.

9. Mahle WT, Spray TL, Gaynor JW, Clark BJ 3rd. Unexpected death after reconstructive surgery for hypoplastic left heart syndrome. *Ann. Thorac. Surg.* 2001; 71:61–65.

10. Simsic JM, Bradley SM, Stroud MR, Atz AM. Risk factors for interstage death after the Norwood procedure. *Pediatr Cardiol*. 2005; 26:400–403.

11. De Oliveira NC, Ashburn DA, Khalid F, Burkhart HM, Adatia IT, Holtby HM, Williams WG, Van Arsdell GS. Prevention of early sudden circulatory collapse after the Norwood operation. *Circulation*. 2004; 110:II133–138.

12. Gaynor JW, Mahle WT, Cohen MI, Ittenbach RF, DeCampli WM, Steven JM, Nicolson SC, Spray TL. Risk factors for mortality after the Norwood procedure. *Eur J Cardiothorac Surg*. 2002; 22:82–89.

13. Pizarro C, Mroczek T, Malec E, Norwood WI. Right ventricle to pulmonary artery conduit reduces interim mortality after stage 1 Norwood for hypoplastic left heart syndrome. *Ann. Thorac. Surg.* 2004; 78:1959–1963; discussion 1963–1964.

14. Bartram U, Grünenfelder J, Van Praagh R. Causes of death after the modified Norwood procedure: a study of 122 postmortem cases. *Ann. Thorac. Surg.* 1997; 64:1795–1802.

15. Wright GE, Crowley DC, Charpie JR, Ohye RG, Bove EL, Kulik TJ. High systemic vascular resistance and sudden cardiovascular collapse in recovering Norwood patients. *Ann. Thorac. Surg.* 2004; 77:48–52.

16. Patel A, Hickey E, Mavroudis C, Jacobs JP, Jacobs ML, Backer CL, Gevitz M, Mavroudis CD. Impact of noncardiac congenital and genetic abnormalities on outcomes in hypoplastic left heart syndrome. *Ann. Thorac. Surg.* 2010; 89:1805–1813; discussion 1813–1814.

17. Vogt KN, Manlhiot C, Van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic growth in children with single ventricle physiology impact of physiologic state. *J. Am. Coll. Cardiol.* 2007; 50:1876–1883.

18. Anderson JB, Beekman RH 3rd, Border WL, Kalkwarf HJ, Khoury PR, Uzark K, Eghtesady P, Marino BS. Lower weight-for-age z score adversely affects hospital length of stay after the bidirectional Glenn procedure in 100 infants with a single ventricle. *J. Thorac. Cardiovasc. Surg.* 2009;

138:397–404.e1.

19. Golbus JR, Wojcik BM, Charpie JR, Hirsch JC. Feeding complications in hypoplastic left heart syndrome after the Norwood procedure: a systematic review of the literature. *Pediatr Cardiol*. 2011; 32:539–552.

20. Garcia X, Jaquiss RDB, Imamura M, Swearingen CJ, Dassinger MS 3rd, Sachdeva R. Preemptive gastrostomy tube placement after Norwood operation. *J. Pediatr.* 2011; 159:602–607.e1.

21. Srinivasan C, Sachdeva R, Morrow WR, Gossett J, Chipman CW, Imamura M, Jaquiss RDB. Standardized management improves outcomes after the Norwood procedure. *Congenit Heart Dis*. 2009; 4:329–337.

22. Hsu DT, Zak V, Mahony L, Sleeper LA, Atz AM, Levine JC, Barker PC, Ravishankar C, McCrindle BW, Williams RV, Altmann K, Ghanayem NS, Margossian R, Chung WK, Border WL, Pearson GD, Stylianou MP, Mital S. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation*. 2010; 122:333–340.

23. Li JS, Yow E, Berezny KY, Rhodes JF, Bokesch PM, Charpie JR, Forbus GA, Mahony L, Boshkov L, Lambert V, Bonnet D, Michel-Behnke I, Graham TP, Takahashi M, Jaggers J, Califf RM, Rakhit A, Fontecave S, Sanders SP. Clinical outcomes of palliative surgery including a systemic-to-pulmonary artery shunt in infants with cyanotic congenital heart disease: does aspirin make a difference? *Circulation*. 2007; 116:293–297.

24. Moffett BS, Mattamal R, Ocampo EC, Petit CJ. Impact of pharmacotherapy on interstage outcomes in single ventricle infants. *Congenit Heart Dis*. 2011; 6:286–293.

25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009; 42:377–381.

26. Growth Charts - Z-score Data Files [Internet]. [cited 2012 Mar 16];Available from: http://www.cdc.gov/growthcharts/zscore.htm

27. Kantor PF, Redington AN. Pathophysiology and management of heart failure in repaired congenital heart disease. *Heart Fail Clin*. 2010; 6:497–506, ix.

28. Williams RV, Ravishankar C, Zak V, Evans F, Atz AM, Border WL, Levine J, Li JS, Mahony L, Mital S, Pearson GD, Prakash A, Hsu DT. Birth Weight and Prematurity in Infants with Single Ventricle Physiology: Pediatric Heart Network Infant Single Ventricle Trial Screened Population. *Congenit Heart Dis*. 2010; 5:96–103.

29. Anderson JB, Iyer SB, Schidlow DN, Williams R, Varadarajan K, Horsley M, Slicker J, Pratt J, King E, Lannon C. Variation in Growth of Infants with a Single Ventricle. *The Journal of pediatrics* [Internet]. 2012 [cited 2012 May 7];Available from: http://www.ncbi.nlm.nih.gov/pubmed/22336578

30. Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. *J. Pediatr. Gastroenterol. Nutr.* 2007; 45:421–427.

31. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of Gastroesophageal Reflux Disease. *The Journal of Pediatrics*. 2009; 154:514–520.e4.

32. Chicella MF, Batres LA, Heesters MS, Dice JE. Prokinetic drug therapy in children: a review of current options. *Ann Pharmacother*. 2005; 39:706–711.

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

34. Winnick S, Lucas DO, Hartman AL, Toll D. How do you improve compliance? *Pediatrics*. 2005; 115:e718–724.

35. Nahata MC, Allen LV Jr. Extemporaneous drug formulations. *Clin Ther*. 2008; 30:2112–2119.

36. Milne C-P, Bruss JB. The economics of pediatric formulation development for off-patent drugs. *Clin Ther*. 2008; 30:2133–2145.

37. Brown DW, Connor JA, Pigula FA, Usmani K, Klitzner TS, Beekman RH 3rd, Kugler JD,

Martin GR, Neish SR, Rosenthal GL, Lannon C, Jenkins KJ. Variation in preoperative and intraoperative care for first-stage palliation of single-ventricle heart disease: a report from the Joint Council on Congenital Heart Disease National Quality Improvement Collaborative. *Congenit Heart Dis*. 2011; 6:108–115.

38. Baker-Smith CM, Neish SR, Klitzner TS, Beekman RH 3rd, Kugler JD, Martin GR, Lannon C, Jenkins KJ, Rosenthal GL. Variation in postoperative care following stage I palliation for single-ventricle patients: a report from the Joint Council on Congenital Heart Disease National Quality Improvement Collaborative. *Congenit Heart Dis*. 2011; 6:116–127.

39. Schidlow DN, Anderson JB, Klitzner TS, Beekman RH 3rd, Jenkins KJ, Kugler JD, Martin GR, Neish SR, Rosenthal GL, Lannon C. Variation in interstage outpatient care after the Norwood procedure: a report from the Joint Council on Congenital Heart Disease National Quality Improvement Collaborative. *Congenit Heart Dis*. 2011; 6:98–107.

Table 1: Types of cardiac diagnoses and stage 1 palliative procedures performed

Cardiac diagnosis associated with single ventricular physiology	n	%
HLH with aortic and mitral atresia	147	37.2%
HLH with aortic atresia and mitral hypoplasia/stenosis	65	16.5%
HLH with aortic and mitral hypoplasia/stenosis	63	15.9%
DORV with left side hypoplasia	25	6.3%
HLH with aortic hypoplasia/stenosis and mitral atresia	15	3.8%
Unbalanced AV canal defect	15	3.8%
DILV	14	3.5%
Other/Unknown	51	12.9%
Stage 1 palliation procedure		
Norwood with BT shunt	121	30.6%
Norwood with RV-PA conduit	227	57.5%
Hybrid Norwood (with PDA stent & PA bands)	31	7.8%
DKS connection with BT shunt	12	3.0%
Other/Unknown	4	1.0%

Abbreviations: HLH, hypoplastic left heart syndrome; DORV, double outlet right ventricle; DILV double inlet left ventricle; AV, atrio-ventricular; RV, right ventricle; PA, pulmonary artery; BT Blalock Taussig; PDA, patent ductus arteriosus; PA, pulmonary artery; DKS, Damus-Kaye-Stansel

Table 2: Overall prescription rates for cardiac and non cardiac medications. Note: percentages of individual drugs may not add up to their drug class because names of drugs prescribed to two or less patients are not presented and/or multiple medications from the same class may have been prescribed per patient.

Cardiac medications		Non cardiac medications	
Diuretics	90.4%	**Anti-clotting agents**	97.5%
Furosemide	85.6%	Aspirin	95.7%
Chlorthiazide	4.1%	LMWH	5.6%
Spironolactone	8.9%	Clopidogrel	1.3%
Digoxin	27.6%	**Proton pump inhibitors**	33.4%
ACE inhibitors	37.7%	Lansoprazole	26.1%
Captopril	21.3%	Omeprazole	6.8%
Enalapril	15.7%	**H2 Blockers**	30.6%
Lisinopril	0.8%	**Prokinetics**	17.2%
Propranolol	4.3%	Metoclopramide	15.4%
Antiarrhythmics	3.8%	Erythromycin	1.8%
Sotalol	1.0%	**Methadone**	6.6%
Amiodarone	2.3%	**Lorazepam**	2.5%
Sildenafil	1.5%	**MultiVitamins**	24.6%
Clonidine	1.5%	**Iron**	20.3%

Abbreviations: ACE, angiotensin convertase enzyme, LMWH, low molecular weight heparin

Table 3: Association between demographics and medications and interstage death.

		Completed S2P (n=281)		Died (n=29)		
		n	(column %)	n	(column %)	p value
Sex	Female	95	33.8	14	48.3	.10
	Male	186	66.2	14	48.3	
Race	White	200	71.2	16	55.2	.35
	African American	45	16.0	6	20.7	
	Pacific Islander	0	.0	0	.0	
	Asian	2	.7	0	.0	
	American Indian or Alaska Native	1	.4	0	.0	
	Other	28	10.0	6	20.7	
Ethnicity	Hispanic	60	21.4	8	27.6	.48
	Non Hispanic	196	69.8	19	65.5	
Medications	**Diuretics**					
	Furosemide	241	85.8	22	75.9	.17
	Chlorthiazide	7	2.5	2	6.9	.20
	Spironolactone	25	8.9	1	3.4	.49
	Digoxin	86	30.6	3	10.3	.03 *
	ACE inhibitors					
	Captopril	60	21.4	4	13.8	.47
	Enalapril	44	15.7	7	24.1	.29
	Lisinopril	3	1.1	0	.0	1.00
	Propranolol	10	3.6	2	6.9	.31
	Antiarrhythmics					
	Sotalol	2	.7	1	3.4	.26
	Amiodarone	8	2.8	0	.0	1.00
	Flecainide	1	.4	0	.0	1.00
	Sildenafil	5	1.8	0	.0	1.00
	Clonidine	6	2.1	0	.0	1.00
	Anti-clotting agents					
	Aspirin	272	96.8	26	89.7	.09
	LMWH	16	5.7	1	3.4	1.00
	Clopidogrel	5	1.8	0	.0	1.00
	Proton pump inhibitors					
	Lansoprazole	81	28.8	4	13.8	.12
	Omeprazole	16	5.7	4	13.8	.10
	H2 Blockers	83	29.5	10	34.5	.67
	Prokinetics					
	Metoclopramide	47	16.7	6	20.7	.61
	Erythromycin	3	1.1	0	.0	1.00
	Methadone	19	6.8	4	13.8	.25

Lorazepam	6	2.1	2	6.9	.17
MultiVitamins	63	22.4	8	27.6	.50
Iron	50	17.8	6	20.7	.62

Abbreviations: S2P, stage 2 palliation; ACE, angiotensin convertase enzyme, LMWH, low molecular weight heparin

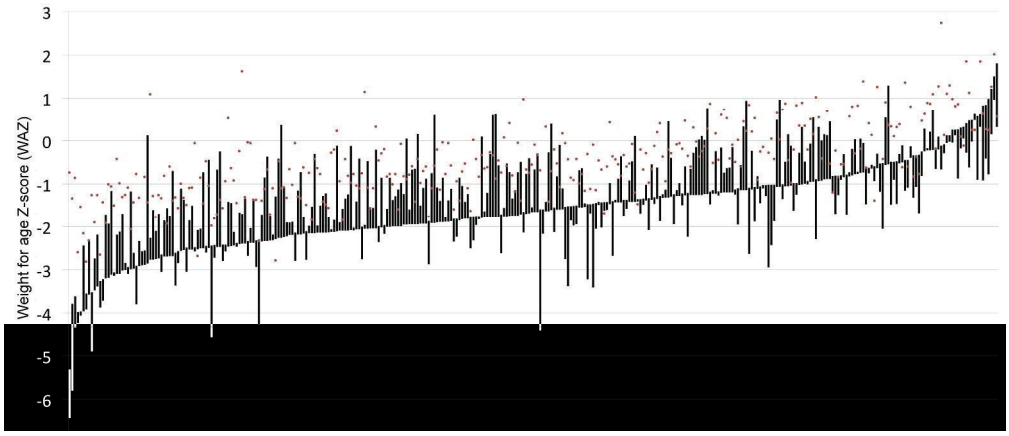

Fig 1: Weight for age Z-scores (WAZ) at birth, S1P and S2P for the entire study population. There is one red dot and one vertical line for each patient. The red dots represent birth WAZ, central end of the vertical line represents S1P WAZ, and the other end (higher or lower) of the vertical line represents S2P WAZ. Hence the length of the vertical line represents interstage change in WAZ. Patients are arranged from left to right in increasing order of S1P WAZ. One can note that birth WAZ (small dots) is the highest WAZ for majority (72.2%) of the patients, and that patients with lower S1P WAZ (towards the left side of the figure) are more likely to have an increase of WAZ during interstage period than those with higher S1P WAZ.
1168x498mm (600 x 600 DPI)

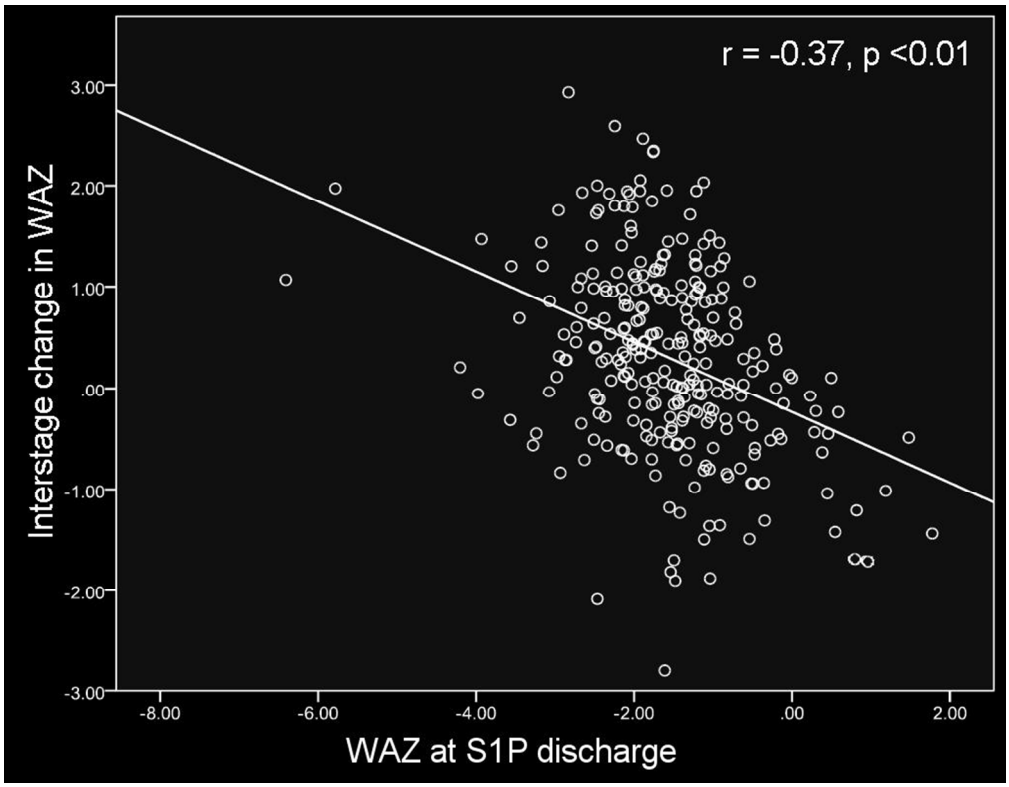

Fig 2: Correlation between S1P discharge WAZ and interstage change in WAZ.

Abbreviations: S1P, stage 1 palliation; WAZ, weight for age Z-score
361x280mm (72 x 72 DPI)