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EDITORIAL COMMENT

The Second Interstage Period Is Just as "Risky" as the First in HLHS*

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In 2006, the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) was established with the goals of reducing interstage mortality between the Norwood procedure and Stage II and improving the quality of life in infants with hypoplastic left heart syndrome (HLHS).[1] Since its establishment, the network has grown from 6 to 69 centers in the United States, Canada, and the United Kingdom. In June 2013, the NPC-QIC demonstrated a decrease in interstage mortality from 9.5% (from 2008 to May 2013) to 5.3%.[2] In 2016, Phase II was launched with data collection extending from Stage II to 1 year of age.

In an analysis of the NPC-QIC Phase II data in this issue of *JACC: Advances* by Bucholz et al[3] of 1,455 infants with HLHS surviving to Stage II, 110 (7.5%) met the composite endpoint of death (n = 76) or referral for transplant (n = 34) at 1 year of age. One-third of events occurred within 30 days and two-thirds within 100 days. Independent factors associated with the outcome included the presence of genetic syndrome, hybrid procedure, right ventricle-pulmonary artery (RV-PA) shunt at Norwood, need for extracorporeal membrane oxygenation (ECMO or concurrent tricuspid valve repair at Norwood, challenges with separation from mechanical ventilation after Norwood, at least moderate tricuspid regurgitation (TR) at Stage II, younger age at Stage II, and longer cardiopulmonary bypass time in those not requiring ECMO after Norwood. The 2 strongest predictors were need for ECMO after Norwood and Hybrid. All these factors have been known to be associated with poor short-term and long-term outcomes in patients with HLHS. The authors have acknowledged 3 major limitations. First, 285 patients were excluded, mostly due to a lack of follow-up; these patients were more likely to have government insurance. The outcome of patients referred for heart transplantation is unknown. This is a high-risk group with worse predicted survival before and after heart transplantation. Thirdly, patients with failing physiology who are unlikely to be suitable candidates for Fontan are classified as survivors.

Cardiologists are relieved when patients survive the interstage period after the Norwood. However, this paper demonstrates that the second interstage period after Stage II may be just as "risky" for a subset of patients and is an important addition to the limited literature on survival between Stage II and Fontan. In 1 of the largest single-center studies spanning more than 3 decades, 8% of children with HLHS failed to undergo the Fontan after discharge from Stage II.[4] Since data collection ended at 1 year of age, it is conceivable that the attrition rate will be higher on further follow up. The study has the advantage of having detailed information from birth to Stage II.

The presence of genetic syndrome and significant TR are lifelong risk factors for patients with HLHS.[5-7] Interestingly, only 2 patients underwent tricuspid valve surgery, even though 17% had at least moderate degree of TR prior to Stage II. The tricuspid valve poses a major challenge in this patient population with ongoing efforts to better delineate abnormalities of the valve with concurrent improvement in surgical techniques.[8] Catheter-based interventions are likely to evolve as interventional cardiologists gain more expertise with the implantation of mitral valve clips.[9]

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However, a durable solution to this problem does not appear to be on the horizon.

The hybrid procedure, which was strongly associated with the composite outcome, has also been associated with death in the traditional interstage period.[10] Of the 87 (6%) who survived to Stage II, 20% did not survive. This strategy, with rare exceptions, is utilized for the highest-risk patients with mostly nonmodifiable risk factors and does not appear to mitigate intrinsic patient-related risk factors. Another notable finding is the association of the RV-PA shunt with the composite endpoint relative to the Blalock Taussig Thomas shunt. This confirms findings from longitudinal follow-up of patients enrolled in the Single Ventricle Reconstruction trial.[11] The higher diastolic pressure seen with the RV-PA shunt no longer confers an advantage after Stage II, but rather exposes the patient to greater distortion of the pulmonary arteries, which is not ideal for the passive pulmonary blood flow expected with Stage II and beyond.

Of the 193 (13%) patients who were not discharged after Norwood, 20% died or were referred for transplant by 1 year of age and represented less than one-third of patients who met the composite outcome. These patients were more likely to have a genetic syndrome and experience adverse events before and after the first palliative procedure. It will be interesting to see how these patients fare beyond 1 year, as many will retain "frailty" with a low likelihood of being long-term survivors.

Age <130 days was independently associated with the composite outcome. Median age at Stage II was 145 days for the whole cohort and 125 days for those not discharged after Norwood. This is a high-risk group, and there is a general tendency to complete Stage II earlier for medical reasons or to finally discharge these patients. It may be prudent to delay the timing of Stage II in patients who do not meet clear medical criteria for proceeding to an early "Glenn." Younger age at Stage II is a known risk factor for worse outcomes including more complications and a longer length of stay.[12] Over the last 2 decades, there has been a steady decrease in the age of performance of Stage II from 6 to 9 months in the 1990s to around 4 months in the current era.[13] In fact, it is 1 of the changes implemented by interstage monitoring programs. Older age potentially allows for greater somatic growth and more growth of the pulmonary arteries, which is essential for a successful Stage II. This begs the question of whether we should go back to the "old" strategy of referring patients for Stage II closer to 5 to 6 months of age.

It is sobering to see at best 85% 1-year survival with or without transplantation in a contemporary cohort of intensely monitored patients with HLHS. As demonstrated by the results of the Single Ventricle Reconstruction III study, these patients remain at ongoing risk for mortality and morbidity.[14] The "ideal" shunt type at Norwood remains elusive. One modifiable factor is a careful assessment of the timing of Stage II. The other factor is the "tricuspid valve," with a focus on developing new and durable techniques for repairing the valve through better delineation of mechanisms of failure. It also behooves us to provide appropriate prenatal and postnatal counseling to families of the highest-risk patients with nonmodifiable risk factors.

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