Editorial Comment

Advancing Knowledge in Pediatric Heart Failure—the Growing Pains

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Heart failure (HF) continues to accrue substantial morbidity and mortality in the United States, as it does in other industrialized[1] and non-industrialized countries. Despite improvements in mortality associated with pediatric and adult HF, outcomes remain worse in children compared with adult patients.[1] Pediatric HF etiology varies widely, with an ~40% of HF outpatient visits being related to congenital heart disease (CHD), 15% to cardiomyopathy, and 2% to myocarditis, with the balance accounted for by a variety of diagnoses.[2] With demographic shifts in CHD populations, proportions of patients with severe forms of CHD have increased by 19% in children and 55% in adults.[3] Therefore, resource utilization for CHD-related HF is increasing, accounting for nearly 70% of pediatric HF admissions in the United States.[1] In a population-based study evaluating HF admissions and associated mortality in 5689 pediatric and 473,416 adult HF-related admissions, length of stay and admission-related mortality rates were significantly worse for pediatric hospitalizations.[1] The question is, "Why?"

Although there has been clear advancement in the management of pediatric HF over the last decades, current clinical practice guidelines[4] remain driven largely by adult HF studies performed on patients with ischemic and dilated cardiomyopathy. In addition, available pediatric HF studies generally involve small and heterogeneous cohorts of patients, diminishing the internal validity and the generalizability of the findings. Similarly, for pediatric heart transplant, the wide age range, heterogeneity of patient populations, and variations in practice between transplant centers have affected our ability to carry out meaningful clinical trials. Transition from pediatric to adult-centered care has been identified as a period at high risk for care gaps that are particularly harmful for patient with chronic conditions.[5] Adolescent age and suboptimal transition have been associated with increased risk of graft rejection as well as a 5% to 10% increase in mortality in a 10-year post-heart transplant period.[5] However, evidence for the effectiveness of transition programs to reduce risks associated with this life stage remains unclear. These observations support the need for more robust evidence to guide resource allocation and care for pediatric patients with heart transplant and HF.

Two articles in this issue of the journal highlight important challenges relative to pediatric patients with HF, thus emphasizing the importance of advancing knowledge in the care of this population. Price et al[6] evaluated the prognostic significance of diuretic responsiveness in children with HF, defined by the authors as the net fluid output produced by patients per milligram of furosemide given during the first 72 hours of treatment with loop diuretics. They calculated the diuretic responsiveness of 108 children consecutively seen at their pediatric hospital from 2011 to 2015. They demonstrated a strong independent association between poor diuretic response and patient mortality or use of mechanical circulatory support, analyzed as a composite endpoint (adjusted OR 5.31 [1.73−16.3], P = .003). The presence of edema, pleural effusion, and impaired renal function were independent predictors of a better diuretic response. This is different from what is known in the adult literature, where impaired renal function has been shown to be associated with a lower diuretic response and poorer outcomes in HF.[7] However, similar to adult studies, the absence of evidence of fluid congestion was associated with poorer diuretic response, pointing toward two potentially different HF physiological states (congestion vs low cardiac output). The authors were limited by the fact that they had no reliable estimate of the degree of fluid overload and that all the urine outputs and medication dosages were recorded retrospectively. This study highlights that HF physiology may differ between adult and children. As such, impaired renal function may be more frequently reversible in children and might not represent the same magnitude of renal injury

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See page XXX for disclosure information.

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as that seen in adult patients with HF and, therefore, may not necessarily affect the diuretic response.

In the second article, Grady et al[8] determined the feasibility of a randomized controlled trial assessing the efficacy of a transition to adult care program. They randomized 143 participants with an average age of 21 years to a 4-month transition intervention versus usual post-heart transplant care. The authors analyzed retention as a measure of feasibility. They also evaluated the level of transplant knowledge, readiness for transfer and social support using validated questionnaires, and they used medication levels and adverse event records as transplant outcome measures. They demonstrated that such a trial was feasible, with a retention rate of 89%. However, the authors could not demonstrate any improvement in treatment adherence by measuring items related to the adherence construct such as medication levels, knowledge, and self-care. This article is one of the first to attempt to demonstrate that a structured transition program is beneficial for adolescents following heart transplantation. The authors were limited by their sample size, particularly relative to the adherence construct. In addition, the reasons for the worse outcome in this age group could be multifactorial, including biological factors, adherence to medical care, parental factors,[5,8] and the increase in risk-taking behaviors associated with this life stage. Grady et al[8] are on the right track, trying to develop targeted, developmentally appropriate interventions to improve outcomes in this age group and address important obstacles in the care of these patients.

It remains unclear at this time whether pediatric patients with HF have worse outcomes related to length of stay and hospital mortality compared with adults[1] because they are sicker or because there is little evidence to guide therapy. Clearly, there is a substantial evidence gap for pediatric HF, and the articles of Price et al[6] and Grady et al[8] in this issue of the journal are tackling important issues. Randomized clinical trials in pediatric populations remain a challenge. Administrative databases have been used to overcome small clinical numbers but are limited by the lack of clinical granularity. Registries to date have focused on heart transplant, representing only one of the available end-stage HF therapies,[4] but new opportunities are now arising in pediatric HF. The development of national and international multicenter networks will help recruit larger cohorts of well characterized patients to study specific questions.[9] Initiatives like the Pediatric Heart Network are making datasets specific to pediatric HF widely accessible.[10] With the growing prevalence of electronic medical records, high-frequency physiological data recording and increasing collection of quality metrics, there is an opportunity to access new data sources. This will create an opportunity to leverage advanced statistics and machine learning to attempt to close the gap between epidemiology and precision medicine. The two articles in this issue of the journal make important contributions to meet the growing pains of a field in need of increasing evidence to support the clinical care of a challenging population to care for and study.

Disclosures

The authors have no conflict-of-interest to declare.

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