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EDITORIAL COMMENT

Outcomes in Pediatric Dilated Cardiomyopathy

Quo Vadis?*

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Pediatric cardiomyopathies are an uncommon group of disorders characterized by heterogeneous etiologies and varied outcomes (1-3). Childhood dilated cardiomyopathy (DCM) has a peak incidence in the first 2 years of life and is the commonest cause of heart failure and the commonest single indication for heart transplantation beyond infancy (4). Whereas case reports and series from individual tertiary centers comprised the earliest shared experience of this disease, observations of the epidemiology, etiologies, and early outcomes have been facilitated by institutional collaboration and the formation of 2 registries—the large North American PCMR (Pediatric Cardiomyopathy Registry) and the smaller, population-based NACCS (National Australian Childhood Cardiomyopathy Study) (5,6). The PCMR collaborators have been instrumental in providing a rich description of childhood DCM, allowing a better understanding of etiology-specific outcomes (7-9), recovery of left ventricular function (10), incidence and risk factors for sudden cardiac death (11), and death while waiting for or after heart transplantation (12,13).

Against this background of collaboration, resources, and considerable effort, the rapid advances in evidence-based medical management available to adult patients with heart failure have not translated to evidence-based strategies for the pediatric DCM population. Despite early encouraging reports on the benefits of carvedilol as medical therapy in children with DCM, a multicenter, randomized-controlled study showed no significant improvement in heart failure outcomes compared with those of placebo (14). Indeed, a single-center study across 2 decades of changing medical therapy was unable to show sustained improvement in transplant-free survival for this population (15). More encouragingly, a recently published multisite, randomized double-blind placebo-controlled trial of ivabradine in children with DCM showed an improvement in secondary endpoints of left ventricular fractional shortening and end-systolic volume in the treatment group (16). Improved wait-list mortality with the advent of durable mechanical circulatory support options and improved survival with cardiac transplantation have been considered major advances of the past decade for this population (17-19). Recent consensus-based guidelines for the management of pediatric heart failure highlight this lack of pediatric-specific evidence for commonly used therapies, while providing a paradigm for consistent patient management (20).

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In this issue of the *Journal*, Singh et al. (21) examine outcomes for 1,953 children with DCM who were enrolled in the PCMR. Children who were diagnosed between 1990 and 1999 (early cohort) were more likely to die without heart transplantation than were children diagnosed between 2000 and 2009 (late cohort). Both cohorts had a similar proportion of children with idiopathic DCM, whereas the later cohort had a higher proportion of children with myocarditis and a lower proportion with

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neuromuscular disease. Rates of echocardiographic normalization and heart transplantation were similar between the 2 cohorts, but mortality without cardiac transplantation was higher in the early cohort. After controlling for the presence of heart failure symptoms at diagnosis, underlying etiology, left ventricular fractional shortening *z*-score, and variation in patient characteristics by treating center, children in the early cohort were 40% more likely to die than those in the later cohort. The difference in survival was not accounted for by any baseline characteristics in the study patients. Whereas it is possible that the era effect may have resulted by chance, the trend toward improved survival was consistent for each diagnostic category of DCM (familial, idiopathic, myocarditis, and neuromuscular) and achieved significance when all DCM types were combined.

This important and well-conducted study from the PCMR is thought-provoking for physicians involved in the care of children with DCM. The large multicenter cohort of more than 1,950 patients provides the power to detect even small differences in outcomes and is inclusive of patients with etiologies represented in clinical practice. It is sobering to reflect that if transplant-free survival has improved between eras, but rates of echocardiographic normalization have remained unchanged, then the additional survivors are those with persisting cardiac dysfunction. A median follow-up duration of <2 years in both cohorts represents a relatively short term of observation in this at-risk population. Normalization of left ventricular function is not completely protective against later deterioration and does not take into consideration abnormalities of diastolic function. Finally, as the number of centers contributing new cases to the PCMR has contracted in recent years, the improved survival in the later era may to some extent reflect current best practice heart failure management in large volume pediatric heart failure centers.

These results, while encouraging for pediatric heart failure physicians, raise the intriguing question of why has survival improved in the absence of evidence-based pharmacotherapy for chronic heart failure in children? Survival curves between the early and late era cohorts diverged early, and continued to diverge, suggesting improved management of both acute and chronic heart failure. There is no medical therapy that has been shown to improve survival in adult patients with decompensated heart failure. The use of early circulatory support, including ventricular assist devices, may well have contributed to improved immediate outcomes, yet the great majority of children who receive circulatory support for DCM are subsequently wait-listed for transplantation (22). In the longer-term, the use of adult-based heart failure therapies aimed at reversing neurohormonal activation may also have contributed to better survival.

One of the most complex interventions for chronic diseases, the multidisciplinary coordination of care, may also have contributed to the improvement in pediatric DCM outcomes across eras. Multidisciplinary care, including measures to improve nutritional status and medication adherence, with early treatment of heart failure exacerbations and intercurrent infections are important components of adult heart failure programs (23). Institution of multidisciplinary chronic heart failure services in adult centers has resulted in lower mortality and reduced hospital admissions (24,25). Similar care models have been instituted and assessed in cystic fibrosis, a more prevalent childhood chronic illness (26). Leadership and collaboration, patient and family involvement, transparency and accuracy of data, standardized improvement with evidence-based change ideas, improvement measurement, and benchmarking against other centers resulted in improved patient outcomes over the prior decade.

Quo vadis—where to from here? Future recommendations for pediatric heart failure research proposed by the National Heart, Blood, and Lung Institute include creation of new paradigms for pediatric heart failure, focusing research on molecular mechanisms relevant to pediatric heart failure, development of relevant surrogate endpoints, expansion of existing registries, and encouraging collaboration within the pediatric heart failure community (27). As we move into the next era of pediatric heart failure management, with strong outcome data from established registries and expert consensus-based guidelines for clinical management of pediatric heart failure, children with cardiomyopathy belong in specialized pediatric heart failure multidisciplinary services. The benefits include appropriate phenotyping, specialized metabolic and genetic diagnostic services, and access to advanced heart failure therapy, including transplantation if required. The less tangible benefits of enrollment in registries and trials of emerging therapies are also facilitated by specialized care. Multiple factors likely contributed to the observed difference in survival between eras in the study by Singh et al. (21), but each of these may well have contributed to better clinical care and therefore improved outcomes for this vulnerable population.

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REFERENCES

1. Cox GF, Sleeper LA, Lowe AM, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. Pediatrics 2006;118:1519–31.

2. Wilkinson JD, Landy DC, Colan SD, et al. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. Heart Fail Clin 2010;6:401–13, vii.

3. Alexander PM, Daubeney PE, Nugent AW, et al., for the National Australian Childhood Cardiomyopathy Study. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation 2013;128:2039–46.

4. Hsu DT, Lamour JM, Canter CE. Heart diseases leading to pediatric heart transplantation: cardiomyopathies and congenital heart diseases. In: Canter CE, Kirklin JK, editors. Pediatric Heart Transplantation. ISHLT Monograph Series 2. Addison, TX: International Society for Heart and Lung Transplantation, 2008:1–17.

5. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647–55.

6. Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003;348:1639–46.

7. Foerster SR, Canter CE, Cinar A, et al. Ventricular remodeling and survival are more favorable for myocarditis than for idiopathic dilated cardiomyopathy in childhood: an outcomes study from the Pediatric Cardiomyopathy Registry. Circ Heart Fail 2010;3:689–97.

8. Alvarez JA, Orav EJ, Wilkinson JD, et al., for the Pediatric Cardiomyopathy Registry Investigators. Competing risks for death and cardiac transplantation in children with dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. Circulation 2011;124:814–23.

9. Rusconi P, Wilkinson JD, Sleeper LA, et al., for the Pediatric Cardiomyopathy Registry Investigators. Differences in presentation and outcomes between children with familial dilated cardiomyopathy and children with idiopathic dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry study group. Circ Heart Fail 2017;10. pii:e002637.

10. Everitt MD, Sleeper LA, Lu M, et al., for the Pediatric Cardiomyopathy Registry Investigators. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy: results from the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol 2014;63:1405–13.

11. Pahl E, Sleeper LA, Canter CE, et al., for the Pediatric Cardiomyopathy Registry Investigators. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol 2012;59:607–15.

12. Singh TP, Sleeper LA, Lipshultz S, et al. Association of left ventricular dilation at listing for heart transplant with postlisting and early posttransplant mortality in children with dilated cardiomyopathy. Circ Heart Fail 2009;2:591–8.

13. Pietra BA, Kantor PF, Bartlett HL, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation 2012;126:1079–86.

14. Shaddy RE, Boucek MM, Hsu DT, et al., for the Pediatric Carvedilol Study Group. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007;298:1171–9.

15. Kantor PF, Abraham JR, Dipchand AI, Benson LN, Redington AN. The impact of changing medical therapy on transplantation-free survival in pediatric dilated cardiomyopathy. J Am Coll Cardiol 2010;55:1377–84.

16. Bonnet D, Berger F, Jokinen E, Kantor PF, Daubeney PEF. Ivabradine in children with dilated cardiomyopathy and symptomatic chronic heart failure. J Am Coll Cardiol 2017;70:1262–72.

17. Blume ED, Naftel DC, Bastardi HJ, et al., for the Pediatric Heart Transplant Study Investigators. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multiinstitutional study. Circulation 2006;113:2313–9.

18. Tsirka AE, Trinkaus K, Chen SC, et al. Improved outcomes of pediatric dilated cardiomyopathy with utilization of heart transplantation. J Am Coll Cardiol 2004;44:391–7.

19. Hsu DT, Canter CE. Dilated cardiomyopathy and heart failure in children. Heart Fail Clin 2010;6:415–32, vii.

20. Kirk R, Dipchand AI, Rosenthal DN, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. [Corrected]. J Heart Lung Transplant 2014;33:888–909.

21. Singh RK, Canter CE, Shi L, et al., for the Pediatric Cardiomyopathy Registry Investigators. Survival without cardiac transplantation among children with dilated cardiomyopathy. J Am Coll Cardiol 2017;70:2663–73.

22. Blume ED, Rosenthal DN, Rossano JW, et al., for the PediMACS Investigators. Outcomes of children implanted with ventricular assist devices in the United States: first analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS). J Heart Lung Transplant 2016;35:578–84.

23. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet 2017;390:400–14.

24. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44:810–9.

25. Sochalski J, Jaarsma T, Krumholz HM, et al. What works in chronic care management: the case of heart failure. Health Aff (Millwood) 2009;28:179–89.

26. Godfrey MM, Oliver BJ. Accelerating the rate of improvement in cystic fibrosis care: contributions and insights of the learning and leadership collaborative. BMJ Qual Saf 2014;23 Suppl 1:i23–32.

27. Burns KM, Gyrne BJ, Gelb BD, et al. New mechanistic and therapeutic targets for pediatric heart failure; report from a National Heart, Lung, and Blood Institute working group. Circulation 2014;130:79–86.

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