Pediatric Heart Transplant Society

PEDIATRIC HEART TRANSPLANTATION TODAY

PHTS NEWSLETTER

February 2024

Dr. Juan "Chuck" Alejos, Senior Editor
Dr. Neha Bansal, Junior Editor

PHTS GROWTH*

12,291	patients enrolled
12,728	total listings/ relistings entered
9,770	transplants entered
498	listings for 2023
404	transplants for 2023
23	listings for 2024
6	transplant for 2024

*as of February 1, 2024

New PHTS President and Vice President



President

Shriprasad Deshpande, MD
Children's National Health System



Vice President

Kevin Daly, MD
Boston Children's Hospital

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www.PHTSociety.org

A Message from the New President

Happy New Year to PHTS Friends!

Dear All,

Wishing you and your family a very Happy New Year!

As we look back on 2023, we are thankful for all the good things that have come to fruition. As we look forward to 2024, we are hopeful that the community grows stronger, and it continues to advance the primary mission of PHTS.

It is worthwhile to reiterate the mission of PHTS is ultimately to advance the science and treatment of children through the journey of heart transplantation. To do so, we have adopted the pathway of science and knowledge. In recent years, PHTS has increasingly adopted the role of being the voice of these children and their families. Over the last few years, the Society has rapidly grown in size, stature and scope as the premier academic society for pediatric heart transplantation. Our strategic vision has helped us achieve important milestones such as expanding work in Healthcare Disparities, in Quality Improvement initiatives, in Family Involvement and Standardizing Care. All of these initiatives have been led by various PHTS members donating enormous amount of their time and effort on a volunteer basis. We have consciously expanded the councils to be an appropriate reflection of our teams that we work with - truly multidisciplinary. Over the last 2 years, we have created more than 8-10 initiatives across these committees. Some of the since coming out of this work is already published or presented. This growth has been much needed and gratifying to see.

As we look forward to the next two years, here is my wish list!
First, we will work hard to converting this early enthusiasm for all of these initiatives into sustainable, consolidated gains. We will focus on adopting a strategy that will identify key areas within every initiative to work on in a deliberate way. This phase of consolidation will create a path for us to learn the best ways to work within the community that continues to move the needle forward but at the same time being conscientious about the impact it has on our teams and everyone at the front line. There will need to be continued effort to bring in more voices and more active participation from our Allied Health team members.

Here, therefore, is a call to each of the site PI to make sure that atleast 2 of their team members are actively participating in PHTS in one way or another. At the same time, we also want to make sure we are broadening our voice by bringing in centers from all over the world that are not yet a part of the Society.

Second, we want to think about strengthening the organization from structural and financial standpoint. The PHTS Foundation continues to do a thankless job of ensuring that PHTS is on sound footing. We will continue to seek ideas from all of you to make sure we create a robust, sustainable organization that can provide increasingly higher quality of data reposition, analysis , reports that will be beneficial to you. It is important that PHTS continues to be more than a data repository.

Lastly, as we continue to take care of some increasingly complex and sick children and their families, let us make sure we are also taking care of our team and team members. Keeping our own team healthy and well cared for should be the priority. Good work will then follow seamlessly !
However, these are my thoughts - the PHTS is your home - please share what your prioritizes are for PHTS. What would you like to see more or less of ? What should we focus on ? How can PHTS better serve you. Please let me know. I will do my best to represent your voice.

Sincerely,
Warm Regards,
Shri

Duchenne Muscular Dystrophy: Current Strategies, and What's On the Horizon

Cheryl Barton MSN, CPNP-PC, CPN; Jennifer A. Su, MD

Improvements in neuromuscular and pulmonary clinical management have increased the long-term survival of patients with Duchenne Muscular Dystrophy. With up to 50% of patients in some reports dying from cardiac related complications, cardiomyopathy has emerged as the leading cause of morbidity and mortality in this population [1-3]. This emphasizes the role that cardiac management plays in the overall care in this patient population. By early identification of myocardial changes, and initiation of medical therapy, cardiac specialists may delay the onset and slow the progression of cardiac related disease [1-2]. Here we summarize consensus guidelines that provide guidance for (1) the timing and testing of cardiac surveillance, and (2) current treatment strategies, including the management of advanced heart failure. Finally, we will discuss several revolutionary therapies that hold great promise for improving quality of life, and potentially as stepping-stones toward an eventual cure for DMD.

Surveillance

Early identification of cardiac disease, close monitoring of disease progression and initiation of medical therapy can positively influence the outcome of patients with DMD. Cardiac assessment should begin at the time of DMD diagnosis [1,3]. Evaluation includes a history of past and present disease, family history, clinical examination, EKG and non-invasive imaging [1,3]. Echocardiography is the primary modality used to detect and monitor LV dysfunction [3]. However, images can be limited by poor acoustic windows due to body habitus or the presence of scoliosis [1-3]. In this respect, cardiac MRI is a superior non-invasive imaging modality, more accurate than the echocardiogram for assessing for LV dysfunction and should be considered in patients whenever feasible to perform without anesthesia [1-2]. Birnkrant et. al, also report that cMRI can detect adverse cardiac remodeling before changes are seen in LV function. The extent of myocardial fibrosis is an independent predictor for cardiac arrhythmias, death, or need for transplant. However, cMRI may not be easily accessible due to cost, availability, or the patient's ability to tolerate the procedure. Regular cardiac follow-up is recommended, although guidelines for exact cadence of surveillance is variable. In 2017 the American Heart Association published recommendations for cardiac re-evaluation every 2 years until age 10, then at least annually [3]. The 2018 Care Duchenne Guidelines recommended closer follow-up, annually after diagnosis, because of the recognition that adverse myocardial changes occur before cardiac dysfunction [2].

Current Treatment Strategies

Guideline directed medical therapies for heart failure are commonly used in the care of patients with DMD. In the early stages of the disease, the goal of medical therapy is to delay the onset or progression of heart failure. Early initiation of medications may improve long-terms outcomes [2]. The consensus guidelines clearly define the use of GDMT in patients with HFrEF or with the presence of myocardial changes like LGE on cardiac MRI. In contrast, the use of medications in the absence of dysfunction is varied. ACE inhibition is currently considered the first line therapy for patients with DMD. Available data suggests that prophylactic initiation in patients with normal LV function may delay the progression of heart failure and is associated with higher survival and lower rates of heart failure hospitalizations [4]. The ACTION DMD Therapy Harmonization Protocol recommends that ACE inhibition may be considered pre-emptively at 10 years of age [4]. The DMD Care Considerations describes that the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist slows the decline in LV function after 2 years. Similarly, the AHA guidelines and the ACTION DMD Therapy Harmonization Protocol propose starting MRA therapy when there is evidence of LGE on CMRI, when the LVEF is reduced, or at age 12 if CMRI is not available. DMD Care Considerations and AHA guidelines both recommend beta blockade for DMD patients with reduced systolic dysfunction [1, 3]. It is also reasonable to consider beta blocker in a patient with continued LV dysfunction or elevated heart rates, although it remains uncertain whether sympathetic blunting will affect long-term cardiac outcome [2]. Typically, in patients with severe heart failure, an angiotensin receptor/neprilysin inhibitor has been shown improve heart function. The use of sacubitril/valsartan in patients with DMD has not been studied although extrapolating data from the non-DMD population suggests that patients may benefit [1].

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The management of the DMD patient in severe heart failure include guidance for AICD placement, ventricular assist device, heart transplant, and palliative care. Patients with DMD are at risk for arrhythmia including ventricular tachycardia and atrial fibrillation. Specific benefit for AICD placement as primary prevention in this particular group has not been established, but AICD implantation in patients with LVEF <35% is reasonable on the basis of current adult heart failure guidelines [1]. Heart transplantation is not typically considered a treatment option in this population due to the underlying degenerative and progressive nature of the disease. However, in patients whom maximal medical management has failed (and for whom a heart transplant is not an option), left ventricular assist device may be considered as destination therapy. Destination therapy with LVAD support in this population has been performed more frequently in adult than in pediatric patients, and numerous additional factors must be addressed. A deep understanding of risks and benefits of LVAD support, as well as complex discussions with regards to potential complications, quality of life, psychosocial support, and end of life issues should be held before moving forward [1-2].

New & Emerging Therapies

In recent years, several revolutionary dystrophin restoration strategies have been reported [5-7]. Of these targeted therapies, exon skipping agents are currently most prominent. These agents work by targeting specific regions of the dystrophin gene, excising the problematic exon segment, and linking the two remaining functional ends together [6]. This process results in a truncated version of the dystrophin gene that is less functional than normal type, but still useable. Importantly, exon skipping is not a cure for DMD, but rather partial restoration with production of a truncated dystrophin protein. Further, not all DMD-causing mutations are treatable with exon skipping approaches – current exon skipping therapies have the potential to help an estimated 30-60% of patients [6]. Most clinical trials have focused on problematic "hot-spots," which are between DMD exons 45-55. Since 2016, the FDA has approved 4 exon skipping therapies which are administered via weekly intravenous infusions. These are casimersen (Amondys 45), eteplirsen (Exondys 51), golodirsen (Vyvondys 53), vitolarsen (Viltepso). All have been generally well-tolerated with side effects typically including headaches, flu-like and inflammatory symptoms [6].

Ongoing clinical trials exploring gene replacement therapy using a non-pathogenic viral vector such as adeno-associated virus (AAV) have shown tremendous promise, with early results demonstrating durable clinical improvements in creatine kinase levels and ambulatory assessments [5]. This strategy been shown to prevent progression of cardiac pathology in animal models [8]. Interestingly, AAV is the vector of choice due to its strong skeletal and cardiac muscle tropism, but only has a maximum capacity of 4.8 kb and so cannot deliver the full-length DMD cDNA (~11.5 kb). Thus, micro-dystrophin transgenes (lacking non-essential internal domains) have been developed. Currently 5 different combinations of micro-dystrophin and AAV serotypes are in clinical trials [7]. There have been several treatment-related serious adverse events reported, including myocarditis, muscle weakness, acute kidney injury, transaminitis, and other immune reactions. Additionally, several deaths have also been reported in recipients of high-dose AAV therapy, raising major safety concerns. Aside from safety issues associated with high-dose AAV, as many as 40% of humans are already positive for anti-AAV antibodies because of natural exposure, meaning that they are effectively immunized against the vector itself. Immune reactivity is a key challenge for application of AAV-derived vectors in patients with DMD and pairing with concomitant immunomodulatory strategies is an active area of exploration.

Gene editing with CRISPR/Cas9-mediated techniques have been widely studied in DMD animal models. This remains an area of active research, with numerous trials ongoing in preclinical phase. Multiple CRISPR/Cas9-based strategies have been proposed for treatment of DMD, but low efficiency remains a key challenge for genome editing. Most CRISPR/Cas9 therapies for DMD require AAV vectors for delivery of the gene editing apparatus and are thus subject to the limitations of these delivery vectors.

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Cell therapy using allogenic cardiosphere-derived cell (CDC) has been developed to treat various conditions including cardiomyopathy related to DMD and is undergoing clinical trials evaluating safety and efficacy. The Halt Cardiomyopathy Progression (HOPE) clinical trials are evaluating CAP-1002, which is a CDC consisting of progenitor or precursor healthy donor heart cells. CAP-1002 secretes extracellular vesicles known as exosomes that can modulate the immune system, possess antifibrotic properties and stimulate cellular regeneration. Unique to the study are endpoints specifically evaluating cardiac outcomes in addition to the progression of skeletal muscle myopathy. Phase II of the trial showed improvement in cardiac function and structure and slowed deterioration of upper limb function, and the phase III study (HOPE-3) is in active recruitment [9].

The illness trajectory of the Duchenne muscular disease is well documented with cardiomyopathy as one of the leading causes of morbidity and mortality. Close surveillance and prompt initiation of GDMT are initial steps in slowing the onset and progression of heart disease. The landscape for clinical research of DMD therapy has shifted dramatically in the past few years, with much scrutiny now on various strategies to restore Dystrophin. These emerging therapies, though still hampered with each their own challenges, bring hope for an eventual cure in the not-so-distant future. It remains to be seen whether (and if so, how much) the myocardium will benefit from Dystrophin restoration strategies. Undoubtedly, even extension of skeletal muscle strength alone will expand therapeutic options for DMD patients with end-stage cardiomyopathy, making them more likely candidates for therapies that are not routinely considered at the present time. Expanded treatment options can potentially ameliorate the impact of cardiomyopathy and offer the possibility for increased longevity and improved quality of life.

References:

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New PHTS Roles

Nursing and Allied Health Representatives



Diane Long, DNP, CPNP-AC/PC



Catriona Drake, BSc Hons.

Foundation Member



Chesney Castleberry, MD, MSCI

PHTS Research



Manuscript accepted for publication in JHLT!

Madeleine Townsend, MD

Statin Use in Pediatric Heart Transplantation Recipients in the Current Era

Enduring Hearts
HEALTHY KIDS • STRONGER HEARTS • LONGER LIVES

New PHTS Live! Panel

To the PHTS community. As many of you already know, Shri has passed the PHTS Live baton to the three of us. We want to acknowledge him for fostering this learning environment and setting such high standards, appreciate you all for bearing with us as we find our groove, and thank you all in advance for agreeing to help lead these important discussions. Look out for an email for our first 2024 session in the coming weeks, and several other important topics being planned over the next few months!

Warm Regards,
Chuck, Lynsey, and Manu





Upcoming Topics

Wednesday, February 14, 2024
Sinusoids or Bust: Transplantation in PA-IVS
Dr. Anna Joong
Dr. Shaan Amdani

Wednesday, March 6, 2024
Breaking the DSA Barrier: Daratumumab in Pediatric Heart Transplantation
Dr. Caitlin Milligan
Dr. Joey Spinner
Dr. Jon Kobashigawa

April 2024
PHTS Live at ISHLT

PHTS at ISHLT 2024

Abstracts Accepted to ISHLT 2024



Jennifer Conway, MD

Oral Presentation

Impact of Primary Graft Failure: Analysis of the PHTS Database



Joseph Atallah, MD

Presentation

Heart Transplantation for Malignant Arrhythmia: Indications and Outcomes



2023 Vanguard Center of Excellence Award Recipients

The PHTS VANGUARD Award was established to recognize the dedication and commitment of the all the team members at a participating PHTS Center that ultimately contribute to a Center's success. This award will recognize individual Centers for their outstanding contribution to the Pediatric Heart Transplant Society Registry.

- Arkansas Children's Hospital
- University of California, San Francisco-Benioff Children's Hospital
- Cleveland Clinic Children's
- Cincinnati Children's Hospital Medical Center
- Nationwide Children's Hospital
- Cardinal Glennon Children's Medical Center
- Children's Hospital of Los Angeles
- Children's Hospital of Wisconsin
- University of Texas, Children's Medical Center
- Children's Mercy Hospital and Clinics
- Children's National Health System
- The Children's Hospital of Philadelphia
- Columbia University – Morgan Stanley Children's Hospital of New York Presbyterian
- Children's Healthcare of Atlanta
- Freeman Hospital, Newcastle upon Tyne
- University of Florida, Shands Hospital
- Hospital for Sick Children
- Joe Dimaggio Children's Hospital
- Le Bonheur Children's Hospital
- Levine Children's Hospital- Atrium Health
- Norton Children's Hospital
- University of Minnesota Masonic Children's Hospital
- Children's Hospital at Montefiore
- Mount Sinai Medical Center
- Nemours Cardiac Center- Children's Hospital and Medical Center
- Ochsner Hospital for Children
- Phoenix Children's Hospital
- UC San Diego, Rady Children's Hospital
- Seattle Children's Hospital
- St. Louis Children's Hospital
- Heart Institute (InCor) University of São Paulo Medical School
- Lucile Packard Children's Hospital at Stanford
- Texas Children's Hospital
- Dell Children's Medical Center of Central Texas
- Children's of Alabama
- Children's Hospital Colorado
- University of Iowa Children's Hospital
- UNC Children's Hospital
- University of Alberta
- Johns Hopkins All Children's Hospital
- University of Virginia Medical Center
- Monroe Carell Jr. Children's Hospital at Vanderbilt

Information Corner

Job Postings

Heart Transplant Position in Nashville

Monroe Carell Jr. Children's Hospital at Vanderbilt in Nashville, Tennessee is recruiting a pediatric heart failure/transplant cardiologist to join our growing program. Applicants should have a formal 4th year of fellowship training in pediatric heart failure, heart transplantation, and mechanical circulatory support or relevant clinical experience.

Interested applicants should send a brief cover letter and current CV to Dr. David Bearl (david.w.bearl@vumc.org).

Faculty Position at Children's Healthcare of Atlanta and Emory University

The division of Pediatric Cardiology at Children's Healthcare of Atlanta (CHOA) and Emory University School of Medicine is seeking a pediatric heart failure and transplant cardiologist to join our faculty and Advanced Cardiac Therapies team. Applicants should have formal training in pediatric heart failure, cardiomyopathies, mechanical circulatory support, and heart transplantation and must be board certified/eligible in pediatric cardiology. Applicants currently in advanced training are welcome to apply.

Applicants should submit a letter of interest and curriculum vitae to: Chad Mao, MD, Medical Director of Advanced Cardiac Therapies at maocha@kidsheart.com

Children's Medical Center of Dallas HFTX Attending

University of Texas Southwestern Medical Center at Dallas and Children's Medical Center of Dallas are delighted to be able to offer a faculty position (Assistant Professor or Associate Professor level) in Heart Failure, Mechanical Circulatory Support and Transplantation. The Heart Failure, MCS and transplant team has six full time heart failure and transplant physicians, nine heart failure and transplant coordinators, three advanced practice practitioners, as well as dedicated pharmacy, social work, child-life and additional support staff. The surgical program is under the direction of Jake Jaquiss, Ryan Davies is the surgical director of ventricular assist device program and transplant program. There is a total of four full time congenital heart surgeons with a strong commitment to expanding further the heart failure, transplant and ventricular assist device program.

For further information or to apply please email Dr Ryan Butts ryan.butts@utsouthwestern.edu

Advanced Practice Provider, Pediatric Heart Transplantation at Northwell Health

We are seeking an Advanced Practice Provider to join our transplant team as we build a world class pediatric heart transplant program. The unique opportunity to build a heart transplant program for the children of Long Island and surrounding areas should not be missed. The program is being built around the pillars of clinical excellence, compassionate patient care, and a culture of teamwork and collaboration.

Interested applicants please send CV to Jake Kleinmahon, MD, Medical Director of Pediatric Heart Transplant and Heart Failure, jkleinmahon@northwell.edu

Arkansas Children's Hospital - Pediatric Heart Transplant Physician

Arkansas Children's and the University of Arkansas for Medical Sciences (UAMS) in Little Rock, Arkansas seek a full-time BE/BC Heart Failure/Transplant Cardiologist for a growing transplant program.

Contact: Dr. Paul Seib, Section Chief of Cardiology - SeibPaulM@uams.edu