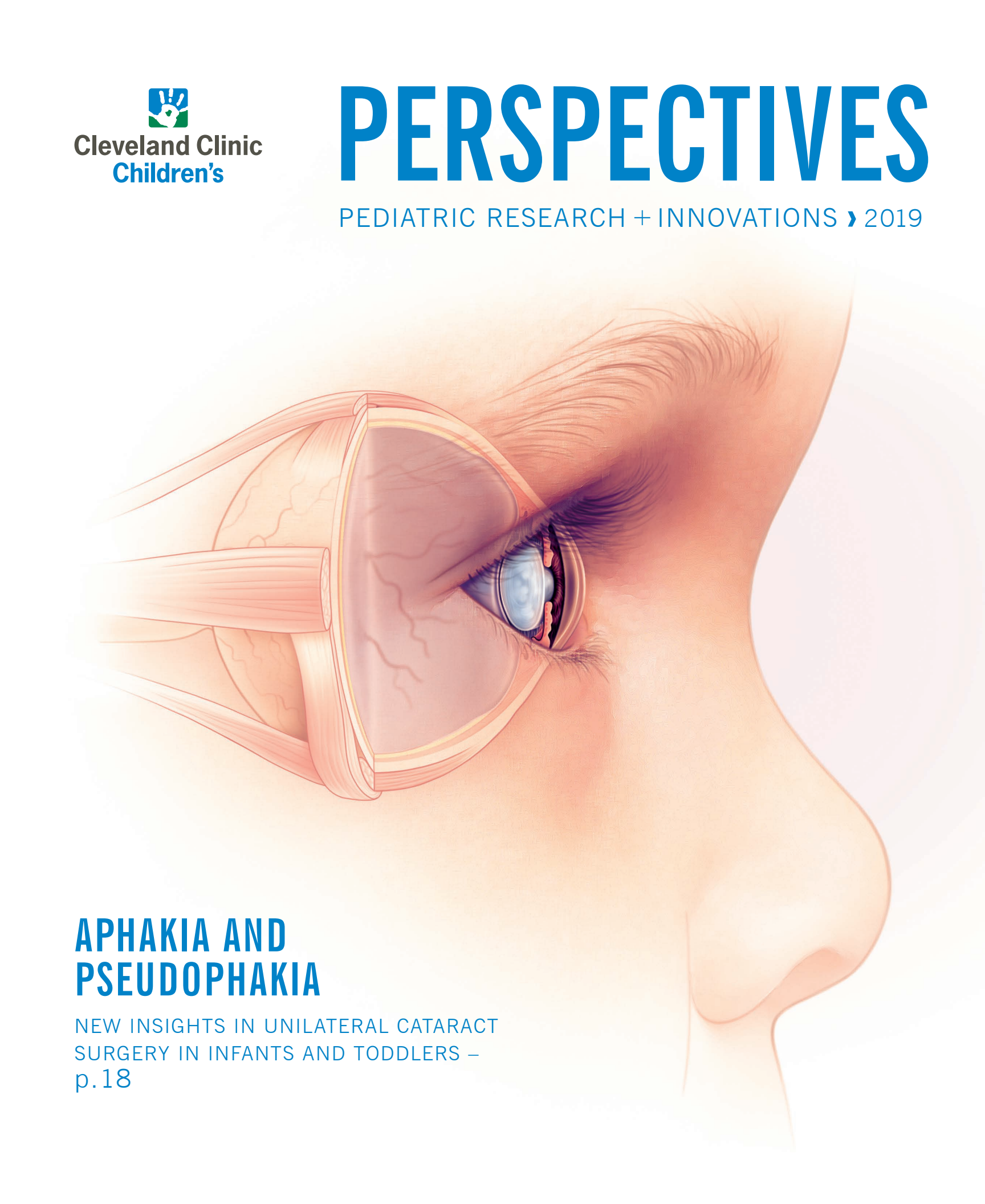
Cleveland Clinic Children's

PERSPECTIVES

PEDIATRIC RESEARCH + INNOVATIONS › 2019



APHAKIA AND PSEUDOPHAKIA

NEW INSIGHTS IN UNILATERAL CATARACT SURGERY IN INFANTS AND TODDLERS –
p.18

Cleveland Clinic Children's provides comprehensive medical, surgical and rehabilitative care for infants, children and adolescents. Our more than 300 pediatric physicians accommodate more than 850,000 outpatient visits and nearly 14,000 inpatient admissions per year at Cleveland Clinic Children's hospital and outpatient facilities on our main campus, at the Cleveland Clinic Children's Hospital for Rehabilitation campus, and at regional hospitals, family health centers and other locations throughout Ohio. Cleveland Clinic Children's offers integrated care and access to cutting-edge research across a variety of pediatric medical and surgical specialties. It is backed by the full resources of Cleveland Clinic, a nonprofit academic medical center that was named a top U.S. hospital in *U.S. News & World Report*'s "Best Hospitals" rankings for 2019-2020, and was named the top hospital in heart care for the 25th consecutive year.

INSIDE

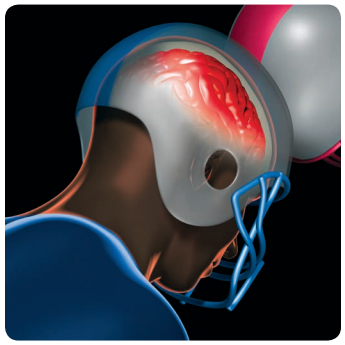


IMAGE OF THE ISSUE ❯

Ambulatory pharmacy services were moved to the newly renovated Cleveland Clinic Children's Outpatient Center in 2018. The infusion pharmacy is equipped with an APOTECA™ robot, offering added safety to customized pediatric chemotherapy doses.

A CONVERSATION WITH KAREN MURRAY, MD

In July, Karen Murray, MD, joined Cleveland Clinic as Chair of the Pediatric Institute, Physician-in-Chief of Cleveland Clinic Children's and President of Cleveland Clinic Children's Hospital for Rehabilitation.

Dr. Murray joins Cleveland Clinic Children's from the University of Washington School of Medicine in Seattle, where she served as Vice Chair of Clinical Affairs for the Department of Pediatrics and Professor and Chief of the Division of Gastroenterology and Hepatology. Dr. Murray held several leadership positions at Seattle Children's Research Institute, including serving on the Steering Committee of the Center for Clinical and Translational Research, and as co-leader for research recruitment for Seattle Children's Strategic Development. Most recently, she was Interim Chair of the Department of Pediatrics and Pediatrician-in-Chief of Seattle Children's Hospital.

In her new role, Dr. Murray will head a group of more than 300 pediatric specialists who are leaders in research for hematology and oncology, nephrology, orthopaedics, neurologigy and cardiac diseases. Cleveland Clinic Children's is consistently rated among the "Best Children's Hospitals."

In this Q&A, Dr. Murray shares her research interests and how she balances academic pursuits with her clinical practice.

You were instrumental in revolutionizing the treatment of hepatitis C virus (HCV) in children and teens. Can you tell us more about that research?

There are a number of highly effective treatment regimens available to adults with HCV; however, the treatment options for children and adolescents do not reflect these medical advances. We conducted several trials of the direct-acting antivirals ledipasvir and sofosbuvir for the treatment of chronic HCV infection in children. These two new medications were approved for use in adults about six years ago. They have no significant adverse effects and virtually eradicate the virus, with sustained virologic response after 12 weeks of therapy (SVR12) reached in 97%-100% of patients, depending on genotype.[1-3] In 2017, the medications were approved by the FDA for use in pediatric patients with genotype 1, 4, 5 or 6 chronic HCV infections, who are 12 years of age or older and weigh more than 35 kg. Very recently, we published trials that extended the use of these medications to children aged 3 to 12 years, which found similar SVR12 rates.[4,5] Before these medications were available, we relied on interferon-based therapies, which were less effective and poorly tolerated. These drugs dramatically change treatment outcomes for our patients.

What do you consider to be the most exciting areas of opportunity in pediatrics in the next 5-10 years?

Innovations in therapeutics — I think we are on the precipice of changes that can really benefit children, such as immunotherapies, gene therapy and the creation of medications to reverse physiological challenges. Take muscular dystrophy, for example — children suffer and ultimately succumb to many such neuromuscular diseases. With the new therapies, we can replace missing proteins, prevent further muscle degeneration, and in turn reduce suffering and perhaps even reverse the course of the disease.

How can physicians optimize their research time?

As physicians, we face a variety of demands on our time and energy, compounded by the needs for high utilization of our clinics, patient access, and of course quality and safety, while sometimes practicing with suboptimal support. In the academic world, the biggest driver of burnout is when providers are unable to spend time in activities they value the most due to inefficiencies or administrative tasks that consume time. I want to ensure that, culturally and operationally, physicians have the ability to optimize the time spent in the various aspects of their professional lives, and can protect their nonclinical time as intentionally as they do their focused clinical time. At Cleveland Clinic Children's, I hope to support academic productivity, safeguarding administrative, research and teaching time,

KAREN MURRAY, M.D.

and encourage a culture in which these activities are valued and celebrated as much as excellence in clinical care.

What is your vision for Cleveland Clinic Children's?

Cleveland Clinic Children's is an amazingly dedicated group of medical providers at a world-class institution. There's more going on than the world knows about. My vision for Cleveland Clinic Children's is that we continue to provide and improve upon the world-class medicine and innovation that are already occurring here while working to expand academic pursuits and enhance our national reputation.

Will you continue to provide patient care in your new role?

Yes. I love practicing clinical medicine; I love developing relationships with my patients and their families and doing what I can to better their lives. Additionally, I think being active in clinical care keeps me grounded and provides insights into the operational side of healthcare and the levels of support our physicians need.

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PARENT TRAINING AS AN EVIDENCE-BASED TREATMENT FOR CHILDREN WITH AUTISM SPECTRUM DISORDER

BY CYNTHIA JOHNSON, PHD

Occupational therapists evaluate fine motor, play, sensory processing and self-care skills in children with autism spectrum disorder. They aim to maximize functional independence by teaching adaptive techniques and using adaptive equipment.


As an adjunct to medication, the parent training program REDUCED disruptive behaviors by
50%–60%
in children with autism spectrum disorder.

PARENT TRAINING AS AN EVIDENCE-BASED TREATMENT FOR CHILDREN WITH AUTISM SPECTRUM DISORDER

BY CYNTHIA JOHNSON, PHD

TAKEAWAYS

Parents can be effective agents for changing problem behaviors in children with autism spectrum disorder.

Randomized trials prove the feasibility of parent training programs, which teach specific tools for managing specific problem behaviors.

Telehealth platforms may help expand access to these interventions.

Children with autism spectrum disorder often have co-occurring behavioral and emotional problems, such as tantrums, aggression, self-injury, hyperactivity, noncompliance and problematic feeding, which can add to parental stress and family burden. Recent studies test new applications and delivery methods, and reflect the feasibility and efficacy of parent training (PT) programs in changing specific problem behaviors.

Psychosocial interventions have been used in the treatment of autism spectrum disorder (ASD) for nearly two decades. Despite the development of several comprehensive programs, there was a dearth of randomized clinical trials (RCTs), with the first identified as recently as 2005. Subsequently, an National Institutes of Health (NIH)-empaneled group identified the research needs in the field, which included cost-effective, time-limited, manual treatments.[1] PT is a fitting model of an intervention that incorporates these parameters — and one that capitalizes on the central role parents play in the lives of young children. PT programs, which are frequently based on the principles of Applied Behavior Analysis, provide specific techniques for behavioral management in children with ASD.

Several PT programs for co-occurring issues in ASD have since been developed and tested in RCTs. One study tested a behaviorally based PT program specifically targeting the ubiquitous disruptive behaviors observed in 50%-60% of children with ASD as an adjunctive treatment to medication.[2] Families receiving combined therapy (i.e., PT plus risperidone for the child) saw greater decreases in challenging behaviors than those with children who received risperidone alone.

A subsequent NIH-funded study evaluated this 11-session, individually delivered, structured program as a stand-alone intervention in a large, multisite RCT. The PT program was compared with a parent education program in which parents learned helpful information about ASD that did not include any behavioral strategies for disruptive behaviors. The PT program was found to be superior to the parent education program in decreasing disruptive behaviors in 3- to 7-year-olds with ASD and improving self-help skills.[3,4] At the time this study was completed in 2015, it was the largest psychosocial trial in ASD, with a sample size of 180 participants. This intervention manual is now available and has been implemented in many clinical programs.[5]

In another, smaller, NIH-funded RCT, a PT program specifically targeting sleep disturbances in young children with ASD was compared with a parent education program.[6] The sleep PT program consisted of five individual clinic sessions, which resulted in significantly reduced bedtime and sleep problems among those children in contrast to the children whose parents received parent education. Improvements in daytime behaviors were also observed. We are currently testing this PT program for sleep in a larger RCT at Cleveland

LEFT: Parent training capitalizes on the central role parents play in the lives of their children.

Clinic Children's, delivered through Cleveland Clinic Express Care Online. The study, which is funded by the Department of Defense, plans to enroll 90 participants aged 2-7 years over the next three years.

Given the success of these PT programs, we developed a PT program focusing only on mealtime and feeding problems. After we conducted a small pilot, an initial multisite RCT was conducted with funding from the NIH. Participants who completed the PT-feeding program reported significant reductions in mealtime and feeding problems compared with the wait-listed control group.[7]

Collectively, these training programs for parents of children with ASD demonstrate that parents can successfully learn and implement skills and strategies to mediate changes in their children's behavior. Parent satisfaction ratings for all of these studies were high. Future studies will test additional PT programs aimed at changing specific behaviors, as well as innovative ways of delivering the training sessions to reach a wider community of families.

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USE OF AUTOMATED EXTERNAL DEFIBRILLATORS IN PEDIATRIC POPULATION REMAINS LOW

BY PETER AZIZ, MD

TAKEAWAYS

Automated external defibrillators (AEDs) remain underutilized despite studies indicating they improve survival from pediatric cardiac arrest.

Child age is the most powerful predictor of AED application.

Public education about the safety and importance of AEDs is desperately needed.

The emotional burden exacted by sudden cardiac death in the young weighs not only on the grieving family members, but also on the community at large. These tragic cases are fortunately rare, and predicting those young patients who are at risk for sudden death is difficult. The survival rate for pediatric out-of-hospital cardiac arrest is dismal at less than 10%, with no significant improvement in the recent past.[1]

The use of automated external defibrillators (AEDs) improves overall survival and neurological outcomes in pediatric patients suffering from cardiac arrest.[2] For this reason, AED use is recommended in the 2010 American Heart Association (AHA) guidelines for all pediatric victims of a sudden cardiac arrest — regardless of age.[3] The 2010 guidelines reflect a change from the 2005 recommendations, in that they call for the application of an AED in children with or without a pediatric-specific AED. However, the use of AEDs in the pediatric population remains low and likely contributes to poor outcomes in young victims.

Child age is the most powerful predictor of AED application

Using prospectively collected data from the Cardiac Arrest Registry to Enhance Survival (CARES),[4] we identified 1,398 pediatric patients (1-18 years of age) who had an out-of-hospital cardiac arrest.[5] AEDs were applied to only 28% of these patients prior to the arrival of emergency medical services (EMS). Univariate analysis identified demographic disparities in AED application, including differences between white versus African American patients, the racial composition of the neighborhood and neighborhood levels of income and education. These disparities dissipated in multivariate analysis.

Looking at patient characteristics in detail, we found that the age of the child was the most powerful predictor of AED application, regardless of race, sex, location or neighborhood characteristics. Older patients (12-18 years of age) were 1.4 times more likely to have AEDs applied than younger patients (2-11 years of age). As predicted, patients who had a witnessed cardiac arrest in public venues were more likely to have AEDs applied prior to the arrival of EMS. Additionally, AEDs were more likely to be applied for an arrest presumed to be of cardiac etiology compared with respiratory events, such as drowning.

Lack of public awareness

This is the largest study to examine the presence of disparities in AED application by first responders in the pediatric population since the AHA guidelines were revised in 2010. The low AED application rate of 28% is likely multifactorial. We hypothesize that the main driver of AED underutilization is lack of public awareness of their safety and utility. Additional factors include limited access, training and low

LEFT: Current resuscitation guidelines recommend the use of AED in cases of out-of-hospital-cardiac arrest in all pediatric individuals regardless of age or the presence of a pediatric-specific AED or attenuator system.

confidence in defibrillator use. Arrests in the pediatric age group are also commonly assumed to be respiratory. AEDs, therefore, are not considered useful. This is certainly at odds with AHA recommendations.

Although the medical community and pediatric providers are aware that AEDs are "safe" to use in the pediatric patient, many responders fear causing harm by using "adult" devices on smaller patients. Ideally, this study — and others like it — will highlight the importance of early and universal AED use in pediatric patients. Public health action is desperately needed to raise awareness and educate the public about the importance and safety of AED use in children of all ages. Additionally, AEDs need to be made readily available in public and residential locations, as the use of AEDs may have a significant impact on survival.

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ARCH OBSTRUCTION FOLLOWING THE NORWOOD OPERATION: NEW INSIGHTS INTO OLD PROBLEMS MAY CHANGE LONG-TERM OUTCOMES

BY TARA KARAMLOU, MD, MSC, AND HANI NAJM, MD, MSC

TAKEAWAYS

Arch obstruction is common in the early phase following the Norwood operation, and surgical techniques vary widely at each institution.

A new technique called interdigitation decreases the risk of recoarctation.

Arch obstruction following the Norwood operation is an important problem that increases the risk of adverse short- and long-term outcomes.[1,2] In fact, despite the relatively long surgical experience, recoarctation in neonates following arch repairs is a persistent and unsolved problem.

Measuring the true impact and prevalence of arch obstruction is challenging for a number of reasons, including:

- There are no standardized definitions for "important obstruction."
- Centers assess arch status using varying imaging and/or non-invasive modalities.
- A significant number of babies die without known cause during the interstage period between the Norwood operation and stage 2 palliation — a window of time in which arch obstruction peaks.

First described by Norwood and colleagues in 1981, the Norwood operation is the first in a series of three operations that are used as standard therapy for neonates with hypoplastic left heart syndrome.[3] One of the major components of this procedure is reconstruction of the hypoplastic arch with amalgamation to the pulmonary artery. Despite multiple iterative described techniques to reduce the prevalence of recoarctation following Norwood, the reported prevalence was still 17% in the NHLBI-Pediatric Heart Network-sponsored Single Ventricle Reconstruction (SVR) trial.[4] Single-institutional studies have reported both much lower (0%) and much higher (46%) rates depending on the institution and the morphology of the patient population. Treatment for arch obstruction in this group is usually percutaneous balloon angioplasty; however, the efficacy of this procedure varies. More important, the timing of deployment may critically influence the degree of physiologic recovery of the univentricular circulation — and therefore the eventual candidacy for Fontan completion.

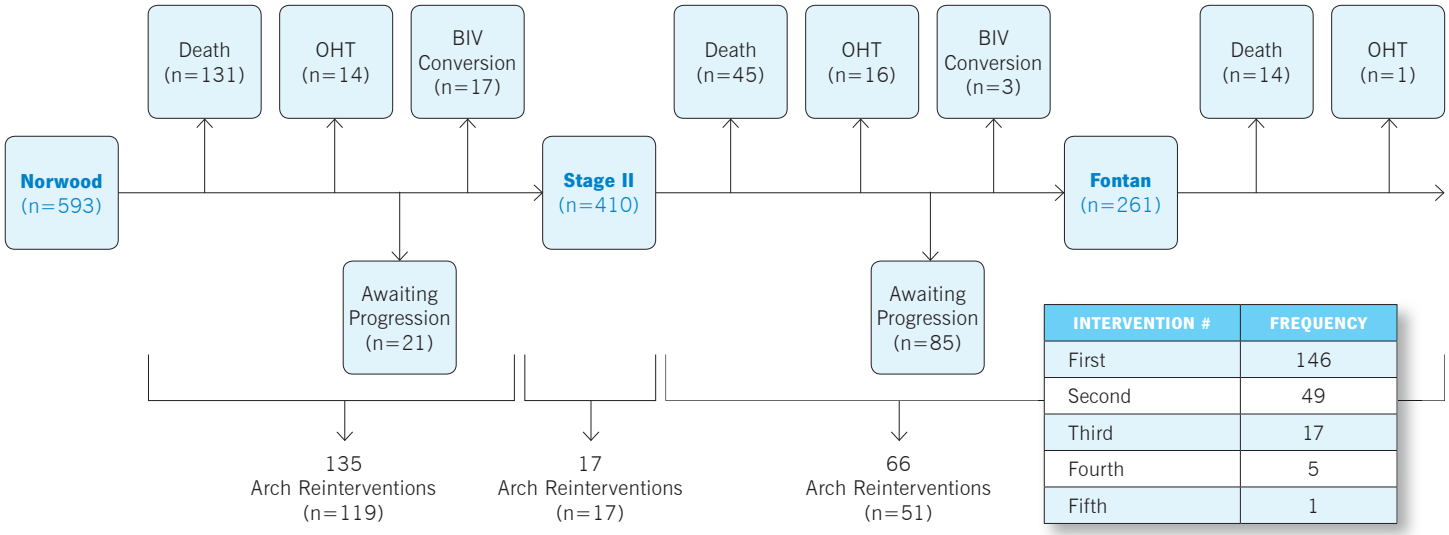
Recoarctation common in early phase following Norwood procedure

We investigated the determinants and time-related outcomes of arch obstruction in a prospective multi-institutional cohort of 593 neonates from 27 participating institutions, all of whom underwent the Norwood operation between 2005 and 2017 as part of the critical Left Ventricular Outflow Tract Obstruction study conducted by the Congenital Heart Surgeons' Society. Because many of these patients undergo repeated interventions to address coarctation, we used complex statistical models including modulated renewal analysis and multiphase parametric modeling to elucidate the relationships between candidate risk factors and endpoints over time.

Concordant with the SVR trial, recoarctation was common in the early phase following Norwood (with a peak hazard at three months), with 146 neonates (26%) undergoing either catheter-based intervention or surgical reintervention. Unfortunately, 49 of these patients required a second intervention and 17 required a third

LEFT: Tara Karamlou, MD

Events among participants following Norwood procedure



INTERVENTION #	FREQUENCY
First	146
Second	49
Third	17
Fourth	5
Fifth	1

reintervention. Although catheter-based therapy was most widely used, surgical intervention was more definitive at mitigating the risk of recoarctation.

Surgical techniques for distal aortic anastomosis: A benefit from interdigitation

Institutional practice was highly variable. The vast majority of surgeons used a medial incision on the undersurface of the arch with patch augmentation. Complete coarctectomy was used in 170 patients, with an end-to-side or end-to-end anastomosis concomitant with medial incision. The complete removal of ductal tissue is widely believed to be necessary to prevent later ductal constriction thought to be operational in recoarctation. A comparably new technique, interdigitation — used most commonly at two institutions — significantly decreased the risk of recoarctation (14%) compared with other distal arch reconstruction techniques (26%).[5,6] This technique involves medial incisions in the ascending hypoplastic aorta, complete coarctectomy to remove all visible ductal tissue, and two longitudinal incisions in the anterior and posterior walls of the descending aorta. An extended end-to-end anastomosis is then performed, which increases the effective orifice of the distal neoaortic anastomosis and maximizes the contribution of native tissue.

Interestingly, we did not find an association between the shunt type (i.e., modified Blalock-Taussig shunt or right-ventricle-to-pulmonary artery [RV-PA] conduit) and outcomes. We hypothesized that, owing to the relative fragility of the aortopulmonary shunt compared with the RV-PA conduit, the former group would have decreased physiologic tolerance for arch obstruction and higher mortality. This relationship and rationale has been intimated in an ad hoc analysis of the SVR trial data.[7]

Implications and inferences: Where do we go from here?

A reproducible technique for arch reconstruction in the Norwood operation seems to decrease the prevalence of recoarctation. This technique can be extrapolated to other forms of aortic hypoplasia, and may pay similar dividends to reduce recoarctation following neonatal repair. Although our study did not find an association with mortality, physiologic correlates such as systemic right ventricular dysfunction and increased grade of tricuspid valve regurgitation were associated with arch intervention, suggesting that the increased afterload will have deleterious long-term consequences on the durability of the univentricular circulation. Moreover, arch reintervention to relieve arch obstruction was common in this cohort — a proactive strategy that also may mitigate mortality risk.

Surveillance and transparency in the reporting of Norwood outcomes beyond the early phase are paramount to understand the

efficacy, safety and risks of implementing new therapies. These initiatives are being championed by multiple collaboratives in the congenital heart community, including the National Pediatric Cardiology Quality Improvement Collaborative and Children's Neurodevelopmental Outcomes Collaborative — Cleveland Clinic Children's actively participates in both. Ultimately, it is only through such thoughtful and unified approaches that we will learn the potential wisdom of our [r]evolutionary steps.

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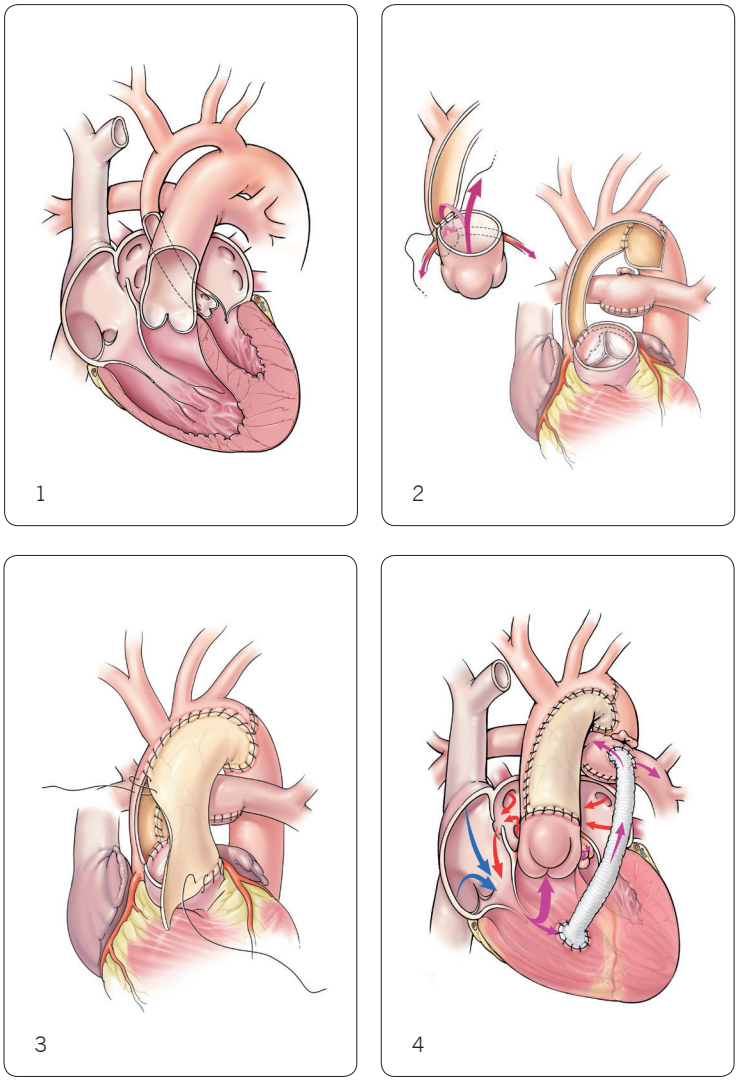

Illustrations: J. Pangrace, ©Cleveland Clinic Foundation

ABOVE

(1) Characteristic anatomy for hypoplastic left heart syndrome. Note diminutive ascending aorta and left ventricle. The systemic circulation is supported by the patent and very large ductus arteriosus.

(2) Arch reconstruction in the Norwood operation involves a long incision on the undersurface of the aortic arch and mobilization of the descending aorta to allow an end-to-side anastomosis to the posterior wall of the ascending aorta. The pulmonary artery has been amalgamated to the ascending aorta.

(3) The aortic arch augmentation is completed using a homograft patch that covers the anterior surface of the amalgamated aorta and pulmonary artery.

(4) Completed repair, depicting the arch reconstruction and the right ventricle-to-pulmonary artery conduit. The colored arrows demonstrate the flow of deoxygenated blood (blue arrows) through the right ventricle, which then mixes with oxygenated blood (red arrows) coming from the pulmonary veins and then through the atrial septum. The admixture of blood is ejected into the right ventricle through the pulmonary artery conduit to the body.

INHERITED BONE MARROW FAILURE SYNDROMES AS EXPERIMENTS OF NATURE FOR BLOOD DISEASES

BY SETH J. COREY, MD, MPH

TAKEAWAYS

Evidence regarding the genetic pathways involved in Shwachman-Diamond syndrome and severe congenital neutropenia is emerging.

As we learn more, we hope to be able to identify patients at highest risk and intervene before acute myeloid leukemia develops.

Cancer is a disease related to the acquisition of somatic mutations; it is a disease of aging. So, why do children develop cancer? That's the question my lab has been studying by focusing on acute myeloid leukemia (AML). Less common than acute lymphoblastic leukemia among the pediatric population, AML has a cure rate of only 50%-60%. We need greater understanding of how AML arises to design more effective therapies.

We appreciate that cancer may have roots in our germline genetic constitution. This is certainly the case with the inherited bone marrow failure syndromes (IBMFS) that I study in the laboratory and manage in the clinic. Types of IBMFS include Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome (SDS), severe congenital neutropenia (SCN, previously known as Kostmann syndrome), GATA2 deficiency and congenital amegakaryocytic thrombocytopenia. Phenotypically, there is some variability in the period of latency to complete bone marrow failure, involvement of other organ systems and risk of transforming into AML or a solid tumor.

These disorders are "experiments of nature." The genes for most of the IBMFS have been identified, and for each disorder, the genes belong to a particular pathway. Fanconi anemia is due to mutation in one of about two dozen genes involved in DNA double strand break repair. Diamond-Blackfan anemia is due to mutation in one of the many genes encoding a component of the ribosome. Dyskeratosis congenita results from a mutation in one of the genes involved in protecting the telomere. Less clear is the pathway involved in the inherited neutropenias (SCN and SDS) that we study. Evidence is emerging that they may result from defects in protein production, quality and trafficking.[1]

One obstacle to understanding these disorders and their complications is the rarity of each condition. They both have an incidence of approximately one in 100,000. We have turned to studying SDS in the zebrafish.[2] There are advantages to studying zebrafish over mice: organogenesis is completed within 96 hours, their development is transparent, they lay hundreds of eggs at a time permitting statistical analysis, and they are inexpensive to maintain. Fortuitously, the similarity between human and zebrafish SDS protein is almost 90%. Using CRISPR genome editing, Usua Oyarbide, PhD, created a zebrafish model of SDS in my lab. The fish display the same features as children with SDS: small stature, neutropenia and pancreatic atrophy. Tissue analysis showed defects that are more widespread. Gene expression analysis identified a cellular stress response involving p53, sometimes referred to as the guardian of the genome. More excitingly, Dr. Oyarbide has introduced one of the mutated genes for human SDS into the fish. This will permit us to identify the additional genetic changes required to produce AML, as children with SDS have a 1,000-fold increased risk of developing AML.

LEFT: Seth Corey, MD, MPH, collaborates with a colleague.

Those with SCN who develop AML acquire mutations in the receptor for granulocyte colony-stimulating factor (GCSF, known as filgrastim). The mutations occur spontaneously in some children, and the high, chronic doses of filgrastim permit clones to flourish and dominate. We have identified signaling events for GCSF receptor and the mutant forms.[3-6] We have identified differences in phosphorylated proteins at early time points (less than two hours) and gene expression changes at later time points (more than two hours). We have used deep sequencing of DNA to determine mutation rates due to intracellular stress responses associated with SCN. We are correlating these biochemical and genetic events with clonal bad behavior, and developing mathematical models to predict clonal competition and outgrowth.[7] With this information and machine learning, our goal is to intervene in those patients at highest risk of AML before the leukemic clones are established.

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UNILATERAL CATARACT SURGERY IN INFANTS AND TODDLERS AGES 7-24 MONTHS: TODDLER APHAKIA AND PSEUDOPHAKIA STUDY

BY ELIAS TRABOULSI, MD, MED

TAKEAWAYS

Complications for infants undergoing implantation of intraocular lenses (IOLs) include the need for additional surgery and other adverse events such as pupillary membrane and corectopia.

A new study of the effects of age on outcomes of cataract surgery finds fewer adverse effects from IOLs in children between the ages of 7 and 24 months, compared with children under 7 months.

Influenced by the results of the Infant Aphakia Treatment Study (IATS), the management of infantile cataracts has undergone significant changes in the past two decades. A new study of surgical outcomes suggests unilateral cataract surgery appears relatively safe for children between the ages of 7 and 24 months.

Before the IATS, which involved investigators from 13 academic institutions in the United States and enrolled patients between 2004 and 2010,[1] there was no agreement on the benefits of implantation of intraocular lenses (IOLs) in infants under the age of 7 months, nor were there any prospective studies that analyzed possible complications thereof. The IATS demonstrated no visual benefits of IOL implantation compared with using contact lenses to replace the natural lens of the eye after its removal. Unfortunately, infants undergoing IOL implantation had high rates of additional intraocular surgery (72%), as well as adverse events such as lens proliferation into visual axis (44%), pupillary membrane (28%), corectopia (28%), glaucoma (19%) and glaucoma suspect (9%).[2] We believe the findings of the IATS have influenced most pediatric ophthalmologists not to implant an IOL in infants under 6 months of age.

The Toddler Aphakia and Pseudophakia Study (TAPS) study was designed to evaluate the outcomes of cataract surgery in children ages 7-24 months and was conducted at 10 of the 13 IATS sites. It is the largest cohort of unilateral cataract outcomes in this age group. Despite limitations of retrospective data including the use of nonrandomized patients and nonstandardized documentation, the close parallels between the care provided to TAPS and IATS patients allows for comparison in determining the effect of age on outcomes.

In this first report of TAPS,[3] children who underwent unilateral cataract surgery with or without IOL placement during the IATS enrollment years of 2004 and 2010 were followed up, and intraoperative complications, adverse events, long-term visual acuity outcomes and the incidence of strabismus were analyzed. Fifty-six children were included, with a mean postoperative follow-up of 47.6 months. Median age at cataract surgery was 13.9 months (range 7.2-22.9). Of patients in the study, 92% received a primary IOL. The only intraoperative complications was an inadvertent capsular disruption in five patients (9%). At 5 years of age, visual acuity of treated eyes was very good (>20/40) in 11% and poor (<20/200) in 44%. Adverse events were identified in 24%, with a 4% incidence of a glaucoma suspect status. An additional unplanned intraocular surgery occurred in 14% of children. Neither adverse events nor intraocular reoperations were more frequent in children who were operated on between 7 and 12 months of age than those who had surgery at 13-24 months. Although most children had

LEFT: Elias I. Traboulsi, MD, MEd, examines a young patient.

IOL implantation concurrent with unilateral cataract removal, the incidence of complications, reoperations and glaucoma was low in children older than 7 months and compared favorably to same-site IATS data for infants operated on before 7 months of age.

Unilateral cataract surgery in infants older than 7 months appears to have a less complicated course than surgery in those younger than 7 months, with fewer intraoperative complications, adverse events, reoperations and high myopic refractive shift. IOL implantation in children 7-24 months of age is associated with fewer adverse events than IOL implantation in children under 7 months of age. The TAPS results suggest that there are no deleterious consequences of implanting IOLs over the age of 7 months compared with leaving the child aphakic and wearing a contact lens.

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OVER
1 MILLION
Number of sports- and recreation-related concussions reported annually among youth in the United States

CONCUSSION APP IDENTIFIES RED FLAG SYMPTOMS AND STREAMLINES INJURY REPORTING

BY JAY ALBERTS, PHD

CONCUSSION APP IDENTIFIES RED FLAG SYMPTOMS AND STREAMLINES INJURY REPORTING

BY JAY ALBERTS, PHD

TAKEAWAYS

Despite fewer red flag symptoms, more youth athletes are referred to the emergency department for concussion evaluation than high school and collegiate athletes.

The Cleveland Clinic Concussion App was designed to facilitate symptom evaluation and streamline injury reporting in the field.

The incidence of sports- and recreation-related concussion is estimated at 1.1 million to 1.9 million annually among youth in the United States.[1] The identification and management of concussive injuries by athletes, parents, coaches and medical providers is complicated by inconsistent approaches to injury detection, delayed symptom onset, misconceptions related to injury management and the dynamic environment in which injuries occur (practice, competition or recreational settings).[2,3]

Regardless of injury severity, medical providers from multiple disciplines commonly participate in the care of athletes with concussion along the continuum of care, from detection and diagnosis to return to school and play. Healthcare systems often lack continuity of care across providers who may be administratively or physically in different departments or locations. These logistical challenges, coupled with the lack of interoperability within and between traditional electronic health record systems, further complicate a team approach to concussion management. These challenges are often compounded in a youth sports environment.

In youth athletics, coaches, parents and other nonmedical personnel often volunteer to provide oversight of all aspects of event safety and injury. The inconsistent or missing documentation of an injury by those who first encounter the injured athlete creates the initial barrier to effective concussion care as subsequent handoffs across providers become challenging and time-consuming. Recognizing the diversity of training and expertise, we developed a mobile application to aid in the clinical management of concussion and communication of symptoms and the injury.

The iPad™-based Cleveland Clinic Concussion Application (C3 app)[4-6] was designed as a concussion management platform for use by providers within the Cleveland Clinic health system.[7] While the initial platform consisted only of evaluation modules, an incident report (IR) module was developed based on evaluation of practice patterns.[8] The IR module was designed to standardize and systematize the characterization of injury severity through the evaluation of red flags, and to document injury-related demographics and athlete disposition. Red flags were operationally defined as any clinical sign or symptom that may be indicative of a more severe injury warranting medical monitoring, additional diagnostic testing or a higher level of management.

Our objectives were to characterize the implementation of the technology-enabled IR and to determine the impact of age and gender on injury presentation and the management of student athletes.[8] We hypothesized that youth athletes would be managed differently from high school and collegiate athletes, due in part to lack of formal medical coverage.

BELOW: A patient completes assessments of cognitive and postural stability using the C3 app.

A total of 1,421 unique incidences of sports-related concussions were included in this sample for analysis. Age cohorts were categorized to correspond roughly with academic age levels as follows: youth (ages 5-13), high school (ages 14-18) and collegiate (ages 19-24).

Headache and dizziness were the two most commonly reported initial symptoms across all age cohorts and genders. However, the top six initial symptoms differed across age categories. Headaches were more common in youth and high school athletes than in collegiate athletes.[8]

Red flag symptoms were reported in 114 (8%) of student athletes, including one youth athlete (1%), 95 high school athletes (8%) and 18 collegiate athletes (11%). I

Despite the lower number and rate of red flags, youth athletes were more likely to be sent to the emergency department for evaluation than were high school or collegiate athletes, likely reflecting the lack of medical triage knowledge of those monitoring youth sport activities.[8]

The electronic IR within C3 has the potential to address such gaps in medical coverage at youth sports. The app presents the user with a series of questions that can be asked of the injured athlete to assess the need to utilize the emergency department in the management of youth concussion.

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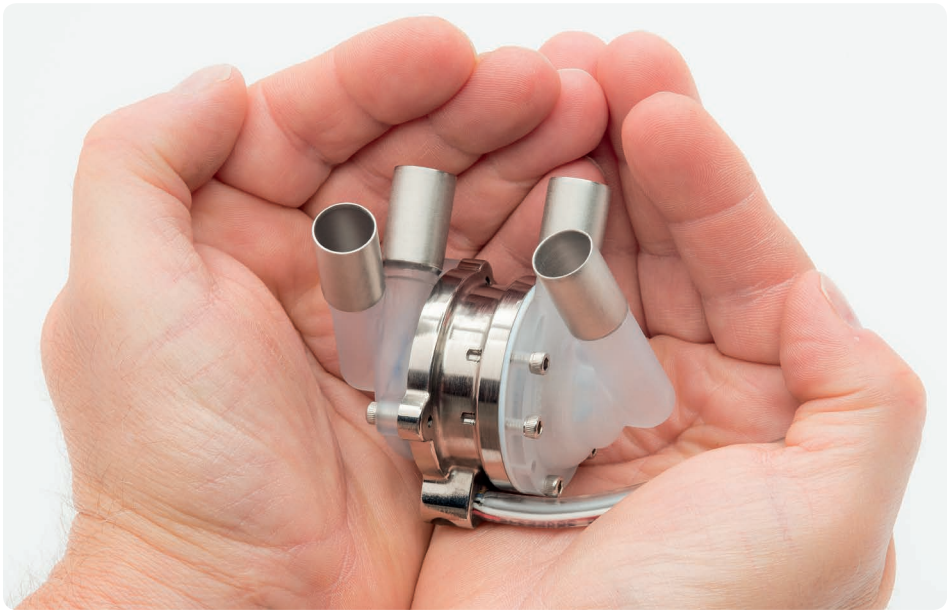
Jay Alberts, PhD, is Director of Cleveland Clinic's Concussion Center.

NEWSWORTHY

Continuous-flow total artificial heart



PEDIATRIC CONTINUOUS-FLOW TOTAL ARTIFICIAL HEART

Mechanical circulatory support (MCS) is standard therapy for adult patients with end-stage heart failure. In children, however, the options for chronic MCS are limited to paracorporeal devices or off-label use of implantable adult devices, as no implantable devices are approved for pediatric patients. Heart transplantation is an accepted therapy, but donor hearts are extremely limited. Kiyotaka Fukamachi, MD, PhD, and his team in the Department of Biomedical Engineering at Cleveland Clinic's Lerner Research Institute have developed a continuous-flow total artificial heart (CFTAH) comprising a motor and a rotating assembly supported by a hydrodynamic bearing for adult patients with stable hemodynamics and good biocompatibility without anticoagulation. The team is currently developing a pediatric version (P-CFTAH) by downsizing the adult device by a scale factor of 0.70 (one-third of total volume). This strategy makes implantation possible in the infant chest. The pump flow range (1.5-4.5 L/min) is intended to support patients weighing up to 50 kg (average weight of 14-year-olds). The P-CFTAH was implanted in four lambs (28.7±2.3 kg), which showed good anatomical fit and easy implantation. Baseline hemodynamics were stable with pump flow of 2.1±0.9 L/min. This initial P-CFTAH prototype met the proposed requirements for self-regulation, performance and pulse modulation. Dr. Fukamachi and his team are currently evaluating the device for biocompatibility in vitro and in vivo, and refining the motor and hydrodynamic bearing for the downsized pump, which may someday be an option for children in end-stage heart failure.

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MYELOMENINGOCELE REPAIRS LAUNCH ERA OF FETAL SURGERY AT CLEVELAND CLINIC

Led by one of the world's most experienced fetal surgeons, Darrell Cass, MD, a Cleveland Clinic team has successfully performed the complex in utero repair of a neural tube defect in a nearly 23-week-old fetus — a first for northern Ohio. The baby, a girl, was delivered by caesarian section near full term June 3. The team has since performed a second successful fetal myelomeningocele (MMC) repair.

Also known as open spina bifida, MMC is the most common central nervous system congenital defect, occurring in approximately 1,645 births annually in the United States. The condition develops in the first four weeks after conception and is characterized by incomplete neural tube closure and a fluid-filled sac containing an exposed, extruded segment of spinal cord and nerves. The defect causes cerebrospinal fluid leakage and depressurization of the spinal column, hindbrain herniation, cerebroventricular obstruction and hydrocephaly.

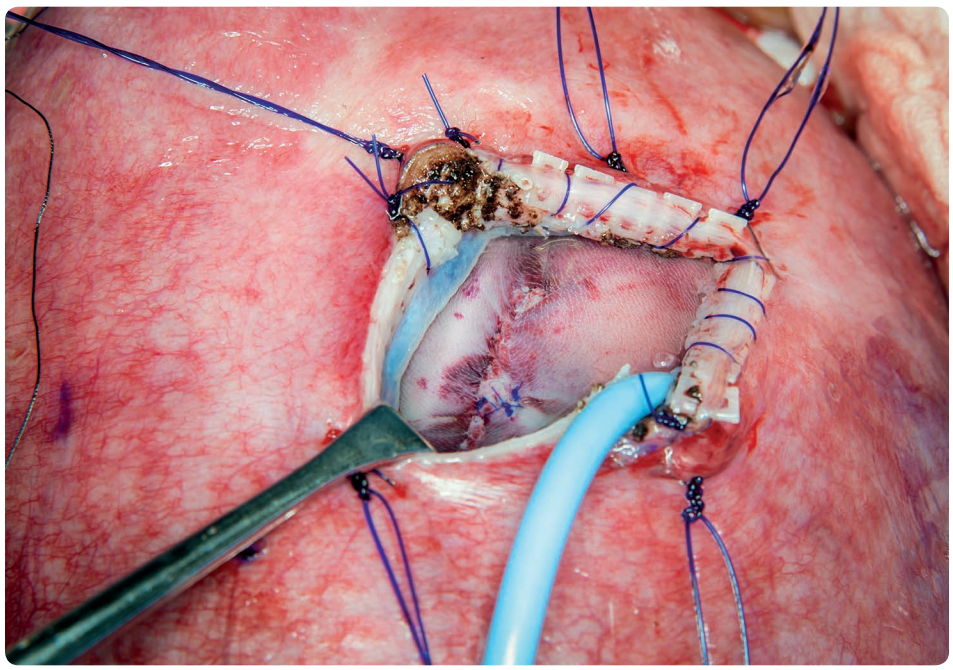
Both infants were cared for in Cleveland

Clinic Children's Neonatal Intensive Care Unit. With the closure of their neural tube defects, both patients' Arnold-Chiari malformations have reversed, thus decreasing the risk for hydrocephalus and need for shunting. Neurological evaluations are ongoing to determine the infants' degree of motor functioning, which is expected to improve as a result of the operations.

DECREASING SIDE EFFECTS RELATED TO PEANUT ORAL IMMUNOTHERAPY

Peanut allergy is a potentially life-threatening condition for which the only approved management involves strict avoidance. Treatments for this increasingly prevalent condition are desperately needed. Oral immunotherapy (OIT) is a promising investigational treatment option that involves feeding a small, increasing dose of peanut to the allergic person to induce desensitization. However, the widespread use of OIT has been limited by high rates of side effects, such as abdominal pain or even anaphylaxis, which often lead to the high subject drop-out rates in published studies.

These OIT studies all used roasted peanut products. Published data demonstrate that boiling peanut results in changes in the proteins that should decrease side effects during OIT while maintaining immunogenicity. To date, however, no published studies have tested this hypothesis in children with peanut allergies. In a pilot study, Jaclyn Bjelac, MD, and colleagues in Cleveland Clinic Children's Center for Pediatric Allergy, children with known peanut allergies will be enrolled in an OIT trial of boiled peanut powder to evaluate its effectiveness in terms of desensitization and the frequency of side effects.

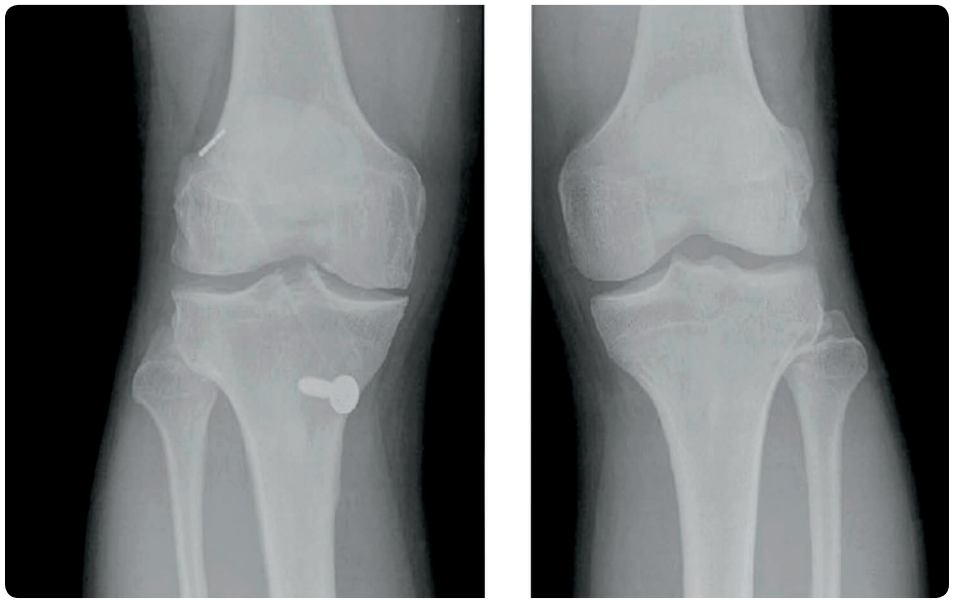


The completed myelomeningocele repair

STEM CELL-BASED THERAPY FOR MITOCHONDRIAL DISEASE IN PEARSON SYNDROME

Pearson syndrome is a rare, fatal, progressive genetic mitochondrial disorder associated with mortality and systemic morbidity, including neurodegeneration, bone marrow failure, cardiac conduction defects, renal disease and pancreatic insufficiency. There are currently no disease-specific treatments available for affected children; however, a new phase I/II study examines a promising novel therapy, mitochondrial augmentation therapy (MAT). The first open trial site is Shelba Medical Center in Israel. The study involves transplantation of

An adolescent patient who had a normal medial meniscus and a medial compartment mJSW 1.97 mm wider on the ACL-reconstructed side compared with the contralateral control side.



autologous CD34+ cells enriched with blood-derived donor mitochondria via a single dose into pediatric patients with Pearson syndrome to increase the levels of normal mitochondrial DNA. Cleveland Clinic Children's and the Mitochondrial Medicine Center, directed by Sumit Parikh, MD, is currently designated by the sponsor, Minovia, as the only U.S. clinical trial site for this novel treatment. While the hundreds of genetic mitochondrial diseases are individually rare, mitochondrial dysfunction is frequent in most common diseases, including Parkinson's and Alzheimer's diseases, and the therapy has the potential to transform treatment for many disorders.

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KIDNEY DISEASE PROGRESSION IN PEDIATRIC AND ADULT POSTERIOR URETHRAL VALVES (PUV) PATIENTS

Posterior urethral valves (PUV) is the most common form of congenital obstructive uropathy in boys, accounting for a significant proportion of pediatric chronic kidney disease (CKD). Approximately 15%-20% of PUV patients progress to end-stage kidney disease (ESKD) by 18 years of age. However, renal disease progression rates, especially for adults with PUV, are not well-described. In a retrospective analysis presented at the 2018 Pediatric Academic Societies (PAS) Annual Meeting, a research team led by Audrey Rhee, MD (Pediatric Urology), and Katherine Dell, MD (Pediatric Nephrology), examined rates of renal function (estimated glomerular filtration rate, eGFR) decline and ESKD in children and adults with PUV. The study found that children <10 years of age had the highest rates of eGFR decline and ESKD. Importantly, adults also showed declining function, with 16% progressing to ESKD after 18 years of age. These findings suggest that the overall lifetime risk of ESKD in PUV patients may be higher than rates reported by published studies that focused only on the pediatric PUV population.

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EFFECT OF AUTOGRAFT CHOICE IN ACL RECONSTRUCTION ON RECURRENT ACL REVISION RATES IN HIGH SCHOOL AND COLLEGE-AGED ATHLETES

Young athletes who have anterior cruciate ligament (ACL) surgery are more likely to need an additional surgery if they received a hamstring graft instead to a bone-patellar tendon-bone (BPTB) graft, according to research presented at the American Orthopaedic Society for Sports Medicine 2019 Annual Meeting.

The Multicenter Orthopaedic Outcomes Network (MOON), led by Cleveland Clinic's Kurt Spindler, MD, followed 839 patients aged 14-22 who were injured while participating in sports such as baseball, football and soccer. Each patient was followed up at two and six years after ACL reconstruction.

Six years after reconstruction, the hamstring graft group had tear rates of 13% for the ipsilateral graft and 8.6% for the contralateral native ACL, while the BPTB graft group had tear rates of 7.1% for the ipsilateral graft and 12.6% for the contralateral native ACL. The predictors of ACL graft re-tear were high-grade laxity, hamstring graft and age. Conversely, for the contralateral ACL tear, the risk factors were type of sport played and age.

Patients receiving a hamstring graft had twice the risk of an ACL graft revision compared with patients who were given a BPTB graft. The difference in graft re-tear risk was dependent on the baseline percentage. ACL graft choice was not a predictor of contralateral native ACL injury. This study may help guide patient and physician decision-making.

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EFFECTIVE DIETARY INTERVENTIONS TO REDUCE RISK OF CARDIOVASCULAR DISEASE

Cardiovascular disease is known to frequently begin in childhood, and the need for effective lifestyle modifications that target the growing group of obese children with dyslipidemia is clear. Effective dietary interventions must be defined for the growing number of children and adults with obesity and hypercholesterolemia. No previous single trial in children and adults has studied the impact of the three diets emphasized in the 2015-2020 U.S. Dietary Guidelines on measures of cardiovascular risk. To shed light on this question, a team of clinician researchers from Cleveland Clinic Children's is conducting a randomized trial of those three major diet types — the American Heart Association (AHA), Mediterranean (MED) and Plant-Based, No-Fat-Added (PB). The group hopes to provide insight on the comparative advantages and disadvantages of these diets in children and their parents for preventing cardiovascular disease. Some of the measures of cardiovascular risk include weight, body mass index, waist circumference, blood pressure, total cholesterol, low density lipoprotein, high density lipoprotein, fasting glucose and insulin, myeloperoxidase, and high-sensitivity C-reactive protein.

Child-parent pairs are randomized to either PB whole food, AHA (which emphasizes whole food fruits and vegetables, legumes, grains and limited added salt, but permits low-fat meats, fish and low-fat dairy) or MED (is similar to the AHA diet with additional emphasis on fish and extra virgin olive oil). Follow-up of study participants is for one year. These diets could improve the lifetime health of those populations who choose to follow them beginning in childhood.

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INSIGHT INTO CHILDHOOD ARTHRITIS AND RHEUMATOLOGIC DISEASE

About 300,000 U.S. children are thought to be affected by juvenile arthritis, and yet we still do not know enough about this disease. The Center for Pediatric Rheumatology at Cleveland Clinic Children's is a long-standing member of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). CARRA is a consortium of pediatric rheumatologists throughout the United States and Canada with the goals of better understanding all pediatric rheumatic diseases, finding better treatments and, eventually, finding cures. Cleveland Clinic Children's participates in the CARRA Registry, a multicenter study that collects disease and patient-reported information on thousands of children and young adults with pediatric-onset rheumatic disease, with the goal of following 10,000 patients for 10 years. Information from this important registry is already helping us understand the manifestations of arthritis and the effects of treatments, and is the jumping-off point for additional studies on comparative treatment effectiveness, pathophysiology and disease phenotyping.

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RESOURCEFULNESS INTERVENTION FOR PARENTS OF TECHNOLOGY-DEPENDENT CHILDREN

Caring for chronically ill children who are dependent on medical technology can be very stressful. Together with partners from Case Western Reserve University and University Hospitals Rainbow Babies & Children's Hospital, pediatric pulmonologist John Carl, MD, is conducting a randomized clinical trial to examine the effectiveness of a theoretically based cognitive-behavioral intervention, Resourcefulness Training©, on parents who care for their technology-dependent child at home.

The intervention includes a face-to-face teaching session with a 30-minute video describing eight self-help and help-seeking resourcefulness skills, ongoing access to video vignettes of

parents describing application of the resourcefulness skills during daily caregiving, skill reinforcement using daily semistructured journal writing, weekly phone calls for the first four weeks, and booster sessions at two and four months post-enrollment. Researchers will evaluate the impact of the intervention on psychological and physical outcomes and family functioning over time, as well as whether changes in resourcefulness skills mediate these outcomes.

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SELECTED CLINICAL STUDIES

Consider offering your patients enrollment in a leading-edge clinical study. To learn more about these and other active Cleveland Clinic Children's studies, please send a message to pedsresearch@ccf.org.

ALLERGY

A Double-Blind, Placebo-Controlled, Randomized Phase 3 Trial to Assess the Safety and Efficacy of Viaskin® Peanut in Peanut-Allergic Young Children 1-3 Years of Age (EPITOPE study).

This phase 3 study aims to assess the safety and efficacy of Viaskin® Peanut, a novel epicutaneous immunotherapy (EPIT) to induce desensitization to peanut in peanut-allergic children 1-3 years of age.

Sponsor
DBV Technologies S.A.

Eligibility
Peanut-allergic children 1-3 years of age currently following a strict peanut-free diet; presence of peanut-specific IgE > 0.7 KU/L; positive skin prick test to peanut extract with the largest wheal diameter ≥ 6 mm; positive double-blind, placebo-controlled food challenge to peanut with an eliciting dose (ED) ≤ 300 mg of peanut protein.

Principal Investigator
Leigh Ann Kerns, MD

AUTISM

Comparative Effectiveness of Early Intensive Behavioral Intervention (EIBI) and Adaptive Applied Behavior Analysis (ABA) for Children with Autism (ISOLDE)

The primary aim of this prospective intervention study is to compare EIBI and adaptive ABA on key child and parent outcomes after 24 weeks of intervention, at a 24-week follow-up, and at 5 years of age.

Sponsor
Department of Defense

Eligibility
Children 18 months to 4 years of age with a diagnosis of ASD who are in the process of being approved or already approved through TRICARE for ABA services for at least 15 hours per week; not yet receiving ABA services; with no plans to move location for the six-month intervention period; medications must be stable for the six weeks prior to enrollment in the study.

Principal Investigator
Cynthia Johnson, PhD

BLOOD AND MARROW TRANSPLANT

Antiviral Cellular Therapy for Enhancing T Cell Reconstitution Before or After Hematopoietic Stem Cell Transplantation (ACES)

This multicenter, Phase 1/2 study conducted by investigators of the Pediatric Blood and Marrow Transplant Consortium (PBMTC) will evaluate whether most closely human leukocyte antigen-matched multivirus-specific T cell lines obtained from a bank of allogeneic virus-specific T cell lines (VSTs) have antiviral activity against three viruses: Epstein-Barr virus (EBV), cytomegalovirus (CMV) and adenovirus.

Sponsor
Children's Hospital of Los Angeles and the California Institute for Regenerative Medicine

Eligibility
Patients who have undergone any type of allogeneic hematopoietic stem cell transplant or those with a diagnosis of primary immunodeficiency disorder who have CMV, adenovirus and/or EBV infection that persists despite standard therapy.

Principal Investigator
Rabi Hanna, MD

CARDIOLOGY/CARDIAC SURGERY

STeroids to REduce Systemic inflammation after infant heart Surgery (STRESS trial)

The objective of this prospective, double-blind, multicenter, placebo-controlled safety and efficacy study is to determine the pharmacokinetics/pharmacodynamics, safety and efficacy of methylprednisolone in infants undergoing heart surgery with cardiopulmonary bypass (CPB).

Sponsor
National Institutes of Health-PTR federal subaward with Duke University and Vanderbilt University

Eligibility
Age < 1 year at the time of surgery; planned heart surgery with CPB as part of standard clinical care.

Principal Investigator
Tara Karamlou, MD

DERMATOLOGY

PF-06651600 for the Treatment of Alopecia Areata (ALLEGRO-2b/3)

The aim of this global phase 2b/3 randomized, double-blind, placebo-controlled, dose-ranging study is to evaluate the efficacy of PF-06651600, a potent, covalent and irreversible inhibitor of Janus kinase 3 (JAK3) for treatment of adults and adolescents with alopecia areata (AA).

Sponsor
Pfizer

Eligibility
Patients age 12 and older with AA and > 50% hair loss.

Principal Investigator
Wilma Bergfeld, MD

ENDOCRINOLOGY

Cleveland Clinic Families Get Fit (CCFit)

This randomized controlled trial of obese children seeks to evaluate the role of an activity monitor in addition to standard dietary and exercise counseling in increasing physical fitness/endurance, achieving weight reduction and improving quality of life. The study will also provide activity monitors for up to three family members, including parents. This will be the first study to look at a family-based intervention using activity monitors in a pediatric population.

Sponsor
Cleveland Clinic Caregiver Catalyst award

Eligibility
Obese children ages 7-17 years evaluated in the Cleveland Clinic Children's Be Well Clinic.

Principal Investigator
Andrea Mucci, MD

GASTROENTEROLOGY

Prospective Quantitative Imaging-Based Evaluation of Visceral Adipose Tissue to Develop a Non-Invasive Marker for Disease Progression in Pediatric Crohn's Disease

This prospective observational study will examine the role of novel magnetic resonance imaging-based radiomics assessments of visceral adipose tissue in predicting response to initial therapy and risk of disease progression in pediatric patients with newly diagnosed Crohn's disease.

Sponsor
Cleveland Clinic Mark Lauer, PhD, Young Investigator award

Eligibility
Children ages 6-17 years diagnosed with new-onset Crohn's disease.

Principal Investigator
Jacob Kurowski, MD

HEPATOLOGY

Double Blind, Randomized, Placebo Controlled, Phase 3 Study to Investigate the Efficacy and Safety of Low Doses and High Doses of A4250 Compared to Placebo in Children With Progressive Familial Intrahepatic Cholestasis (PFIC; deficiencies of familial intrahepatic cholestasis-1 or bile salt export pump).

The goal of this multicenter study is to demonstrate the efficacy of two different doses of A4250 (Odevixibat), a potent and selective inhibitor of the ileal bile acid transporter in children with PFIC Types 1 or 2.

Sponsor
Albireo AB

Eligibility
Males and females, aged 6 months to 18 years with the clinical and genetic diagnosis of PFIC Types 1 or 2 and a body weight above 5 kg; elevated s-BA concentration ≥ 100 μmol/L; significant pruritus.

Principal Investigator
Vera Hupertz, MD

HEMATOLOGY

Hydroxyurea Optimization Through Precision Study (HOPS): A Prospective, Multicenter, Randomized Trial of Personalized, Pharmacokinetics-Guided Dosing of Hydroxyurea Versus Standard Weight-Based Dosing for Children With Sickle Cell Anemia

This prospective, multicenter, randomized trial will evaluate whether dosing of hydroxyurea using a novel precision medicine strategy of pharmacokinetic-based dosing for children with sickle cell anemia is superior to standard step-wise dose escalation.

Sponsor
Doris Duke Charitable Foundation/Cincinnati Children's Medical Center

Eligibility
Patients ages 6 months to 21 years with sickle cell anemia for whom the clinical decision has been made to initiate hydroxyurea therapy.

Principal Investigator
Ravi Talati, DO

NEONATOLOGY

Safety of Sildenafil in Premature Infants at Risk of Bronchopulmonary Dysplasia (BPD)

This is a Phase 2, multicenter, randomized, placebo-controlled, sequential dose-escalating, double-masked safety study of sildenafil in premature infants at risk of BPD.

Sponsor
National Institutes of Health/National Institute of Child Health and Human Development

Eligibility
Premature infants < 29 weeks' gestational age at birth who are 7-28 (inclusive) days postnatal age at time of randomization; receiving positive airway pressure (nasal continuous airway pressure, nasal intermittent positive pressure ventilation or nasal cannula flow > 1LPM) or mechanical ventilation (high frequency or conventional).

Principal Investigator
Hany Aly, MD

NEPHROLOGY

Imaging Assessments of Autosomal Recessive Polycystic Kidney Disease (ARPKD) Progression

The overall goal of this longitudinal, prospective observational study is to evaluate the T2 magnetic resonance imaging (T2-MRI) and novel MR fingerprinting (MRF) techniques as sensitive and reproducible imaging biomarkers to monitor ARPKD kidney disease progression.

Sponsor
National Institutes of Health/NIDDK

Eligibility
Children and young adults — ages 6-25 years — with the clinical diagnosis of ARPKD and no history of solid organ transplantation; able to lie still for an MRI scan up to 60 minutes.

Principal Investigator
Katherine Dell, MD

NEUROLOGY

Cortical Localization in Epilepsy: Cognitive Outcome in Children After Epilepsy Surgery

Word retrieval or "naming" is often at risk following dominant hemisphere epilepsy surgery. This multicenter study will utilize recently developed and validated pediatric naming tests and other cognitive measures to identify clinical and demographic predictors of short- and long-term postoperative cognitive/language change in children who undergo epilepsy surgery. .

Sponsor
National Institutes of Health/Columbia University

Eligibility
Participants are children ages 6-15 years with medically refractory epilepsy who are being evaluated for potential epilepsy surgery; must speak English fluently and have no history of intellectual disability, psychosis or other medical conditions that could affect cognitive performance.

Site Principal Investigator
Robyn Busch, PhD

OTOLARYNGOLOGY

Cochlear Implant Quality of Life (QOL) Study

The goal of this prospective observational study is to evaluate and compare QOL differences in children with neurologic impairment who undergo cochlear implantation and children who do not have impairment.

Sponsor
Cleveland Clinic internal funds

Eligibility
Children who were born deaf (or were deafened by age 3 years) and have had a cochlear implant for at least two years.

Principal Investigator
Samantha Anne, MD

PRIMARY CARE/GENERAL PEDIATRICS

BP-CATCH: Boosting Primary Care Awareness and Treatment of Childhood Hypertension

Building on an existing quality improvement network, this prospective, cluster-randomized, stepped wedge design study's goal is to determine whether the following factors reduce errors in pediatric hypertension diagnosis and management compared to each other and usual care:

- A quality improvement collaborative (QIC) intervention without subspecialist involvement;
- A QIC with subspecialists and primary care physicians (PCPs) mutually engaged; and/or
- A hub-and-spoke codiagnosis, comanagement model in which PCPs diagnose and manage pediatric hypertension with a supporting subspecialist advisor.

Sponsor
Montefiore Medical Center and the Agency for Healthcare Research and Quality (AHRQ)

Eligibility
Patient age > 3 years old and < 21 years old; blood pressure (BP) is elevated > 90th percentile for patient's height, weight and sex, or > 120/80 (regardless of height/sex/weight) at a healthcare maintenance visit or non-acute care visit.

Principal Investigator
Kimberly Giuliano, MD

PULMONOLOGY

Dextromethorphan Pediatric Acute Cough Study

This placebo-controlled, double-blind, randomized, parallel group pilot study that evaluates the efficacy of dextromethorphan hydrobromide (DXM) on acute cough in a pediatric population.

Sponsor
Pfizer

Eligibility
Otherwise healthy males and females aged 6-11 who are experiencing acute cough as a symptom of common cold or upper respiratory tract infection; onset of symptoms within three days of screening.

Principal Investigator
John Carl, MD

IMPROVING CARE WITH THERAPEUTIC INNOVATIONS

KATHERINE DELL, MD, VICE CHAIR OF RESEARCH, CLEVELAND CLINIC PEDIATRIC INSTITUTE

Research is an integral part of the mission of Cleveland Clinic Children's. Providing the most up-to-date treatments through participation in cutting-edge clinical trials and support of novel, investigator-initiated studies improves the care that we provide to our patients.

This issue of *Perspectives in Pediatric Research and Innovations* highlights some of the timely and relevant clinical and translational research conducted by my colleagues across a spectrum of pediatric specialties. Recently published reports provide new information in several areas, including:

- Parent training as an evidence-based psychosocial intervention for children with autism spectrum disorder and co-occurring behavioral and emotional problems.
- Underutilization of automated external defibrillators (AEDs) in children who had out-of-hospital nontraumatic cardiac arrests, despite the American Heart Association's updated 2010 guidelines and evidence that AED use improves survival and neurological outcomes.
- Favorable outcomes and decreased complication rates in children in the multicenter Toddler Aphakia and Pseudophakia Study who underwent unilateral cataract surgery with intraocular lens placement at > 7 months of age compared with those < 7 months of age.

As a network site for the Institute for Advanced Clinical Trials for Children, Cleveland Clinic Children's is committed to ensuring that new, well-designed pediatric treatment trials across a spectrum of diseases are readily available to our patients.

We continue to expand our portfolio of clinical trials in our search for the most advanced treatments. Notable studies that opened this past year (see pp. 28-29) involving novel medications or new applications of existing medications include:

- A randomized controlled study comparing the efficacy of high versus low doses of a novel medication for the treatment of progressive familial intrahepatic cholestasis.
- A phase 2 study of sildenafil in premature infants at risk for bronchopulmonary dysplasia.
- A randomized controlled trial of a novel epicutaneous immunotherapy to induce desensitization to peanut in young children with peanut allergy.
- A prospective, multicenter, randomized trial of personalized, pharmacokinetics-guided dosing of hydroxyurea versus standard weight-based dosing for children with sickle cell anemia.
- A randomized controlled trial of methylprednisolone in infants undergoing heart surgery with cardiopulmonary bypass.
- A phase 2b/3 study of a novel medication for the treatment of alopecia areata.

We look forward to continuing to expand our pediatric research programs and increasing the number and scope of clinical studies available to our patients.

ConsultQD

To stay up to date on the latest research and innovation at Cleveland Clinic Children's, be sure to visit our ConsultQD physician website at **consultqd.clevelandclinic.org/pediatrics**.

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  24/7 access to information on our specialists and services
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  Establish a secure online DrConnect account at clevelandclinic.org/drconnect for real-time information about your patients' treatment.
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ABOUT CLEVELAND CLINIC

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,600 physicians and researchers represent 140 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 19 full-service family health centers and three health and wellness centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

Cleveland Clinic was named a top U.S. hospital in U.S. News & World Report's "Best Hospitals" rankings for 2019-20, and it was named the top hospital in heart care for the 25th consecutive year.

Pediatric Perspectives is written for physicians and should be relied on for medical education purposes only. It does not give a complete overview of topics covered and should not replace a physician's independent judgment about the appropriateness or risks of a procedure for a given patient.

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