HIGHLIGHTS

New Destination Program for Glycogen Storage Disease  8
Breathing New Life into Fatty Liver Disease Detection 10
Reducing Radiation and Customizing Devices for Congenital Heart Disease Treatment 12
Haploidentical Blood and Marrow Transplant  17
Regenerating the Physis to Repair Growth Plate Injuries 28
Childhood Vasculitis: No Case Too Rare 36

DOUBBLE DUTY

Special Delivery Unit
Equipped to Manage Complex Conditions in Both Newborns and Their Moms
PAGE 2
02 Cover Story | Neonatology: Double Duty: Special Delivery Unit Provides Comprehensive Care at Deliveries Complicated by Serious Fetal or Maternal Conditions — Sabine Iben, MD

06 Autism: Early Intensive Behavioral Intervention for Autism Spectrum Disorders Maximizes Mainstream Educational Placements — Thomas W. Frazier II, PhD

08 Endocrinology: Glycogen Storage Disease: Bringing Singular Expertise to Bear for a Rare Metabolic Disorder — Laurie Tsilianidis, MD, and Carrie Gonzales, RD, CSP, LD

10 Gastroenterology: Fatty Liver Disease in Obese Children: Noninvasive Tool Breathes Life into the Prospect of Earlier Detection — Naim Alkhouri, MD

12 Heart Disease: Congenital Heart Disease: As Percutaneous Procedures Become More Versatile, Innovations in Radiation Reduction and Customized Devices Matter More than Ever — Lourdes R. Prieto, MD, and Alex Golden, MD

15 Heart Disease: Reduced-Radiation Ablation for Pediatric Tachyarrhythmias: Emerging Data Offer Reassurance of Uncompromised Efficacy — Peter F. Aziz, MD

17 Hematology and Oncology: Progress in HLA-Haploidentical Hematopoietic Stem Cell Transplant: Are We Closer to a Universal Donor? — Rabi Hanna, MD

20 Hospital Medicine: Joining Forces Against Inappropriate Use: Pediatric Hospitalists Take a Lead Role in Two National Initiatives — Rita Pappas, MD; Michelle Marks, DO; and Shannon Phillips, MD, MPH

22 Nephrology: Challenges in Pediatric Urinary Tract Infection and Vesicoureteral Reflux: Perspectives Beyond Where the Guidelines Go — Halima Janjua, MD

24 Neurology: Rasmussen Encephalitis: Sizing Up the Role of Hemispherectomy, Exploring the Autoimmune Therapy Alternative — Ahsan N.V. Moosa, MD

26 Neurosurgery: Hydrocephalus: Can the Brain Adapt to a Chronic Squeeze? Can We Help? — Mark Luciano, MD, PhD, FACS, and Abhishek Deshpande, MD, PhD

28 Orthopaedics: Regenerating the Physis: New Insights and Tissue Engineering Advances Could Transform Repair of Pediatric Growth Plate Injuries — R. Tracy Ballock, MD

30 Physical Medicine and Rehabilitation: Augmentative and Alternative Communication Strategies for Children with Angelman Syndrome — Jackie Kearns, CCC-SLP, and Douglas Henry, MD

32 Psychiatry: Electroconvulsive Therapy: Underutilized Modality Can Be Safe, Effective for Severe Mood Disorders in Adolescents — Joseph Austerman, DO

34 Pulmonary Medicine: Could RSV Be Transmitted Through the Placenta into Developing Fetal Lungs? — Giovanni Piedimonte, MD

36 Rheumatology: No Case Too Rare: Bringing Deep Experience Plus Cross-Specialty Coordination and Consultation to Childhood Vasculitis — Steven J. Spalding, MD

38 Transplantation: Formal Pediatric Lung Transplant Program Rounds Out World-Class Transplantation Offerings — Nathan Kraynack, MD

40 Urology: Is Preoperative Hormonal Stimulation Helpful in the Treatment of Proximal Hypospadias? — Audrey Rhee, MD

42 Quality and Safety: Sustaining a Culture of Patient Safety: Advice and Insights from Cleveland Clinic Children’s Quest — Vera Hupertz, MD, and Amrit Gill, MD

44 Quality and Safety: Creation of Disease-Specific Care Paths: A Key Step in the Journey from Volume to Value — Steven J. Spalding, MD

46 Staff List

48 CME Events from Cleveland Clinic Children’s

48 Resources for Pediatricians

49 Cleveland Clinic Children’s Locations
Dear Colleagues,

Making a difference as an individual in the lives of individual children is what drew many of us to pediatrics. Yet while there is plenty to be said for rugged individualism, both within and outside of healthcare, I am increasingly convinced collaboration is where the future of medicine lies.

At Cleveland Clinic Children’s, we benefit from sharing knowledge, energy and expertise across pediatric subspecialties and disciplines — as well as back and forth with our adult-care colleagues throughout Cleveland Clinic.

This issue of *Pediatric Perspectives* abounds with examples of teamwork:

- Our cover story (page 2) reviews successes of our new Special Delivery Unit, the first in the nation equipped to serve both mothers and babies with critical medical needs. As the article notes, this singular unit is a testament to the high degree of coordination among our teams of neonatologists and pediatric critical care specialists with colleagues in obstetrics and maternal-fetal medicine.
- The profile of our new Glycogen Storage Disease Program (page 8), one of the few such dedicated programs in the world, explains how our pediatric endocrinologists partner with colleagues in gastroenterology, critical care and genetics to refine the titration of therapy for children from across the country with this rare metabolic disorder.
- On page 20, three of our pediatric hospitalists share their experience and insights from a pair of multicenter collaborations in which they helped lead nationwide efforts to identify and reduce common culprits in the inappropriate utilization of medical resources in pediatric inpatient care.
- The overview of our destination program for childhood vasculitis (page 36) describes how our pediatric rheumatologists collaborate with experts from all reaches of Cleveland Clinic Children’s to manage diverse aspects of rare, complex forms of pediatric vasculitis that many providers see only once or twice in a career.

Young patients who are referred here enjoy the benefits of this spirit of collaboration among Cleveland Clinic Children’s more than 300 pediatricians and pediatric subspecialists. We regularly draw on each other’s deep and diverse clinical and research expertise — some of it spotlighted in the 20 articles that follow here — in our quest for the best outcome and experience for each young patient and his or her family.

In the end, we all may find that teamwork is the best way to deliver truly individualized care.

Respectfully,

Giovanni Piedimonte, MD

Chairman, Pediatric Institute  |  Physician-in-Chief, Cleveland Clinic Children’s
President, Cleveland Clinic Children’s Hospital for Rehabilitation
piedimg@ccf.org
In the first 17 months after Cleveland Clinic Children’s Special Delivery Unit (SDU) opened in February 2012, 130 mothers with complicated pregnancies delivered there. What’s notable is that more than a quarter of those deliveries (n = 35) occurred in the SDU because of serious maternal conditions. To our knowledge, Cleveland Clinic Children’s has the first SDU in the nation designed to provide specialized care for both mothers and newborns with serious medical issues.

A Distinctly Diverse Case Mix

The SDU’s multidisciplinary team of specialists cares for two broad groups of patients:

- Mothers with significant, potentially life-threatening health issues (see sidebar for examples) complicating a sometimes long-desired pregnancy
- Babies with prenatally identified birth defects requiring subspecialty care not available outside a dedicated children’s hospital (see sidebar for examples)

Our patient population also includes women requiring surgical interventions during pregnancy who are monitored perioperatively in the SDU to ensure fetal well-being. When required, certain fetal interventions, such as percutaneous umbilical blood sampling and fetal transfusions, can also be performed in the SDU.

The aim of the SDU across all these populations is to optimize our ability to provide the best possible care for the infant-mother dyad.
Realizing a Vision of Mother-Child Togetherness, Care Coordination

More than 11,000 deliveries occur within the Cleveland Clinic health system each year, so there are many families in need of meticulous management and delivery planning because of fetal or maternal health issues.

Our past practice, like the current practice of many freestanding children’s hospitals, was to transport critically ill newborns immediately after delivery from community level III intensive care units to receive sometimes lifesaving subspecialty care. This practice inevitably resulted in separation of critically ill infants from their mothers, who often had surgery themselves and were not able to accompany their newborns during this critical time.

A significant number of women are referred to the SDU for their own medical issues (Figure 1). This includes pregnant women who were born with congenital heart disease and are at high risk for cardiac decompensation and death from carrying a pregnancy. Our maternal-fetal medicine specialists and renowned cardiologists specializing in heart disease management during pregnancy are involved in these women’s care early on and ensure that those risks are minimized. Close postpartum monitoring may require admission to a cardiac intensive care unit that is readily available on Cleveland Clinic’s main campus, very close to the SDU.

The SDU was not designed to handle a large number of patients but rather provide individualized care for high-risk situations. Most families delivering in the SDU have received comprehensive care, careful evaluation and delivery planning coordinated by Cleveland Clinic Children’s Fetal Care Center. These families include those expecting babies with lethal malformations for which interventions may be limited to comfort care and maximizing time spent with the family. Preparation and education of families, arranging for needed support, specialty consultation, imaging and follow-up are all part of the Fetal Care Center’s antenatal preparation services.

A Glimpse Inside: SDU Facilities and Staffing

The SDU includes the following physical components:
- Two labor and delivery suites
- A dedicated operating room large enough to accommodate teams for both mother and baby
- A triage room
- An advanced neonatal resuscitation area

Adjacent to the SDU is a pediatric hybrid cardiac catheterization suite where patients with congenital heart disease can receive lifesaving interventions combining catheterization and surgical procedures immediately after birth.

The unit is staffed by experienced labor and delivery room nurses who also rotate through one of the high-volume delivery units at our community hospitals as well as by 24/7 in-house obstetric staff with support from a team of maternal-fetal medicine specialists who are on call.

The neonatal intensive care and pediatric critical care units are located close to each other, and both are staffed around the clock with in-house intensivists, neonatal nurse practitioners and experienced nursing staff. A neonatal and pediatric extracorporeal membrane oxygenation (ECMO) program is available and co-managed by the neonatal and critical care teams. Babies with congenital heart disease requiring surgical intervention shortly after delivery are cared for in the pediatric intensive care unit in close collaboration with the consulting neonatology team.

To our knowledge, Cleveland Clinic Children’s has the first SDU in the nation designed to provide specialized care for both mothers and newborns with serious medical issues.
CASE STUDY OF A DISTINCTIVE SDU:
Equipped to Serve Moms (as Well as Babies) with Serious Conditions

Tabitha McClendon was born with a bicuspid aortic valve but had no symptoms until she became pregnant in her late 20s, when an echocardiogram revealed aortic stenosis. She was referred to Cleveland Clinic, where she was managed collaboratively by an adult congenital heart disease specialist and a high-risk maternal-fetal medicine specialist.

Tabitha’s stenosis progressed dramatically over the course of her pregnancy. By the third trimester, she was having chest pain, lightheadedness and dyspnea. She was told she would need a valve replacement, but her management team was confident it could wait until after her baby’s birth.

With close monitoring and vigilant care, she was able to carry to term and deliver a healthy baby, Olivia, by cesarean section under general anesthesia in Cleveland Clinic Children’s Special Delivery Unit (SDU) in May 2012. After the birth, Olivia was monitored in the SDU while Tabitha was monitored in the nearby cardiac intensive care unit.

Five months later, Tabitha underwent a successful tissue valve replacement, and she is now expecting her second baby under care from Cleveland Clinic specialists.

---

**Distribution of Indications in the SDU**

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>71 Fetal heart disease</th>
<th>59 Other fetal anomalies</th>
<th>35 Maternal indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Distribution of indications for Special Delivery Unit referrals over the unit’s first 17 months of operation. Total exceeds 130 because some deliveries involved more than one indication.

---

**ABOUT THE AUTHOR**

Dr. Iben is a staff physician in the Department of Neonatology and the Neonatology Director of the Fetal Care Center. She can be reached at 216.445.4810 or ibens@ccf.org.
The Early Childhood Program within Cleveland Clinic Children’s Center for Autism provides intensive applied behavior analysis services to children 18 months to 6 years old. These services allow a majority of children who exit the program to transition to a less intensive educational placement.

The Early Childhood Program, which is also part of Cleveland Clinic Lerner School for Autism, provides early, intensive behavioral intervention to young children who are diagnosed with autism spectrum disorders. Children receive 30 or more hours per week of intervention year-round through partnership between the education team and the child’s parents/guardians.

Using the science of applied behavior analysis and child development principles, an individualized curriculum is designed to teach communication, social interaction, play and a range of functional and adaptive skills.

**Making Mainstream and Less Intensive Placements the Rule**

Since the program opened in 2002, 101 students have graduated. The majority of children who have exited the Early Childhood Program over the past decade have moved on to mainstream placements with minimal or no educational supports needed (39 percent) or less intensive special education placements (26 percent) that do not require intensive behavioral intervention (Figure 1). A minority of students (35 percent) continue to need intensive behavioral intervention.

As a comparison, previous studies of intensive behavioral intervention programs for preschoolers have found rates of minimal-support placements of approximately 30 percent.

Over the past five years, increasing percentages of preschoolers have exited to settings where intensive behavioral intervention is no longer required for student success (Figure 2). These placements include mainstream classrooms without any additional support or with either pullout intervention (e.g., individualized instruction in mathematics or reading) or an aide providing behavioral and academic support as necessary. Higher baseline language scores after six months of intervention nearly perfectly predicted minimal-support placement at exit.

**Early Intervention Reduces Public Costs**

These findings indicate that young children with autism who attend the Early Childhood Program experience substantial improvements in their ability to function independently, resulting in decreased resource utilization and cost to the public education system.

**ABOUT THE AUTHOR**

Dr. Frazier is Director of the Center for Autism and a staff psychologist in the Center for Pediatric Behavioral Health. His research interests include studies to better understand autism symptoms and diagnosis, identification of autism traits in unaffected relatives and brain imaging studies of autism. He can be reached at 216.448.6440 or fraziert2@ccf.org.

**SUGGESTED READING**


Higher language scores after six months of intervention nearly perfectly predicted more favorable placement at exit.

Figure 1. Cumulative Early Childhood Program placement outcomes, 2002 to 2012 (N = 101), show that a majority of graduates exited to less intensive educational placements that did not require intensive behavioral intervention.

Figure 2. A steady increase has been observed in the percentage of Early Childhood Program students who exit to educational placements where intensive behavioral intervention is no longer required for student success.

A student in the Early Childhood Program works 1-to-1 with a behavior therapist during a group art project. Each student works on individualized goals that are developed based on his or her abilities and needs.
Glycogen Storage Disease: Bringing Singular Expertise to Bear for a Rare Metabolic Disorder

By Laurie Tsilianidis, MD, and Carrie Gonzales, RD, CSP, LD

Until the early 1970s, the most severe and well-known form of hepatic glycogen storage disease (GSD) was almost always fatal, marked by extreme failure to thrive, life-threatening hypoglycemia and acidosis. Today, infants and children diagnosed with this form of GSD (Type I, or von Gierke disease) or other GSD types can expect to live full, healthy lives with no limitations from their disease.

The primary reason for the turnaround was the discovery in 1971 that cornstarch was an effective therapy for hepatic forms of GSD, a heterogeneous group of inherited metabolic disorders characterized by defective glycogen utilization or synthesis. Though each form of GSD is distinct in presentation (Table 1), all forms manifest as fasting hypoglycemia and metabolic acidosis if untreated. Uncooked cornstarch taken by mouth is digested slowly, which helps keep blood sugar levels normal for extended time periods. Refinements in the precise dosing and timing of cornstarch administration over recent decades have helped GSD specialists go beyond keeping patients alive to allow them to live normal lives.

Cleveland Clinic Children’s is among a very small number of centers worldwide dedicated to providing comprehensive clinical care to patients with GSD and increasing knowledge of this rare group of diseases through research. Since the initiation of our GSD Program in December 2012, children and families from all over the country have traveled to Cleveland Clinic Children’s to receive expert care from our specialized multidisciplinary team (Figure 1).

Essentials of GSD

Incidence. The overall incidence of GSD is estimated to be 1 in 100,000 births. Mild forms of GSD are likely underdiagnosed.

Diagnosis. Definitive diagnosis of GSD previously required a liver biopsy and assay of enzyme activity, but now all types can be diagnosed noninvasively. When a particular type of GSD is suspected based on characteristic clinical and biochemical abnormalities, mutation analysis is recommended to confirm the diagnosis.

Treatment objective. In all types of GSD, the goal of treatment is to maintain normal blood glucose levels and minimize the metabolic derangements associated with hypoglycemia.

Treatment overview. The mainstay of therapy for all types of GSD is uncooked cornstarch. Patients mix the starch in water or other sugar-free liquid and drink it at specified intervals throughout the day. Uncooked cornstarch is a slowly digested dietary source of glucose that maintains blood glucose levels in the normal range for hours longer than other carbohydrate sources can.

The exact dose and interval that maintain normal blood glucose levels will vary by type of GSD, patient age and individual factors. Patients with GSD Type I require the highest doses and most frequent dosing because the enzyme that is deficient in these patients is also required in the gluconeogenic pathway. For this reason, protein or other nonglucose substrate cannot be used to decrease the amount of cornstarch required. For the same reason, galactose and fructose are monosaccharides that cannot be utilized by patients with GSD Type I. Sucrose, fructose and lactose are strictly avoided to prevent overstorage in the liver.

Our Approach: Individualized and Multidisciplinary

Our unique program at Cleveland Clinic Children’s offers patients with GSD a comprehensive approach to assess and optimize metabolic control by tailoring therapy to the individual.

Patients are admitted to our program for a stay ranging from one night to more than a week. During the stay, the patient undergoes a thorough metabolic evaluation in which blood glucose and lactate concentrations are assessed hourly as the patient receives his or her current treatment regimen or a regimen that has been empirically adjusted. All data collected during the hospitalization are used to adjust therapy to the exact regimen that will keep the individual’s blood glucose normal while preventing metabolic acidosis and other hypoglycemia-induced derangements. Patients also undergo screening laboratory studies, liver ultrasound and other tests as appropriate to assess for long-term complications of GSD.
Our team includes dietitians and physicians specializing in endocrinology, critical care, gastroenterology and genetics. We work together to address every issue related to the patient’s condition.

Prognosis Is Excellent with the Right Treatment

The prognosis for all types of GSD is excellent with appropriate treatment. Tailoring therapy to the individual can achieve excellent metabolic control. Virtually every long-term complication of GSD has been associated with metabolic control, and ameliorating the metabolic derangements from hypoglycemia can prevent morbidity.

Patients with GSD can expect to grow normally throughout childhood and participate in activities without any limitations. Long-term complications, once believed to be universal in the more severe forms of GSD, can be avoided with good metabolic control and near-normalization of laboratory tests. Liver transplantation is no longer routinely recommended for any type of GSD.

### Table 1. Profile of the More Common Types of Glycogen Storage Disease (GSD)

<table>
<thead>
<tr>
<th>TYPE</th>
<th>ENZYME DEFICIENCY</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD 0</td>
<td>Glycogen synthase</td>
<td>No hepatomegaly; ketotic hypoglycemia; postprandial hyperlactatemia</td>
</tr>
<tr>
<td>GSD I</td>
<td>Glucose-6-phosphatase</td>
<td>Hepatomegaly; most severe hypoglycemia; elevated lactate, uric acid and triglycerides; no response to glucagon</td>
</tr>
<tr>
<td>GSD III</td>
<td>Glycogen debranching enzyme</td>
<td>Firm hepatomegaly; AST/ALT often &gt; 1,000 IU/L; elevated creatine kinase (in some cases)</td>
</tr>
<tr>
<td>GSD VI/IX</td>
<td>Phosphorylase/phosphorylase kinase</td>
<td>Hepatomegaly with fasting ketosis</td>
</tr>
<tr>
<td>GSD XI</td>
<td>GLUT2 transporter</td>
<td>Hepatomegaly; ketotic hypoglycemia; postprandial hyperlactatemia; chronic glucosuria and diarrhea</td>
</tr>
</tbody>
</table>

**Figure 1.** In its first 10 months of operation, Cleveland Clinic Children’s Glycogen Storage Disease Program managed the care of 33 patients with GSD from 13 states (in blue) across the nation.
Imagine a noninvasive, painless and easy test that can tell if an obese child has fatty liver disease. Establishing such a test was our team’s objective when we took advantage of recent advances in breath testing to investigate novel biomarkers for nonalcoholic fatty liver disease (NAFLD) in obese children.

**Urgent Need for NAFLD Detection**

NAFLD is the most common form of chronic liver disease in childhood, affecting up to 50 percent of obese children. It is the hepatic manifestation of metabolic syndrome and should be suspected in all overweight or obese children and adolescents. The spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis to fibrosis and eventually cirrhosis and its complications. The diagnosis of NAFLD relies on blood testing, imaging studies and liver biopsy. In view of the childhood obesity epidemic sweeping our nation and the high prevalence of NAFLD, noninvasive methods of identifying children with NAFLD are urgently needed.

**Why Breath Testing Makes Sense**

The human body emits a wide array of volatile organic compounds (VOCs) in the breath that can be considered the “breath prints” of each individual. Pathological conditions such as obesity and NAFLD can lead to production of new VOCs or a change in the ratio of VOCs that are produced normally. Technological advances in breath testing and analysis through gas and liquid chromatography and mass spectrometry have made it possible to identify hundreds of VOCs in the breath. Breath testing offers major advantages in children because it is noninvasive and safe and because serial measurements are easy to obtain.

**Methods at a Glance**

Patients for our study were recruited from Cleveland Clinic Children’s Pediatric Preventive Cardiology and Metabolic Clinic, which was established in 2008 to evaluate and manage overweight and obese children for obesity-related comorbidities. Using selected ion flow tube mass spectrometry, our team analyzed exhaled breath from 37 obese or overweight children with NAFLD and 23 obese or overweight children without NAFLD. The children were asked to complete a mouth rinse with water before the exhaled breath collection to eliminate mouth sources of certain VOCs. Next they were asked to inhale to total lung capacity and then exhale into a collection bag against 10 cm of water pressure at a constant flow. The bag was taken to the laboratory and the analysis was completed using the mass spectrometry machine (Figure 1).

**Bottom-Line Results: NAFLD Has a Breath Print**

We found distinctive breath prints among children with NAFLD, as the concentrations of more than 15 VOCs differed significantly in these children relative to those without NAFLD. Further analysis revealed that concentrations of all the following compounds were significantly higher in children with NAFLD:

- Isoprene, a byproduct of cholesterol synthesis
- Acetone, a byproduct of glucose metabolism
- Trimethylamine, a byproduct of choline metabolism by the gut flora
- Acetaldehyde, a byproduct of ethanol metabolism
- Pentane, a marker of oxidative stress

We also developed a predictive model that included a number of the VOCs and correctly identified 90 percent of the children with NAFLD ($P < .0001$) (Figure 2).

Our findings were presented at Digestive Disease Week 2013 in Orlando, Fla.¹

**The Ultimate Goal: Early Tailored Intervention**

Exhaled breath analysis is a promising noninvasive method of detecting NAFLD in obese children. We hope our findings will ultimately help permit early detection of NAFLD and enable physicians to create tailored early intervention plans (in terms of lifestyle, diet and physical activity) to fight this epidemic one child at a time.
Concentrations of more than 15 volatile organic compounds differed in children with NAFLD relative to those without NAFLD.

Figure 1. Dr. Alkhouri with the selected ion flow tube mass spectrometry equipment used to analyze volatile organic compounds in children's breath.

Figure 2. Sensitivity and specificity results from our study. Breath testing can identify obese children with NAFLD with 90 percent accuracy.

REFERENCE


ABOUT THE AUTHOR

Dr. Alkhouri is Clinical Director of the Pediatric Preventive Cardiology and Metabolic Clinic, Co-Director of the Be Well Kids Clinic, and Director of Research in the Department of Pediatric Gastroenterology. His specialty interests include nonalcoholic fatty liver disease, childhood obesity, viral hepatitis, autoimmune liver disease and liver transplantation. He can be reached at alkhoun@ccf.org or 216.445.7126.
Congenital Heart Disease: As Percutaneous Procedures Become More Versatile, Innovations in Radiation Reduction and Customized Devices Matter More than Ever

By Lourdes R. Prieto, MD, and Alex Golden, MD

Percutaneous interventions are playing an ever-increasing role in the care of patients with congenital heart disease. Many lesions previously requiring open heart surgery can now be treated less invasively on an outpatient basis with minimal recovery times.

This progress, while enthusiastically welcomed, gives rise to new challenges, including the need to limit radiation exposure from these interventions and to develop devices tailored to the small bodies of our youngest patients. Here we profile a few examples of how we are meeting these challenges in Cleveland Clinic Children’s Center for Pediatric and Congenital Heart Disease.

Reducing Radiation with the Latest Angiography Technology …

As procedures become more complex and patients require multiple catheterizations over a lifetime, radiation exposure becomes an important consideration. The Center for Pediatric and Congenital Heart Disease is committed to the principle of ALARA, or “as low as reasonably achievable,” when delivering radiation in the catheterization laboratory.

We have worked with Siemens Healthcare to update one of our two catheterization laboratories with the newest available detector technology, the Artis Q.zen angiography system, approved by the FDA in March 2013. This system, which includes a crystalline silicon detector, reduces electronic noise, allowing imaging at much lower radiation levels than previously possible.

In addition to reducing radiation exposure to ultralow levels, the system is equipped with Siemens’ newly developed GIGALIX X-ray tube, which uses flat emitter technology to provide small focal sizes and strong, short X-ray pulses. The result is improved contrast and spatial resolution of small moving vessels. The laboratory is projected to be completed by the end of 2013.

…and Through Shorter Procedures with 3-D/2-D Registration

Another crucial factor in lowering radiation exposure is reducing procedure times. To that end, we are testing pediatric applications of a 3-D/2-D registration technology (syngo iGuide Toolbox, Siemens Healthcare) that allows anatomic structures from a prior cardiac MRI or CT to be superimposed onto fluoroscopic images. This technology facilitates access to a desired structure — for example, a collateral vessel, pulmonary artery branch or pulmonary vein — by providing a road map visible on fluoroscopy. It will likely result in decreased radiation exposure and reduced contrast administration.

In the catheterization lab we have the capability to perform rotational angiography (Figure 1), which reveals the 3-D anatomy of a structure, improving the diagnostic quality of the procedure and enabling more accurate selection of the best angiographic angles for a given intervention. This 3-D data set also makes it possible to register the location of a vessel on fluoroscopy, reducing the time and radiation needed to access a desired structure.

Assessing New Device for Atrial Septal Defects

Along with implementing the latest technology to minimize radiation while optimizing image quality, our interventional group is participating in the testing and development of leading-edge technologies to continue to advance pediatric cardiac intervention.

Cleveland Clinic Children’s was the first hospital in the world to use the new 3-French intravascular catheters approved specifically for pediatric use.
We are now enrolling patients in the GORE® Septal Occluder (GSO) Clinical Study to evaluate the safety and efficacy of a newly designed atrial septal defect closure device with many advantages over its predecessor, the HELEX® Septal Occluder (W.L. Gore & Associates). The GSO delivery mechanism significantly improves ease of use. Other design features enhance device apposition to the atrial septum and tissue response, which will likely increase atrial septal defect closure rates while also improving safety.

**Pioneering the Use of Pediatric-Tailored Intravascular Catheters**

Cardiac catheterization in infants is limited by the size of the sheath that can be safely inserted in the femoral artery for vascular access. Use of larger sheaths can result in significant complications, including arterial occlusion with compromised perfusion to the leg.

Our pediatric interventional cardiology group has worked with a nonprofit company, PediaWorks/PediaVascular, to design a system of 3-French intravascular catheters (Figure 2). 3-French catheters were previously available but did not allow accurate pressure measurements or adequate angiograms and were therefore rarely used. The FDA cleared the new catheters in January 2013, making these the only intravascular catheters approved specifically for pediatric use in the U.S. These catheters enable us to obtain hemodynamic information and perform

---

**Figure 1.** Three-dimensional rotational angiography following a fenestrated extracardiac Fontan procedure in a 5-year-old girl with hypoplastic left heart syndrome. The fenestration was subsequently closed with a device. This type of 3-D imaging can be used as a real-time map for live guidance during procedures.

**Figure 2.** The Mongoose® 3-French catheters developed by PediaWorks/PediaVascular with assistance from Cleveland Clinic Children’s pediatric cardiologists. These are the first intravascular catheters cleared by the FDA specifically for use in children.
angiography more safely than ever before. Cleveland Clinic Children’s was the first hospital in the world to use these new catheters.

Building a Robust Experience Base in Placing Percutaneous Pulmonary Valves

Since we began our percutaneous pulmonary valve program in 2010, we have placed these valves (Figure 3) in 37 patients ranging in age from 8 to 61 years. The Melody® Transcatheter Pulmonary Valve (Medtronic), the only FDA-approved percutaneous pulmonary valve, has been successfully implanted in all these patients, with no significant complications. Follow-up, now exceeding three years for the earliest patients, continues to demonstrate excellent valve function, with no patient requiring repeat intervention.

As a crucial safeguard in performing these procedures, we participate in a multi-institutional study that allows us access to covered stents in the rare case of a disruption in the conduit from the right ventricle to the pulmonary artery during preparation to implant the valve. These stents, which are not currently FDA-approved, are available to only a select group of institutions.

ABOUT THE AUTHORS

Dr. Prieto is Director of the Pediatric Catheterization Laboratory in the Center for Pediatric and Congenital Heart Disease. Her specialty interests include interventional catheterization in patients with congenital heart disease and pulmonary vein stenosis. She can be reached at 216.445.3865 or prietol@ccf.org.

Dr. Golden is a pediatric cardiologist in the Center for Pediatric and Congenital Heart Disease. His specialty interests include diagnostic and interventional cardiac catheterization and congenital heart disease. He can be reached at 216.445.7116 or goldena2@ccf.org.
Reduced-Radiation Ablation for Pediatric Tachyarrhythmias: Emerging Data Offer Reassurance of Uncompromised Efficacy

By Peter F. Aziz, MD

As fewer than 9 percent of pediatric cardiologists specialize in electrophysiology, research is essential to advancing knowledge in this subspecialty discipline. Cleveland Clinic Children’s Center for Pediatric and Congenital Heart Disease has a range of electrophysiology-related research projects underway. One of them, profiled here, has yielded results with the potential to impact treatment of children with tachyarrhythmias by providing reassurance that radiation exposure can be curbed or eliminated during catheter ablation procedures without compromising efficacy.

Catheter Ablation with Minimal to No Fluoroscopy

The risks of radiation exposure are dose-dependent and cumulative over time, which makes reduction of radiation exposure in pediatric patients highly desirable. Radiation exposure can be decreased during catheter ablation with a relatively new technique using a 3-D electroanatomical navigation system. Major cardiac structures are mapped and used as reference points for tracking the location of the ablation catheter with magnets (Figures 1 and 2). The system allows right heart ablation to be performed without fluoroscopy. When an arrhythmia is generated on the left side, fluoroscopy and intracardiac echocardiography are used to perform the transseptal puncture. However, ablation can be performed without fluoroscopy.

Sixty percent of the patients in our study who underwent 3-D electroanatomical mapping for catheter ablations required no fluoroscopy use.

Filling Knowledge Gaps with a Case-Control Study

Because 3-D electroanatomical systems are relatively new, our understanding of their efficacy relative to that of conventional catheter ablation is still evolving. To fill gaps in that understanding, we reviewed the charts of 20 pediatric patients (mean age, 14.1 years) who underwent 3-D electroanatomical mapping for catheter ablations in the treatment of supraventricular tachyarrhythmias at Cleveland Clinic Children’s from October 2012 to May 2013. All procedures were done by a single operator. Safety, efficacy and outcomes were compared with those of 20 age-matched control patients who underwent the same procedures by the same operator using conventional fluoroscopic guidance.

Although mean procedure time did not differ significantly between the two groups, mean fluoroscopy time was significantly lower with the 3-D mapping system (5.1 min) than with conventional fluoroscopic guidance (35.44 min) \( (P < .001) \). The average radiation dose was also significantly lower with 3-D
Figure 2. A snapshot of our “interface” of imaging using the 3-D electroanatomical navigation system. Intracardiac electrical tracings are shown during an atrial arrhythmia, along with the 3-D anatomical image of the right atrium. These tools are used simultaneously and provide an excellent map for use in targeting ablation.

mapping (7 mGy vs. 137.4 mGy; \( P < .0001 \)). Twelve patients in the 3-D mapping group (60 percent) required no fluoroscopy use.

Acute procedural success was achieved in 18 of 20 patients in each group. Recurrence of the tachyarrhythmia was seen in only one patient in each group at follow-up.

We are currently adding more patients to this data set and will soon be publishing our full results.

New Urgency to Shift to Reduced-Radiation Ablation

When we began this study in 2012, only about 1 in 50 electrophysiologists was using the 3-D mapping system to minimize fluoroscopy. Today, that number may be closer to 1 in 15.

Because the system’s manufacturer does not currently offer courses on using the system, I am training electrophysiologists in its use here at Cleveland Clinic Children’s. Our adult electrophysiology fellows frequently adopt this technique and take it to their new practice settings after they complete their training. I believe that the sooner this new system can be adopted, the more quickly we can reduce radiation exposure in our patients, young or old.

ABOUT THE AUTHOR

Dr. Aziz is a pediatric electrophysiologist in the Department of Pediatric Cardiology in the Center for Pediatric and Congenital Heart Disease. He can be reached at 216.445.6532 or azizp@ccf.org.
Progress in HLA-Haploidentical Hematopoietic Stem Cell Transplant: Are We Closer to a Universal Donor?

By Rabi Hanna, MD

For children with malignant or nonmalignant diseases affecting hematopoietic stem cells and their derivatives, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially lifesaving treatment. Yet donor availability remains one of the major challenges to the success of allo-HSCT.

Lingering Challenges in Donor Availability

Of all potential sources of allografts, transplantation of stem cells from a human leukocyte antigen (HLA)-matched sibling has generally produced the best overall and progression-free survival rates. Unfortunately, only about one-third of candidates for allo-HSCT have HLA-matched siblings. Advances in HLA typing have enabled excellent results to be achieved from appropriately HLA-matched unrelated donors. However, the chance of finding an HLA-matched unrelated donor varies significantly by the recipient's racial and ethnic background, ranging from more than 60 to 70 percent for whites to about 10 to 20 percent for ethnic minorities. The search for an HLA-matched unrelated donor is also hindered by the typically long time from search initiation to donor identification.

For patients who lack HLA-matched siblings or appropriately HLA-matched unrelated donors, there are alternative sources of stem cells for allo-HSCT:

- Umbilical cord blood unit(s)
- Partially HLA-mismatched unrelated donors
- HLA-haploidentical related donors

Table 1 outlines advantages and disadvantages of each source.

Haploidentical Transplantation: The Basics

An HLA-haploidentical donor is one who shares identity with the recipient for one HLA haplotype on chromosome 6 and is variably mismatched for HLA genes on the unshared haplotype. As each individual inherits exactly one HLA haplotype from each biological parent and passes on exactly one HLA haplotype to each biological child, any patient with a living parent or child has a potential HLA-haploidentical donor for stem cell transplantation, or haplo-HSCT. Additionally, each sibling or half-sibling has a 50 percent chance of sharing exactly one HLA haplotype with a patient (Figure 1).

Advantages of Haploidentical Transplantation

The major advantage of haploidentical HSCT is that it provides an opportunity for nearly all patients to benefit from HSCT, which takes us a step closer to the concept of a universal donor. Moreover, haploidentical donors can generally be identified quickly, are highly motivated to donate for a family member, and can donate lymphocytes in the event of post-transplantation relapse for purposes of donor lymphocyte infusion or other cellular therapies.

How Haploidentical Transplantation Became Safer

Haploidentical HSCT was once considered too dangerous for all but the sickest patients because of a high incidence of severe graft-vs.-host disease (GVHD). However, improvements in reduced-intensity conditioning regimens and GVHD prophylaxis with high-dose post-transplant cyclophosphamide made HLA-haploidentical replete HSCT a feasible option with acceptable outcomes for patients with high-risk malignancy and even those with life-threatening nonmalignant disorders.

Reduced-intensity conditioning haploidentical HSCT with high-dose post-transplant cyclophosphamide is associated with a cumulative incidence of acute grades II-IV GVHD of approximately 30 percent and with incidences of chronic GVHD and nonrelapse mortality of less than 15 percent. Post-transplant cyclophosphamide appears to nullify the detrimental effects of HLA mismatching on the outcome of haploidentical HSCT, thereby permitting selection of haploidentical donors based on criteria other than HLA matching. We include other criteria in choosing haploidentical donors, such as noninherited maternal antigens, natural killer cell function and killer cell immunoglobulin-like receptors (KIRs) mismatch.

Our Efforts to Refine Haploidentical Transplantation

Cleveland Clinic Children’s Pediatric Hematopoietic Stem Cell Transplant Program is taking part in a number of multicenter trials involving haploidentical HSCT, including:

- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Protocol 1101, a phase III prospective trial comparing reduced-intensity transplant using HLA-haploidentical donor cells vs. a double cord blood transplant regimen
The major advantage of haploidentical HSCT is that it provides an opportunity for nearly all patients to benefit from HSCT, taking us a step closer to the concept of a universal donor.

- A collaboration with the Fred Hutchinson Cancer Research Center titled “Nonmyeloablative Hematopoietic Cell Transplantation for Patients with Fanconi Anemia Using Alternative Marrow Donors: A Phase II Dose-Finding Study”

Additionally, we are developing a different protocol using a myeloablative conditioning regimen to reduce the risk of relapse and ultimately improve overall survival among patients who undergo haploidentical HSCT. We also hypothesize that increased intensity of conditioning therapy will enable us to reduce the graft rejection rate in patients with nonmalignant disorders such as sickle cell and aplastic anemia.

**The Goal: Providing a Chance for Cure to All**

At Cleveland Clinic Children’s, we strongly believe every patient who needs a blood or bone marrow transplant for a potential cure should have the chance to be cured, and HLA-haploidentical transplantation is a step toward achieving that dream. We are developing different haploidentical HSCT protocols to individualize treatment choices for our patients based on their particular disease, the condition they are in and their comorbidities.

**About the Author**

Dr. Hanna is Director of the Pediatric Hematopoietic Stem Cell Transplant Program. To refer patients to the program, call 216.444.3608. Dr. Hanna can be reached at hannar2@ccf.org.

---

### Table 1. Comparative Profiles of Alternative Hematopoietic Stem Cell Sources

<table>
<thead>
<tr>
<th>DONOR SOURCE</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| Umbilical cord blood unit(s)        | • Near-universal availability  
• Less GVHD per HLA mismatch | • High graft failure rate  
• Delayed immune reconstitution  
• High transplant-related mortality  
• Repeat donation unavailable  
• Expensive (especially for multiple units) |
| Partially HLA-mismatched unrelated donor | • Near-universal availability  
• Repeat donation may be available  
• Faster engraftment | • High GVHD rate  
• High transplant-related mortality  
• Long time from referral to transplant  
• Lower overall survival |
| HLA-haploidentical related donor | • Almost universally available  
• Repeat donation available and feasible  
• Low transplant-related mortality  
• Less expensive than cord blood units | • Higher risk of relapse |

*HLA = human leukocyte antigen; GVHD = graft-vs.-host disease*
Program Earns Fresh FACT Accreditation

Effective September 2013, Cleveland Clinic Children’s Pediatric Hematopoietic Stem Cell Transplant Program received three-year accreditation from the Foundation for the Accreditation of Cellular Therapy (FACT) for all services and facilities inspected, including:

- Pediatric allogeneic and autologous hematopoietic progenitor cell transplantation
- Marrow and peripheral blood cellular therapy product collection
- Cellular therapy product processing with minimal manipulation

Accreditation signifies that the program meets or exceeds national standards in patient care and laboratory practices.

Figure 1. Schematic of a family study illustrating haplotype matching. Sibling 1 is the patient in need of a hematopoietic stem cell transplant (proband). Sibling 2 shares 6/6 HLA genes and is considered fully matched with the patient. Siblings 3 and 4 each share only 3/6 HLA genes with the patient and are considered only one haplotype match (Sibling 3 is a haplotype “a” match; Sibling 4 is a haplotype “c” match). Sibling 5 does not share any HLA genes with the patient and is considered a mismatch or “no match.” In this scenario, the patient could consider receiving stem cells from Sibling 2 (preferred, because she is a full match), from Siblings 3 or 4 (haplotype matches), or from one of his parents, who are also haplotype matches.
Joining Forces Against Inappropriate Use: Pediatric Hospitalists Take a Lead Role in Two National Initiatives

By Rita Pappas, MD; Michelle Marks, DO; and Shannon Phillips, MD, MPH

It’s no secret: Keeping up with the rapid changes in medicine is challenging and takes thoughtful practice. The challenge can be greatest in the care of children, as 70 percent of pediatric patients receive care outside freestanding children’s hospitals, often at emergency departments and urgent care centers where adult-care providers have limited pediatric training. As a result, many patients undergo unnecessary testing and ineffective treatments for common pediatric problems for which practice guidelines exist.

To help stem this tide, Cleveland Clinic Children’s Department of Pediatric Hospital Medicine has recently partnered with pediatric hospitalist colleagues across the nation to increase awareness of appropriate, guideline-based treatments for common but often-mistreated pediatric diseases in the inpatient setting. We profile here two such collaborations that came to fruition in the past year.

Taking on Broken Bronchiolitis Management

Bronchiolitis (Figure 1) is the most common viral lower respiratory tract infection in infants. At least five different viruses can cause bronchiolitis, the most common being respiratory syncytial virus (RSV). RSV affects 90 percent of children before age 2 at an annual U.S. cost of $500 million to $700 million.

Care for bronchiolitis varies dramatically, and overutilization of ineffective therapies is common. In 2006, the American Academy of Pediatrics issued clinical practice guidelines for bronchiolitis. At Cleveland Clinic Children’s, we used these guidelines to craft a customized care pathway that directs and standardizes care. However, the large number of bronchiolitis patients we admit who have not been treated according to the guidelines was a continuing cause for concern.

When we realized the extent to which pediatric hospitalists nationwide were encountering the same problem, a group of us from 17 institutions formed a voluntary quality improvement collaboration we named the Value in Inpatient Pediatrics (VIP) network. Two of us (Drs. Rita Pappas and Michelle Marks) represented Cleveland Clinic Children’s. Our objective was to connect academic and community hospitalists to disseminate evidence-based management strategies for acute bronchiolitis. Specifically, we sought to reduce use of the following in hospitalized children diagnosed with uncomplicated bronchiolitis:

- Bronchodilators
- Steroids
- Chest physiotherapy
- Chest radiography
- Viral testing

Near-Term Payoffs in Bronchodilator Use as Education Continues

The effort began in 2008, with the collection and analysis of data on 11,568 hospitalizations for bronchiolitis from the 17 institutions using hospital administrative data from 2007 and 2008. Members of our VIP network were completely transparent and shared protocols, scores, order sets and key bibliographies in order to establish group norms for reducing utilization of ineffective treatments and promoting guideline-directed care.

After the data analysis, participating hospitals adopted guidelines at their own pace. By 2010, bronchodilator use had decreased by 12 percentage points from the baseline level. Chest physiotherapy use declined significantly, but no changes in steroid use, chest radiography or viral testing had yet been seen.

Today, educational efforts continue at these hospitals and others nationwide. Many are following the same techniques we have used at Cleveland Clinic Children’s since 2006 — creating a care pathway and educating physicians, nurses, respiratory therapists and families about bronchiolitis treatment on an ongoing basis.

Further Focus on Bronchiolitis Within Choosing Wisely Campaign

As a result of our participation in the VIP network, two of us (Drs. Rita Pappas and Shannon Phillips) were privileged to be chosen by the Society of Hospital Medicine to participate in the Choosing Wisely campaign, an initiative of the American Board of Internal Medicine Foundation. The overall group was charged with identifying five overused procedures that put hospitalized pediatric patients at risk for common but avoidable problems, such as hospital-acquired infections and adverse drug events, and warning against common but inappropriately used tests and treatments with limited effectiveness.
As representatives of Cleveland Clinic Children’s, we were charged with performing a literature review of bronchodilator use in children with bronchiolitis; other members of the group did the same for other issues of concern. Through this process, we arrived at an initial list of 20 possibilities, which we shared with our 8,000 pediatric hospitalist colleagues nationwide. With their input, our group arrived at our top five choices for the Choosing Wisely campaign, which were recently published2 and include avoiding routine use of bronchodilators in children with bronchiolitis (see sidebar).

It was clear from our group’s research that these five recommendations have not been standard practices nationwide. The identification of these issues has provided pediatric hospitalists with incentive to change order sets in their hospitals when needed — and with both evidence-based support and collegial support to help them do so.

Unnecessary tests and procedures increase the cost of care without bringing benefit to our patients. We are proud to have had the chance to contribute to collaborative efforts to drive down their use among our pediatric hospitalist colleagues nationwide. We look forward to further opportunities to do so and invite ideas and suggestions for future collaborations of this type.

Top 5 Pediatric Hospital Medicine Recommendations from the Choosing Wisely Campaign

- Don’t order chest radiographs in children with uncomplicated asthma or bronchiolitis.
- Don’t routinely use bronchodilators in children with bronchiolitis.
- Don’t use systemic corticosteroids in children under 2 years of age with an uncomplicated lower respiratory tract infection.
- Don’t treat gastroesophageal reflux in infants routinely with acid suppression therapy.
- Don’t use continuous pulse oximetry routinely in children with acute respiratory illness unless they are on supplemental oxygen.

REFERENCES


ABOUT THE AUTHORS

Dr. Pappas is a hospitalist in the Department of Pediatric Hospital Medicine as well as Medical Director, Department of Medical Operations, Cleveland Clinic. She can be reached at 216.444.4998 or pappasr@ccf.org.

Dr. Marks is Interim Chair, Department of Pediatric Hospital Medicine, and Medical Director, Inpatient Pediatrics. She can be reached at 216.444.4998 or marksm@ccf.org.

Dr. Phillips is a hospitalist in the Department of Pediatric Hospital Medicine as well as Quality and Patient Safety Officer, Main Campus, in the Quality and Patient Safety Institute. She can be reached at 216.444.4998 or phillis@ccf.org.
The evaluation and management of urinary tract infection (UTI) and vesicoureteral reflux (VUR) in children have been topics of debate, confusion and controversy for many practitioners. Although recent guidance has come in the form of clinical practice guidelines from the American Academy of Pediatrics (AAP) on diagnosis and management of initial UTI in febrile infants and children 2 to 24 months old and from the American Urological Association on management of primary VUR, standardization of care remains to be achieved. Moreover, these guidelines do not address some frequent clinical challenges — at least not with the specificity that real-world practice can demand.

To begin a conversation on how such guideline gaps might best be filled by front-line practitioners, this article shares perspectives on how we manage UTI and VUR challenges at Cleveland Clinic Children’s Center for Pediatric Nephrology when guideline recommendations may be lacking.

**Imaging**

The AAP clinical practice guideline recommends a renal and bladder ultrasound upon initial febrile UTI in children 2 to 24 months of age. The AAP does not recommend routine voiding cystourethrogram (VCUG) in this age group, though VCUG is recommended after a second febrile UTI. There is no clear recommendation by the AAP for children older than 2 years.

At Cleveland Clinic Children’s, we do not routinely perform VCUG in children older than 2 years, especially not in those with symptoms of lower urinary tract dysfunction. We perform a dimercaptosuccinic acid (DMSA) renal scan when renal and bladder ultrasonography is abnormal, when there is grade III-V VUR, or if there are signs of renal damage such as hypertension, proteinuria or elevated serum creatinine.

**Antibiotic Treatment**

At Cleveland Clinic Children’s, we treat initial uncomplicated cystitis with five to seven days of antibiotics, whereas we treat febrile UTI, complicated cystitis and recurrent cystitis with 10 to 14 days of antibiotics. Oral antibiotics are used in most cases. We admit children for intravenous antibiotic therapy if they are younger than 1 month of age, have high-grade fever for more than 48 hours after initiating antibiotics, present with nausea and vomiting, or require intravenous fluid for rehydration.

Most children with febrile UTI experience defervescence by 48 hours with adequate treatment. If it takes longer than 48 hours for fever to improve, we obtain a renal ultrasound and broaden antibiotic coverage for Enterococcus and/or Pseudomonas organisms.

**Test of Cure**

We do not routinely perform repeat urine cultures to prove eradication of UTI; exceptions are cases of recurrent infections, infections with drug-resistant organisms, immunosuppression or urological abnormalities.

**Bladder/Bowel Dysfunction**

About one-third of children with higher-grade VUR experience symptoms related to bladder/bowel dysfunction (BBD). These symptoms include urinary incontinence, dysuria, urinary frequency or infrequent voiding, constipation, and encopresis. The urinary bladder may not empty completely in BBD, and incomplete bladder emptying can lead to UTI. BBD adversely affects the resolution of VUR, and children on prophylactic antibiotics for recurrent UTI tend to experience breakthrough UTI more frequently if they have BBD than if they do not have it. Children with VUR and BBD may be at greater risk for renal damage.

**Antibiotic Prophylaxis**

At Cleveland Clinic Children’s, we provide antibiotic prophylaxis to children less than 1 year old if they have febrile UTI and have any grade of VUR or if they have grade III-V VUR without a history of febrile UTI. We also provide antibiotic prophylaxis to children who have BBD and VUR, as they are at increased risk of UTI while their BBD is being treated.

**Biofeedback and Pelvic Floor Muscle Retraining**

At Cleveland Clinic Children’s, we treat BBD with constipation management, behavioral therapy, anticholinergic medications,
alpha-blockers, biofeedback and pelvic floor muscle retraining. Therapy is tailored to each child’s individual needs.

We use electromyography-based biofeedback therapy to retrain pelvic muscles and to strengthen and coordinate bladder contractions. We employ animated biofeedback designed to encourage patients’ interest and help attain results much more quickly.

**Fever a Poor Indicator of Renal Parenchymal Involvement**

Persistent high fever is often used as a clinical marker to differentiate between upper and lower UTI, although it might not be a reliable marker. The risk of renal scarring is comparable between children with and without persistent high fever. Therefore, we recommend meticulous treatment and prevention of both nonfebrile and febrile UTI in pediatric patients.

**REFERENCES**


**ABOUT THE AUTHOR**

Dr. Janjua is a pediatric nephrologist in the Center for Pediatric Nephrology. Her specialty interests include pediatric kidney transplantation. She can be reached at 216.448.6420 or janjuah@ccf.org.
Cleveland Clinic has long offered hemispherectomy for severe epilepsy associated with Rasmussen encephalitis (RE). Now our pediatric epilepsy and immunology specialists are teaming up to offer immune modulatory therapy to help children with RE who are not favorable candidates for surgery.

Rasmussen Encephalitis at a Glance

RE is a unique inflammatory disorder of the brain that leads to progressive destruction of one hemisphere. Typical manifestations include drug-resistant epilepsy, progressive hemiparesis and cognitive/language deficits.

The precise etiology of RE remains unknown, but immune-mediated injury is considered central in the pathogenesis. Current evidence suggests neuronal and astrocyte injury mediated by granzyme B-expressing T cells. Similarities in the histopathological changes between RE and viral encephalitis have long suggested possible viral infection as an initiating event, leading to an inflammatory cascade over the entire hemisphere. This hypothesis remains viable, but no specific viruses have been found to date.

RE typically affects children between 5 and 7 years of age. Patients often present with motor seizures that quickly become medically refractory; many patients also develop epilepsia partialis continua. Over several months, motor and cognitive deficits due to hemispheric injury ensue (Figure 1). The perirolandic cortex appears to be at the epicenter of the disease process, thus explaining motor seizures and hemiparesis.

RE sometimes presents with atypical features, as noted in Figure 2. Atypical features may occur in various forms, as follows:

- Younger age (often associated with more rapid progression, and occasionally involving both hemispheres)
- Older age (frequently slow progression and localized disease)
- Location of brain injury outside the perirolandic region (e.g., temporal lobe, basal ganglia involvement)
- Atypical clinical features (infrequent or no seizures, early hemiparesis or no hemiparesis)
- Dual pathology (10 percent of patients have additional pathology such as dysplasia)

---

**Figure 1.** Natural course of Rasmussen encephalitis in a typical patient. EPC = epilepsia partialis continua.

**Figure 2.** Atypical presentation of Rasmussen encephalitis with case examples. EPC = epilepsy partialis continua.
Treatment Options for Seizure Freedom

Treatment options for children with RE are outlined in Figure 3. Hemispherectomy or some form of hemispheric disconnection is the most effective treatment leading to seizure freedom. Though several different variations of hemispherectomy are available, all procedures aim to disconnect the diseased hemisphere from the opposite hemisphere and the brain stem. In our recent study at Cleveland Clinic examining longitudinal outcomes of 170 children after hemispherectomy (Neurology, 2013;80:253-260), 71 percent of 21 patients with RE were seizure-free on long-term follow-up.

No anti-epileptic drug is particularly effective in RE. Surgery is undertaken once there is no additional risk of neurological deficits after hemispherectomy. In an ideal candidate, hemispheric disconnection offers maximal chances for seizure freedom without the risk of additional neurological deficits.

In practice, surgery is usually considered when patients lose hand function on the affected side. Rarely, some patients with life-threatening recurrent status epilepticus may be subjected to hemispherectomy even in the absence of hemiparesis. Focal cortical resections have not been found to be of benefit in RE.

Immunotherapy Effect: Modest at Best

The presence of inflammatory changes on pathology and early reports of an association with the Glut3 receptor antibody prompted clinicians and researchers to try various forms of immunotherapy. Autoimmune disorders may be viewed as “autoimmune errors” committed by the host’s immune system. Recovery from autoimmune disorders depends on the host’s ability to correct its own error. In some autoimmune disorders, this occurs in a few weeks — and in others, a few years. Immune therapy reduces ongoing injury when the organs self-correct the autoimmune error.

As a general rule, in most autoimmune disorders, immunosuppression reduces injury by inflammation but has a minor role in reversing the primary disease process itself. Injury to the brain, unlike other organs, is frequently irreversible, resulting in debilitating neurological deficits. For this reason, every attempt should be made to preserve function in patients who are not candidates for hemispherectomy.

The effect of immunotherapy on the course of RE is still modest at best. The goal of “no seizures and no progression of disease” by immunotherapy remain elusive. Initial reports of steroid use (pulse intravenous steroids followed by oral steroids) have revealed only short-term improvement with no benefits in long-term outcomes. Side effects related to long-term use of steroids further compromised any benefits.

Currently, most centers use intermittent intravenous immunoglobulin (IVIg) or continuous tacrolimus as long-term immune therapy. A recent trial of IVIg vs. tacrolimus in RE showed a decrease in progression of neurological deficits in some patients, but there was little effect on epilepsy (Epilepsia. 2013;54:543-550).

In short, immunotherapy may delay the onset of neurological deficits, but it does not reduce seizure burden. This may at times lead to a protracted course of continued seizures (prolonged active stage) without hemiparesis, making surgery undesirable. Nevertheless, immunotherapy remains an option and should be considered in patients at risk for major deficit(s) after surgery.

The combination of immunotherapy agents (e.g., IVIg and tacrolimus) and newer biologicals used in other autoimmune diseases may be considered for trials in RE. Rare patients with fairly well-controlled seizures without clinical evidence of progression may be observed with anti-epileptic drugs alone.

Bottom Line

Hemispherectomy remains the best available treatment for intractable epilepsy due to RE. Further research on pathogenesis and treatment may guide us toward the elusive goal of “no seizures and no progression of disease” without surgery.

ABOUT THE AUTHOR

Dr. Moosa is a pediatric epilepsy staff physician in the Neurological Institute’s Epilepsy Center and the Center for Pediatric Neurology. He can be reached at 216.445.6746 or naduvia@ccf.org.
What happens to a child’s brain when it is compressed by expanding ventricles? It is well understood that when anything enlarges relatively quickly in the closed skull, whether a tumor or growing ventricles, pressure rises and blood flow to the brain is threatened. At the same time, masses like the cerebral ventricles also may enlarge more slowly and the brain may anatomically and functionally accommodate to some extent.

In chronic hydrocephalus, dramatic thinning of the cortex may be observed, but it is accompanied by a surprisingly high level of cognitive function. This raises a series of questions:

- What is compressed or missing in that thinned cortical mantle?
- How is function preserved?
- Can we learn how to help the brain cope even better with the compression of chronic hydrocephalus or any other chronic deforming force?

At Cleveland Clinic Children’s Center for Pediatric Neurology and Neurosurgery, we have been actively working to address those questions for more than a decade.

A Surprising Finding from Our Early Work

We began by asking what specifically is compressed when the brain is squeezed by expanding ventricles. Previous work by others had indicated that the low-pressure vessels, such as capillaries and venules, were the most vulnerable and that neurons themselves would be resistant to the compression. In our first studies, we indeed also found reduced vascularity and, specifically, a reduced density of capillaries in the early weeks of hydrocephalus development. This reinforced a general hypothesis that hydrocephalus disrupted neuronal function in part by decreasing cerebral blood flow.

However, our longer-term findings, after 12 weeks of hydrocephalus, were a surprise: There was a dramatic two- to threefold increase in capillary density that suggested the creation of new vessels, or angiogenesis. Could new blood vessel growth in chronic hydrocephalus (Figure 1) be an adaptive response to a state of low blood flow and relative hypoxia?

More Findings Suggestive of Angiogenesis

Subsequent studies further suggested an angiogenic response to chronic hydrocephalus. Hypoxia, an established trigger for angiogenesis, was observed. CSF oxygen saturation was lower in chronic hydrocephalus, improved with shunting and decreased again with shunt removal. Receptors for vasoactive endothelial growth factor (VEGF), a promoter of angiogenesis, increase in the hydrocephalic hippocampus and caudate (Figure 2) and decrease with shunting. Finally, VEGF levels are measurable in human and animal CSF and are elevated in hydrocephalus. In many but not all cases, increased VEGF receptor densities correlated with increased density of capillaries.

Remaining Questions Center on the Role of VEGF Changes

Although the story emerging is consistent with an adaptive angiogenic response to chronic hydrocephalus, the role of VEGF increases and angiogenesis is still unknown. The effects of VEGF on blood vessel permeability and tissue edema also have been suggested to play a pathophysiologic role in fluid accumulation. VEGF may indeed be increasing capillary density in some situations, but whether this translates into more blood flow to tissue is uncertain. Other known effects of VEGF, such as neuroprotection, also may be pivotal in any attempt to mitigate the injury of hydrocephalus. This is especially intriguing in view of the observation of increased VEGF receptors on neurons in the hydrocephalus-affected hippocampus.

To explore the role of VEGF changes in hydrocephalus, current studies focus on the net effect of blocking VEGF systems in experimentally induced hydrocephalus with an eye toward answering the following:

- Does VEGF stimulation in chronic hydrocephalus result in an adaptive response?
- Can we use this physiologic response as an avenue to improve function in children or adults with chronic ventriculomegaly?

These questions underlie the vision that will guide this research in the coming years — a vision we look forward to helping carry out.
Dr. Luciano is a pediatric neurosurgeon in the Center for Pediatric Neurology and Neurosurgery. He can be reached at 216.444.5747 or lucianm@ccf.org.

Dr. Deshpande, a neuroscience researcher in the Department of Neurological Surgery, is the recipient of a Young Investigator Development Grant from the Hydrocephalus Association for the study of angiogenesis in hydrocephalus. He is participating in a pilot study to block VEGF in hydrocephalus. He can be reached at deshpaa2@ccf.org.

REFERENCES
Regenerating the Physis: New Insights and Tissue Engineering Advances Could Transform Repair of Pediatric Growth Plate Injuries

By R. Tracy Ballock, MD

Childhood fractures are practically a rite of passage: Approximately 42 percent of boys and 27 percent of girls suffer at least one broken bone by the time they reach age 16.

About 20 to 30 percent of fractures of long bones in children involve the growth plate, the area of growing tissues near the end of the long bones in children and adolescents that determines the future length and shape of the mature bone. The growth plate, also known as the epiphyseal plate or physis, is the weakest area of the growing skeleton and is therefore susceptible to injury.

Growth Plate Injuries: Why the Stakes Can Be High

Although most fractures through the cartilage growth plates of the long bones heal uneventfully, specific types of injury may cause growth arrest with subsequent leg length inequality and progressive deformity. This growth arrest is due to formation of a bony bar or bridge across the injured growth plate that acts as an effective tether to resist further longitudinal growth. Once a physeal bar forms, surgical excision is technically difficult and is often unsuccessful in restoring normal growth.

Physeal Cartilage Regeneration Would Be Transformative

Our understanding of factors that regulate the proliferation and differentiation of growth plate chondrocytes, combined with advances in cartilage tissue engineering, now provides a unique opportunity to develop strategies for regenerating physeal cartilage in vivo following serious growth plate injuries. Successful regeneration of growth plate cartilage architecture would have a transformational impact on the practice of pediatric orthopaedic surgery, making it possible for the first time to replace growth plates irreversibly damaged not only by trauma but also by infection or irradiation.

Our Work to Replicate Columnar Growth In Vitro

An essential step in achieving the overarching goal of growth plate regeneration is to understand the factors required for recapitulation of the normal columnar architecture of growth plate cartilage. Alignment of growth plate chondrocytes into columns is necessary to impose direction on longitudinal bone growth. Though the precise cellular and molecular mechanisms governing columnar morphogenesis remain unknown, our laboratory has developed a three-dimensional cell culture model (Figure 1) that replicates in vitro the critical features of an integrated systemic and local signaling network that appears to regulate columnar morphogenesis in the growth plate in vivo.

Using this model to investigate the molecular mechanisms governing columnar morphogenesis at the growth plate, we have demonstrated that column formation can occur in vitro under low serum conditions — or under chemically defined, serum-free conditions in the presence of thyroid hormone and growth hormone. Activation of the local Wnt planar cell polarity signaling pathway also induces morphogenesis of columnar cartilage, a process significantly enhanced by overexpression of the Wnt receptor Frizzled-7 and receptor-associated proteins (Figure 2).

Where We Aim to Take Our Research

These preliminary data are consistent with the existence of an integrated systemic and local signaling network that regulates columnar morphogenesis at the growth plate. The objective of our future work is twofold:

• To determine how these systemic and local signaling pathways interact to achieve the orchestrated control of chondrocyte column formation in the growth plate that produces oriented longitudinal bone growth in children
Successful regeneration of growth plate cartilage architecture would make it possible for the first time to replace irreversibly damaged growth plates.

- To use this information to eventually optimize column formation of growth plate cells in vitro as a prelude to eventually regenerating growth plate tissue in vivo

Elucidating how this signaling network functions to regulate columnar morphogenesis will facilitate regeneration of the columnar architecture of the growth plate in vitro, which is a crucial step in achieving the ultimate goal of regenerating damaged growth plates in vivo.

The research described here is supported by grants from the National Institutes of Health and the Musculoskeletal Transplant Foundation.

Dr. Ballock is a surgeon in the Center for Pediatric Orthopaedics and Spine Deformity, Professor of Surgery at Cleveland Clinic Lerner College of Medicine and a staff member in the Department of Biomedical Engineering. His clinical interests include skeletal development, hip dysplasia, clubfoot, deformity correction, leg lengthening, pediatric foot and ankle problems, and pediatric fractures. He can be reached at 216.444.5775 or ballock@ccf.org.
Augmentative and Alternative Communication Strategies for Children with Angelman Syndrome

By Jackie Kearns, CCC-SLP, and Douglas Henry, MD

Cleveland Clinic Children’s experts in pediatric speech and language pathology are using cutting-edge technology to improve communication skills for children with Angelman syndrome and other neurological disorders. Through the use of augmentative and alternative communication strategies, speech-language pathologists work to shorten the gap between a child’s receptive and expressive language skills.

An Approach Well Suited to Angelman Syndrome

Augmentative and alternative communication (AAC) refers to a set of procedures aimed at improving, temporarily or permanently, the communication skills of those who have minimal to no functional speech and/or writing. AAC can use both unaided (manual signs, gestures, finger spelling, eye gaze) and aided (picture communication symbols, voice output communication aids) forms of communication. While all speech-language pathologists generally have some cursory knowledge of AAC, not all therapists specialize in this area of communication.

At Cleveland Clinic Children’s, AAC has been especially rewarding for children with Angelman syndrome. This disorder is caused by a disruption in chromosome 15, with the most common disruption caused by a large deletion of the maternal chromosome. Despite several differences in gene mutation, some characteristics are present in all cases of Angelman syndrome. In addition to severe developmental delays, Angelman syndrome is characterized by a movement or balance disorder, ataxia, which can vary from mild to severe. Affected children demonstrate an apparent happy demeanor and hypermotoric behavior.

Children with Angelman syndrome have severe to profound communication impairments. Receptive language is typically more advanced than expressive language. Verbal speech is extremely limited, so all children with Angelman syndrome are excellent candidates for AAC.

Early Intervention Is Critical

Children with Angelman syndrome vary greatly in the types of AAC they use, often employing more than one mode of communication. It has been observed that early communication milestones include the use of eye gaze, facial expression and body posturing.

While these behaviors are unintentional initially, it is crucial for early intervention services to train caregivers to interpret these unintentional actions. Only then will these unintentional acts be shaped into more conventional forms of communication.

A common example of language shaping can be seen with infants, who go through a period of reduplicated babbling. A typical child may spontaneously babble an approximation of “mama” or “dada.” This is not intentional at first. A caregiver, on hearing the child use that approximation, will say, “That’s right! You said ‘mama/dada’ … that’s me!” Shortly after receiving this consistent praise and attention, the child begins to use “mama” and “dada” purposefully.

Turning the Unintentional into the Deliberate

While the child initially demonstrates early, unintentional communication acts, it is really the caregiver who provides the necessary supports and encouragement to shape those unintentional acts into true communication. Similarly, this strategy is often used for children with complex communication needs.

Gestural communication is another strong skill in children with Angelman syndrome. Initially, these gestures may begin by physical contact. For example, a child may push away an unwanted object or take a caregiver’s hand to lead him or her toward a desired object. The 2002 article by Stephen Calculator (see Suggested Reading) provides an excellent therapeutic technique for creating enhanced natural gestures for children with severe communication impairments, including Angelman syndrome.

A Role for Communication Aids Too

In addition to nonaided forms of AAC, aided AAC techniques have proved quite successful in children with Angelman syndrome. These methods may include use of single pictures, communication books/boards or voice output communication aids (VOCAs). A wide range of VOCAs are available on the market today, from simple single-message communicators to dynamic display communication aids (see Figures 1 to 3). iPad® tablets with apps such as Proloquo2Go®, TouchChat™ or LAMP Words for Life™ also may be suitable communication aids for children with Angelman syndrome.
A Team-Based Approach to Care

The Technology Resource Center at Cleveland Clinic Children's Hospital for Rehabilitation helps all children whose ability to communicate has been hindered by injury, chronic illness or congenital issues. The therapists at the Technology Resource Center help children interact with others by teaching AAC.

Every child is first seen by a speech-language pathologist who specializes in AAC. The therapist may consult with occupational therapists, physical therapists and physicians to help evaluate a child’s strengths and barriers. Parents, teachers and other professionals already involved with the child are important members of the team and participate in planning and decisions.

Based on team recommendations, a communication plan is developed. If a child needs specialized equipment, Technology Resource Center staff will help families find it. The staff not only prescribes communication devices but also teaches patients, family members and other members of a child’s care team how to use them.

ABOUT THE AUTHORS

Ms. Kearns is a senior speech-language pathologist and Coordinator of the Technology Resource Center in Cleveland Clinic Children’s Hospital for Rehabilitation. She works with children with a variety of complex communication needs. She can be reached at 216.448.6157 or kearnsj@ccf.org.

Dr. Henry is Director of Developmental Pediatrics and Physical Medicine and Rehabilitation. He can be reached at 216.448.6179 or henryd@ccf.org.

SUGGESTED READING


Electroconvulsive Therapy (ECT) is a highly effective treatment modality for multiple psychiatric and medical illnesses. Although commonly used in adults, this therapy is significantly underutilized in the adolescent population. Cleveland Clinic is the only medical center in Northeast Ohio offering ECT for pediatric patients. The therapy is administered here by a team of child and adolescent psychiatrists who are accredited in its use.

Effective use of ECT has been demonstrated in adolescents since 1942. Yet despite the longevity of its use and endorsement by the American Academy of Child and Adolescent Psychiatry, ECT remains highly stigmatized and misunderstood.

ECT Knowledge Gaps Persist — Even Among Specialists

Even mental health professionals have knowledge gaps about the use of ECT. In a survey of child psychiatrists and psychologists, 53.8 percent reported their knowledge about ECT to be minimal, 75 percent said they lacked confidence in giving a second opinion about the treatment modality and 70 percent regarded it as a treatment of last resort.1

ECT also is not well understood by the public, and few pediatric patients receive the treatment. In a study in Switzerland, only 1.2 percent of a representative sample of the public was in favor of the use of ECT, and 75 percent considered it a harmful treatment.2 In a survey of 113 hospitals in Australia, out of 7,469 patients who received ECT, only 0.2 percent were younger than 18 years.3

Determining Appropriate Indications

The adult population is referred for ECT most often for mood disorders, while adolescents are referred most often for schizophrenia or schizoaffective disorders. This contrasts with findings that the adolescent population responds to ECT for mood disorders and psychosis as well as, or even better than, the adult population, while experiencing fewer or the same degree of side effects. Substantial empirical evidence supports the benefit of ECT in adolescents for severe, persistent mood disorders, psychosis or catatonia. There also are multiple reports demonstrating benefits for self-injurious behavior in autism spectrum disorders and Tourette syndrome.4

As with adults, ECT should be considered in adolescents when there are severe, persistent and significantly disabling symptoms. Unless there is an urgent need, such as the refusal to eat or drink, severe suicidality, uncontrollable mania or florid psychosis, ECT should be considered only after usual treatment modalities have failed. There should be at least two adequate trials of appropriate psychopharmacologic agents accompanied by other appropriate treatment modalities such as psychotherapy.2

Best Practices When Administering ECT

Adolescent patients should undergo a full psychiatric and medical evaluation in a standardized fashion when ECT is being considered (Table 1).2 Collateral information should be obtained from parents and treatment providers. Target symptoms should be assessed using reliable rating instruments.

Before ECT is administered, a comprehensive physical should be done that includes a complete blood cell count, differential white blood cell count, thyroid function test, liver function test, urinalysis and toxicology screen, ECG and brain CT. A serum urine pregnancy test should be obtained for females. Also, it is recommended that adolescents undergoing ECT have a memory assessment before treatment. Permission must be obtained from the parent/guardian and assent obtained from the child.

When considering ECT, every patient should receive an independent evaluation from a psychiatrist who is knowledgeable about ECT and not directly responsible for treatment of the patient. While supportive treatment of adolescents should continue during the course of ECT whenever possible, ECT should be administered without concurrent medications, as some psychotropic medications may affect the quality of ECT or confer a neurocognitive risk with the concurrent use of ECT.2

Low Incidence of Side Effects

There are no absolute contraindications to the use of ECT; however, active chest infection, recent myocardial infarction and tumors of the CNS associated with increased CSF pressure are considered relative contraindications.

A few side effects are associated with the use of ECT, the most common of which are transient: headaches, delirium lasting less
than one hour post-procedure, hypomanic symptoms and memory loss. Cognitive effects associated with ECT are comparable to those in adults, and there are no data to support long-term cognitive effects.

One rare side effect may include tardive seizures arising in the first 20 to 48 hours after ECT is administered. This effect was seen more often in those patients experiencing a prolonged seizure (>180 seconds).

Fatality is rare, with an overall fatality rate similar to that in adults (0.2 per 10,000). The risk of anesthesia-related complications is believed to be no greater than 1.1 per 10,000 incidents, which is cited as comparable to adults.²

**Despite the Stigma, Consider ECT in the Right Circumstances**

ECT in adolescents is most beneficial for the treatment of severe mood symptoms, acute suicidality, catatonia and psychosis. Some studies report a remission rate of approximately 60 percent for treatment of refractory unipolar depression.³

Although ECT is commonly misunderstood and stigmatized, it is a valid, safe and effective treatment modality for adolescents suffering from mood or psychotic symptoms and should be considered as a rational treatment option.

**Table 1. Recommended Assessment Protocol in Adolescents with Depression**

<table>
<thead>
<tr>
<th>STEPS</th>
<th>ACTIONS/NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient selection</td>
<td>• Symptoms are severe and persistent</td>
</tr>
<tr>
<td></td>
<td>• Failed at least two adequate antidepressant trials accompanied by other appropriate treatment modalities such as psychotherapy</td>
</tr>
<tr>
<td></td>
<td>• Active suicidality, florid psychosis or life-threatening symptoms such as refusal to eat</td>
</tr>
<tr>
<td>Psychiatric assessment</td>
<td>• Detailed clinical interview incorporating past treatments</td>
</tr>
<tr>
<td></td>
<td>• Reliable rating instruments administered</td>
</tr>
<tr>
<td></td>
<td>• Second opinion obtained by a psychiatrist knowledgeable about ECT who is not treating the patient</td>
</tr>
<tr>
<td></td>
<td>• Cognitive and memory assessment</td>
</tr>
<tr>
<td>Medical assessment</td>
<td>Complete physical assessment</td>
</tr>
<tr>
<td></td>
<td>Laboratory data:</td>
</tr>
<tr>
<td></td>
<td>• CBC with differential</td>
</tr>
<tr>
<td></td>
<td>• Thyroid function test</td>
</tr>
<tr>
<td></td>
<td>• Liver function test</td>
</tr>
<tr>
<td></td>
<td>• Urinalysis and toxicology</td>
</tr>
<tr>
<td></td>
<td>Imaging:</td>
</tr>
<tr>
<td></td>
<td>• ECG</td>
</tr>
<tr>
<td></td>
<td>• EEG</td>
</tr>
<tr>
<td></td>
<td>• CT</td>
</tr>
<tr>
<td>Consent</td>
<td>Complete explanation of the procedure, risks, benefits and alternative treatments to both the patient and the parent/guardian</td>
</tr>
<tr>
<td>Monitoring</td>
<td>• Monitor patients during and after treatment until fully recovered from anesthesia</td>
</tr>
<tr>
<td></td>
<td>• Monitoring should continue at least 24 hours after the procedure</td>
</tr>
<tr>
<td></td>
<td>• Cognitive assessment prior to acute ECT series, immediately after the acute series</td>
</tr>
</tbody>
</table>

Source: Based on recommendations in Ghaziuddin et al²

---

ABOUT THE AUTHOR

Dr. Austerman is a staff physician in the Center for Pediatric Behavioral Health and Section Head of Child and Adolescent Psychiatry. He specializes in the acute care of medically ill children who require hospitalization for physical illnesses. He can be reached at 216.445.7656 or austerj@ccf.org.

REFERENCES

Could RSV Be Transmitted Through the Placenta into Developing Fetal Lungs?

Animal studies demonstrate vertical transmission in utero, paving way for potentially paradigm-shifting human studies

By Giovanni Piedimonte, MD

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and young children. Strong epidemiologic evidence suggests that when infants are infected, they are predisposed to chronic respiratory dysfunction and asthma, possibly due to persistence of the virus or its effects on lung development.

For many years, it has been generally accepted that the pathophysiology of RSV bronchiolitis is driven by the inflammatory response mounted by horizontal (i.e., interpersonal) transmission of the virus in the first few months after birth.

However, my colleagues and I recently published an animal study in *PLOS ONE* that has brought to the forefront a striking new idea: RSV may be transmitted vertically from the respiratory tract of the mother to the lungs of the fetus. Until now, we believed that when a pregnant woman got a cold, the developing fetus was protected by the placenta from RSV and other respiratory viruses.

**Intriguing Findings: Transplacental Transmission and Beyond**

In our study, pregnant rats were inoculated with recombinant RSV. The RSV genome was subsequently found in 30 percent of fetuses (Figure 1) and in the lungs of 40 percent of newborn rats and 25 percent of rats born to inoculated mothers when tested in adulthood (10 weeks after birth). These data support transplacental transmission of RSV from mother to offspring and the persistence of vertically transmitted virus in lungs after birth.

Notably, we also found that exposure to RSV in utero changes the way that lungs function through dysregulation of neurotrophic pathways, thereby predisposing the subject to the postnatal airway hyperreactivity that is the hallmark of asthma.

**Rethinking RSV Transmission**

While this is the first time to our knowledge that vertical transmission of RSV — or any common respiratory virus — has been reported, a number of infectious agents, including herpesviruses and retroviruses, have been shown to cross the placenta and establish persistent infection in offspring.

Our research was driven by two key factors:

- Human and animal research showing that while RSV primarily targets the lungs, the virus can spread to extrapulmonary sites, which can have systemic implications. We postulated that if RSV can spread beyond the lungs, it is possible that the virus also could penetrate the placenta.
- The possibility that some infections, such as RSV, once regarded as temporary may be longer-lasting and more pervasive than we thought. While the acute phase of an RSV infection typically resolves in a few weeks, my colleagues and I found in a separate study that RSV’s molecular signature persists in the bone marrow long after the virus has cleared — even well into adulthood. This finding has implications for both mother and fetus in terms of the potential for in utero transmission and its sustained effects.

**Potential Implications: A New Focus on Prevention in Pregnancy?**

If our findings can be confirmed in human studies, we may have to rewrite the books on RSV transmission. If our recent findings can be confirmed in human studies, we may have to rewrite the books on RSV transmission. The general idea we have been working under for decades in pulmonology is that nothing bad happens in the lungs until the baby is born — even with serious conditions such as cystic fibrosis. This study suggests that a certain percentage of patients who develop asthma may do so because of viral exposure in utero.
This study suggests that a certain percentage of patients who develop asthma may do so because of viral exposure in utero.

The next step in our research will be to see if these observations are replicated in ex vivo studies of human cells. Eventually, research will focus on in vivo human studies in mothers naturally infected with RSV. Cleveland Clinic Children’s plans to work closely with our colleagues in Cleveland Clinic’s Ob/Gyn & Women’s Health Institute to carefully administer these studies.

If human studies replicate our findings from animal models, our understanding of the pathogenesis of RSV infections would be completely changed. It would turn back the clock of respiratory developmental diseases by months and mean that we would need to start thinking about lung development and pathology during pregnancy rather than at birth. This could create a paradigm shift by extending our focus on prevention from the first few years after birth to also include the last few months before birth.

Figure 1. Propagation of vertically transmitted RSV in the rat. Magnified at 60×, extracts of whole fetuses are shown that were delivered from dams inoculated with recombinant RSV (rRSV; bottom row) or from pathogen-free controls (top row) and co-cultured with human airway epithelial cells. The micrographs show red fluorescence in the cytoplasm of cells exposed to fetal extracts from rRSV-infected dams, confirming the presence of actively replicating infectious virus associated with markedly increased green nerve growth factor (NGF) immunoreactivity. Reprinted from Piedimonte et al, PLOS ONE.1

The author, Dr. Piedimonte, is Chairman and Physician-in-Chief of Cleveland Clinic Children’s. He can be reached at 216.444.2344 or piedimg@ccf.org.

REFERENCES
Families with children suffering from chronic forms of vasculitis are often frustrated by the lack of knowledge and coordination of care required to manage these rare disorders. Chronic childhood vasculitic conditions such as Takayasu arteritis, granulomatosis with polyangiitis (GPA; Wegener’s granulomatosis) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) affect several hundred children in the U.S. and can lead to life-threatening complications.

Given the rarity of these diseases, many pediatric rheumatologists have cared for only a handful of patients with vasculitic conditions over their careers. In cases when surgical interventions are required, many highly skilled pediatric surgeons have never operated on patients with such rare and complex conditions. And when these children mature into young adults, transitioning their care to adult subspecialists often proves difficult.

Cleveland Clinic Children’s Center for Pediatric Rheumatology has developed a nationally recognized comprehensive evaluation and treatment service for children with chronic vasculitis. Over the past eight years, our center has evaluated more than 125 patients with chronic vasculitis and published or contributed to several groundbreaking papers detailing our work and observations in this rare population.¹⁻⁴ We’ve also recently submitted for publication a manuscript detailing our experience with Takayasu arteritis.

At the Core of a Collaborative Approach

As Director of the Center for Pediatric Rheumatology, I am privileged to lead the vasculitis team, which consists of a variety of pediatric subspecialists from across Cleveland Clinic Children’s with extensive knowledge in the evaluation and management of diverse aspects of chronic pediatric vasculitis. These subspecialists include (among others):

- Matthew Eagleton, MD, a vascular surgeon with experience in surgical correction of complications from large vessel vasculitis
- Paul Krakovitz, MD, a pediatric otolaryngologist with expertise in managing airway stenoses resulting from childhood GPA
- Neil Friedman, MBChB, a pediatric neurologist and national expert in pediatric stroke

These talented physicians actively collaborate with staff in the Center for Pediatric Rheumatology to provide comprehensive evaluation and recommendations to patients and their families. Additional services, including nephrology, pulmonary medicine, gastroenterology and ophthalmology, provide input on a regular basis as well.

As our vasculitis patients age, their care is easily transitioned to adult-care specialists in the internationally renowned Center for Vasculitis Care and Research in the Department of Rheumatic and Immunologic Diseases within Cleveland Clinic’s Orthopaedic & Rheumatologic Institute. Coordination and discussion of care plans among providers across medical and surgical subspecialties is a key differentiator of our program often noted by families during their time at Cleveland Clinic Children’s.

How We Work with Referring Providers

Referrals are often initiated by patients’ families or their local treatment teams. The staff at Cleveland Clinic Children’s will typically discuss the case via phone and attempt to provide general care recommendations to families and local providers. If an in-person evaluation is required, the scheduling team coordinates visits with all necessary specialists as well as diagnostic imaging procedures over three to five days. Prior clinical documentation, laboratory studies and diagnostic imaging information can be scanned into our electronic medical record system before the patient’s arrival for use by all providers during the patient’s stay.

Following evaluation, patients and their local provider teams are given a summary of the visit and recommendations for their records and consideration. The Message My Doctor function in Cleveland Clinic’s MyChart® online personal healthcare management tool enables families to directly and securely email the treatment team at Cleveland Clinic Children’s at any time. Return visits to Cleveland Clinic are largely dependent on patient needs and family wishes and typically occur one to two times a year. See the sidebar for an illustrative case study of our coordinated approach.
**PERSPECTIVE**

**CASE STUDY:**

**Coordinated Expertise Yields Dramatic Turnaround in Takayasu Arteritis**

An 11-year-old girl diagnosed with Takayasu arteritis developed severe stenosis of the left renal artery and superior mesenteric artery, resulting in hypertension and intestinal angina (Figure 1). Despite aggressive and appropriate immunosuppression by her local pediatric rheumatologist, the stenosis worsened and her uncontrolled hypertension, which was unresponsive to numerous antihypertensive medications, resulted in posterior reversible encephalopathy syndrome and heart failure. She was eventually transported to Cleveland Clinic Children’s by fixed-wing aircraft from the Cleveland Clinic Critical Care Transport fleet for further evaluation.

In collaboration with the Center for Pediatric Rheumatology, our vascular surgeon performed autologous bypass grafts to correct the diminished perfusion that was causing the patient’s symptoms. She tolerated the procedure well and had significant improvement in her heart function, blood pressure and intestinal angina, which allowed us to reduce the intensity of her immunosuppressive and antihypertensive regimens.

Two weeks after her transfer, the patient boarded a commercial flight back to her home state and now returns for visits with the Cleveland Clinic Critical Care Transport fleet for further evaluation.

Figure 1. Magnetic resonance angiogram showing the patient’s stenotic arteries.

**REFERENCES**


**ABOUT THE AUTHOR**

Dr. Spalding is Director of the Center for Pediatric Rheumatology. He can be reached at 216.445.1099 or spaldis@ccf.org.
Cleveland Clinic Children’s has established a pediatric lung transplant program to provide children and adolescents with end-stage lung disease access to this life-extending intervention.

Our program combines the expertise of Cleveland Clinic’s adult lung transplant program — one of the most active programs in the world — with the experience of our comprehensive pediatric heart, kidney/pancreas, liver, intestinal/multivisceral and bone marrow transplant programs. We believe this model gives young patients with terminal lung diseases the best possible chance for an optimal outcome.

The Imperative for Collaboration

The collegial and collaborative atmosphere at Cleveland Clinic has been invaluable in developing this program. Staff physicians and surgeons involved in successful adult and pediatric transplant programs have shared their expertise and advice to ensure that our program takes advantage of every lesson learned. Since joining Cleveland Clinic Children’s in early 2013, I have been impressed by how often I hear “How can I help?” from my colleagues.

Every year, only a small number of pediatric lung transplants (< 100) are performed around the world. This spirit of collaboration is vital in light of the complex, systemic nature of end-stage lung disease in children, which can manifest in the following ways:

- **Comorbidities.** Children and adolescents with these conditions often have significant comorbidities, including malnutrition, endocrine problems and renal dysfunction.
- **Side effects** from medications used to treat chronic lung diseases and from the immunosuppressants needed after transplantation can lead to other end-organ dysfunction, particularly renal and hepatic compromise. Severe dysfunction of the kidneys or liver requires comprehensive, subspecialized pediatric care. In the worst cases, it may lead to the need for renal or hepatic transplantation.

- **Need for dual-organ transplant.** Children with pulmonary hypertension in isolation or as a component of their lung disease may need a heart transplant in conjunction with a lung transplant.

The structure of Cleveland Clinic Children’s — which brings together pediatric subspecialists with expertise in transplantation as well as in disorders of the lungs, heart, liver, kidneys and other organ systems — fosters the provision of comprehensive care to our patients in a cohesive, timely, convenient manner.

Limited Procedures Worldwide Have Hindered Progress

Pediatric lung transplantation has inherent challenges that Cleveland Clinic is well positioned to take on and overcome. Compared with adult lung transplants, only a small number of pediatric lung transplants (< 100) are performed every year around the world, and they are performed by just a handful of programs. Several factors likely explain this small number of procedures:

- The relatively few diagnoses leading to end-stage lung disease in children
- Limited availability of organs
- An inferior survival rate relative to other solid organ transplants

This limited volume of procedures restricts the pediatric lung transplant community’s ability to gather data to determine drivers of better outcomes. Although five-year survival for pediatric lung transplant is similar to that for adult lung transplant (50 to 55 percent), outcomes for adolescents are more challenging, with a median survival of 4.3 years. Although multiple factors underlie these differences, it is imperative that we learn which ones interfere with success in order to improve outcomes. Cleveland Clinic Children’s hopes to help accelerate this process by adding our program to the network of pediatric lung transplant programs and freely sharing our experiences and ideas.
The key to success in pediatric lung transplant is having the judgment to pinpoint when the patient is sick enough to require transplantation yet still well enough to tolerate the surgery.

Our Program: Deep Roots, Abundant Branches to Support Growth

Cleveland Clinic’s lung transplant program has successfully transplanted and cared for children since 1991. At its center are five pediatric pulmonologists skilled in the care of all pediatric pulmonary diseases, including those that may lead to end-stage respiratory failure requiring lung transplantation. Our pulmonologists have expertise in cystic fibrosis, pulmonary hypertension and childhood interstitial lung disease as well as rare diseases such as congenital anomalies of surfactant proteins. They evaluate patients and determine the need for and timing of transplantation, provide comprehensive pulmonary care before and after transplantation, and coordinate care with other pediatric subspecialists as needed.

The physicians and surgeons are supported by a large team of pediatric nurse practitioners, nurse coordinators, nurse educators, social workers, respiratory therapists, physical and occupational therapists, dietitians and psychologists. This multidisciplinary team provides care in a friendly, pediatrics-focused environment and is experienced in the unique issues facing young patients undergoing transplantation and their families.

Timing: Early Is Good for Referral, but Not Always for Transplant Itself

In general, children with life-threatening lung disease should be referred early. This allows for the time needed to evaluate the underlying lung disease, identify any comorbidities or other areas of concern, and provide education about lung transplantation.

Infants with surfactant protein deficiencies should be referred as soon as the diagnosis is made, since clinical decline is variable and transplantation may be urgent.

Children with cystic fibrosis or other chronic lung disease should be referred when their clinical status worsens to the point that quality of life is poor despite maximal medical therapy.

As a general rule, the presence of any of the following is an indication for referral for transplantation:

- Lung function of approximately 30 percent or less
- Rapid decline of lung function even if greater than 30 percent
- Requirement for chronic oxygen supplementation

Paradoxically, there is no advantage to early transplantation. With the average five-year survival rate being only about 50 percent, surgery should be delayed as long as possible. The key to success is having the judgment to pinpoint the time when the patient is sick enough to require transplantation yet still well enough to tolerate the surgery.

At Cleveland Clinic Children's, we are eager to refine that judgment in collaboration with colleagues in our institution's renowned adult lung transplant program and our fellow pediatric subspecialists throughout the various reaches of our comprehensive pediatric transplant offerings.

ABOUT THE AUTHOR

Dr. Kraynack is a staff physician in the Center for Pediatric Pulmonary Medicine and Medical Director of Cleveland Clinic Children's Lung Transplant Program. He can be reached at 216.445.2200 or kraynan@ccf.org.
Hypospadias is the second most common birth defect involving the male genitalia (first is cryptorchidism). The incidence of this defect, in which the urethral opening is not located at the tip of the penis, is 1 in every 250 male births in the United States. Normal sexual differentiation of the external genitalia is believed to result from a combination of normal genes and a normal hormonal environment. Any disruption of these factors can result in hypospadias.

Complications of Surgical Repair

The goal of surgical repair is to create a straight phallus and a urethral meatus at the tip of the glans. The risk of complications from surgical correction increases with more proximal meatus location and with smaller phallus or glans size. These complications include glans dehiscence, urethrocutaneous fistula, meatal stenosis and postoperative scarring.

Considerable controversy surrounds the use of hormonal stimulation to temporarily increase phallic size, specifically glans size, to reduce the risk of complications from surgical repair of hypospadias. Since its successful use in 1973 for micropenis and increase in penile length in prepubertal boys, hormonal stimulation has demonstrated penile enlargement with both topical and parenteral administration and has become common practice for most pediatric urologists. Its side effect profile includes acceleration in bone age, sexual precocity, aggression and premature growth of pubic hair. With cessation of use, most of these side effects will resolve.

Koff and Jayanthi reported their work with preoperative hormonal stimulation in the proximal hypospadias population. In 12 boys, they found that preoperative human chorionic gonadotropin (β-HCG) not only increased penile length and glans size but also reduced the severity of hypospadias and chordee and increased the vascularity and thickness of the proximal corpus spongiosum. These preoperative changes permitted a simpler repair. They reported one complication, a urethrocutaneous fistula.

Not So Simple?

In theory, these findings would suggest that reducing the complexity of the hypospadias repair with androgen stimulation should result in a decrease in postoperative complications. However, two recently published large retrospective studies suggest that the matter is likely more nuanced.

Gorduza et al reviewed 300 “severe hypospadias cases” treated with urethroplasty with or without preoperative androgen stimulation over a 10-year period. The indications for androgen stimulation (either β-HCG or systemic testosterone) were penis < 25 mm, marked hypoplasia of the ventral tissues of the penis or association of cryptorchidism. There was significant variance in the timing of hormone administration. No difference in complication rates was observed between those who received β-HCG and those given systemic testosterone. Healing complications occurred in 26 patients; the incidence of healing complications was 30 percent among patients who received androgen stimulation vs. 17.7 percent among patients who did not. The difference was not statistically significant (P = .23), which the authors attributed to the power of their study. In looking at the trend, they concluded that androgens inhibit cutaneous wound healing and promote inflammation, as had been demonstrated in the mouse model. They also suggested that the shorter the interval between androgen stimulation and surgery, the higher the incidence of healing complications.

Snodgrass et al reviewed 641 patients who underwent transurethral incision of urethral plate repair, 56 of whom had proximal hypospadias. Of the total patient population, 32 patients (5 percent) developed postoperative glans dehiscence, which occurred in 20 of 520 distal repairs (4 percent), 1 of 47 midshaft repairs (2 percent) and 11 of 74 proximal repairs (15 percent). Hormonal stimulation was given to the patients whom the surgeons judged to have inadequate glans. Comparison of patients who underwent preoperative hormonal stimulation with those who had matched preoperative factors but did not receive hormonal stimulation revealed no difference in glans dehiscence. Notably, patients with a proximal meatus location had an odds ratio of 3.60 for developing glans dehiscence relative to those with a distal meatus.

The Questions That Remain

This leads to several questions:

- Isn’t the patient with a proximal meatus, small phallus and small glans the same patient who not only is predisposed to postoperative complications but also is likely to be recommended for preoperative hormonal stimulation?
- Is there a standard regimen that pediatric urologists use?
- Is there a dose that could reduce these apparent complications?
To address these questions, Wright et al recently published a meta-analysis after reviewing several studies in patients who had undergone proximal hypospadias repair. Among the 288 citations, only 11 studies met the researchers’ criteria. The most common method of preoperative stimulation was intramuscular testosterone. Of the 11 studies, only four addressed postoperative complications. Dose schedule, time to surgery and indications for stimulation were not well recorded. There were no documented persistent side effects from the hormones. The authors commented on the low quality and small number of studies in the literature but noted that the data suggest a possible relationship between preoperative hormonal stimulation and increased complication rates.

The Bottom Line — for Now

While a number of retrospective studies have evaluated whether preoperative hormonal stimulation is beneficial and assessed possible complications from its use, the quality of the data is mediocre at best. A randomized, prospective, controlled study is necessary to answer the questions above.

In Cleveland Clinic Children’s Center for Pediatric Urology, we believe there is merit in the use of androgens in a select group of patients — specifically, those with a very small glans. As we advance in our understanding, there will likely be an evolution of set indications for these select patients (instead of reliance on the surgeon’s subjective assessment), which would be a welcome development.

REFERENCES


Key Takeaways on Hormonal Stimulation for Hypospadias

• Though most pediatric urologists consider preoperative androgen stimulation to temporarily increase phallic size to reduce complications from surgical repair of hypospadias, controversy continues to surround this practice.

• Reducing the complexity of hypospadias repair with androgen stimulation theoretically should reduce postoperative complications, but recent large retrospective studies do not bear this out and suggest that androgens may in fact inhibit cutaneous wound healing and promote inflammation.

• A recent meta-analysis reveals the low quality and small number of studies addressing this question and underscores the need for randomized, prospective, controlled investigations.

• At Cleveland Clinic Children’s, we believe there is merit in the use of androgens in a select group of hypospadias patients, primarily those with a very small glans.


ABOUT THE AUTHOR

Dr. Rhee is a pediatric urologist in the Center for Pediatric Urology and the Glickman Urological & Kidney Institute. She can be reached at 216.636.9483 or rhee@ccf.org.
At Cleveland Clinic Children’s we are preoccupied with failure. One child experiencing a serious safety event due to failure of a safety process is one child too many.

This preoccupation with failure has led to a documented and unmistakable change in our safety culture. Over the past two years we have nearly doubled the number of low-level safety events reported while decreasing the number of serious safety events in Cleveland Clinic Children’s inpatient settings (Figure 1). We encourage the reporting of near misses and precursor safety events, as such reporting helps us identify and fix gaps in the system that could lead to serious consequences if left unaddressed. The goal, of course, is zero children harmed.

The mission of Cleveland Clinic Children’s Quality and Patient Safety team is to promote standard-setting performance in safety, quality and patient experience by creating and sustaining a culture of safety. Every caregiver attends error prevention training designed to provide simple tools for promoting and reinforcing behaviors that lead to consistently safe performance and high reliability.

Setting the Tone: Daily Safety Briefs

For more than a year, Cleveland Clinic Children’s leaders have held a daily phone “huddle” for a multidisciplinary safety briefing. The huddles focus on problem awareness, identification and resolution. Operational leaders in areas ranging from emergency departments and operating rooms to food service, security and clinical risk take part in the calls, which last an average of 10 minutes.

Since the daily safety briefing started, it has expanded to include several community hospitals in the Cleveland Clinic health system as well as Cleveland Clinic Children’s Hospital for Rehabilitation. Huddle participants look back over the previous 24 hours to review events that may have threatened safety and look ahead to anticipate anything new or different that may increase the probability of an error. This exercise encourages situational awareness that has led to several great safety catches and averted errors that may have occurred had problems not been anticipated.

Getting Parents’ Perspective

In an effort to include patients and family members in decisions that impact the safe delivery of care to children, Cleveland Clinic Children’s Quality and Patient Safety team has enlisted parents of patients in an advisory capacity. Our goal is to be consistent with our family-centered care philosophy and use a parent advisory council to maintain the focus on what matters — the safety of our patients. We realize that parents can be excellent advocates and evaluators of healthcare, and we want to use this parent advisory council as a vehicle for organizational transformation.

Knowing When and How to Escalate

Prompt escalation of care is critical to preventing serious safety events. Cleveland Clinic Children’s has developed escalation guidelines to serve as a resource for caregivers. In addition to knowing when to escalate care concerns, knowing how and to whom to escalate those concerns is critical. Our message is that when caregivers are in doubt, it is acceptable and highly encouraged to escalate a situation. It is the responsibility of those receiving the concern to thank others for involving them in patient care and safety concerns.

Simple Changes, Big Returns

Our experience shows that simple changes in safety practices can sometimes yield major payoffs. In 2011, for example, Cleveland Clinic Children’s had 18 central line-associated bloodstream infections (CLABSIs). These infections are estimated to have resulted in 144 extra hospital days, adding $810,000 to the cost of care.

As hospitals have grown increasingly aware that CLABSIs are largely preventable, we have collaborated with other children’s hospitals to confirm that most pediatric central line infections are related to care and maintenance of the line and that the single
most important part of the maintenance bundle is to scrub the hub properly. By focusing on these simple measures, we have seen a 70 percent reduction in CLABSIs in our pediatric ICUs.

**Taking Safety to the Front Lines**

On weekly safety rounds, the Quality and Patient Safety team leaders talk to front-line staff and to patients and their families about threats to safety and safety concerns. The focus is identifying threats and finding solutions. These rounds make clear that safety is a team sport and that success comes from an abundance of dedicated caregivers who believe safety begins with them.

---

**Figure 1.** The number of lower-level safety events reported at Cleveland Clinic Children’s through the Safety Event Reporting System (SERS) rose steadily over the 2.5 years from 2011 through mid-2013. The number of serious safety events generally declined during the same period, with a low rate of one per quarter over the four most recent quarters.

**ABOUT THE AUTHORS**

Dr. Hupertz is Cleveland Clinic Children’s Vice Chair of Quality and Safety as well as Director of Pediatric Hepatology and Transplantation in the Department of Pediatric Gastroenterology. She can be reached at 216.444.0964 or hupertv@ccf.org.

Dr. Gill is Cleveland Clinic Children’s Patient Safety Officer and a hospitalist in the Department of Pediatric Hospital Medicine. She can be reached at 216.444.4998 or gilla5@ccf.org.
Ask any provider practicing in the United States what most concerns him or her about the future of healthcare, and the answer is likely to be managing the transition to a value-based care system.

Getting Ahead of the Changing Tide

Reimbursement in the United States has been based on volume and focused on procedures and acute care delivery. Providers have had little incentive to reduce utilization or improve outcomes and actually are sometimes rewarded for increasing utilization, as reimbursement has been based solely on the number of encounters or procedures. Now, however, both private and federal payers are slowly changing this reimbursement structure to reward providers based on outcome and quality measures instead of volume. With the advent of accountable care organizations, risk-based contracting and federal value-based purchasing programs, changes in the reimbursement and practice of medicine have begun to materialize, and many more are on the way.

At Cleveland Clinic Children’s, we have recognized this impending sea change and are taking steps to be leaders in the delivery of value-based care for children across the nation. One of our first steps has been to embark on the creation of standardized care paths.

More Than Practice Guidelines

Cleveland Clinic Care Paths are evidence-based algorithms embedded within our electronic health record (EHR) system that guide providers and patients through episodes of care for a specific disease state. They are more than just sets of practice guidelines but are instead electronic tools built on top of guidelines to help providers make guidelines operational.

The more than 50 care paths in development or completed across all of Cleveland Clinic represent an opportunity to reduce variation in clinical care (including in utilization and cost) while maintaining or improving outcomes. This requires a significant change in the nationally ubiquitous culture in which each physician, division and department has operated independently of all other contingent systems within an organization.

How They're Developed and What They Do

To accomplish this change, Cleveland Clinic Children's leadership has created a series of multidisciplinary teams led by physician champions within each of several targeted disease states to create an initial guide detailing a needs assessment and best practices. These guides are then reviewed by individuals from stakeholder areas, including nursing, quality and patient safety, patient experience, and compliance, as well as from ancillary services such as finance, radiology, laboratory medicine and pharmacy. Cleveland Clinic Children’s now has care paths under development for the following:

- Diagnosis and management of hyperbilirubinemia in term neonates
- Inpatient asthma care
- Care of inpatients with diabetic ketoacidosis

After completing these care path guide documents, the work team that creates the guide partners with a multidisciplinary technical team to translate the documents into electronic tools. There are front-end user tools such as standardized documentation templates, order sets, and clinical decision-support and predictive analytical tools that assist providers in delivering care according to standards set forth in the guide (see sidebar for example).

Additional reporting tools are developed to monitor performance of physicians and facilities in meeting the guide's standards. Finally, condition-specific outcome metrics are collected and reported for individual physicians, divisions, departments and facilities. An overarching steering committee has been formed to regularly review the performance data and ensure that performance goals are being met, to identify best practices, and to assist groups encountering operational challenges.

A Tool for the Long Haul

Cleveland Clinic Children’s leadership believes these standardized Cleveland Clinic Care Paths present multiple opportunities for long-term strategic success. Experience with optimization of EHR tools and performance measurement strategies will reduce unnecessary variation in care while driving best practices through increased transparency and accountability. This initiative
Snapshot of the Hyperbilirubinemia Care Path’s Protocol

Under Cleveland Clinic Children’s Hyperbilirubinemia Care Path, logic within our IT servers monitors newborns for characteristics to identify infants at high risk of developing hyperbilirubinemia. Based on these risk factors, recommendations are made to providers within the context of the EHR. Additionally, discrete variables such as patient age, demographics and vital signs (e.g., birth weight) are used to compare bilirubin levels against standardized nomograms to alert providers to patients with hyperbilirubinemia.

Once a diagnosis is made, providers document within standardized templates to ensure capture of discrete data for further refinement of predictive modeling tools and performance measures. In the lead-up to discharge, standardized discharge instructions and follow-up appointments are provided to the family. Nurses and case managers responsible for post-discharge follow-up are provided a list of these patients to enable monitoring of their status at home and, ideally, to prevent readmissions.

The care path guide includes a flowchart for recommended management; here is an excerpt covering outpatient office presentation:

---

**PER S P E CT I V E**

Dr. Spalding, Director of the Center for Pediatric Rheumatology, is overseeing Cleveland Clinic Children’s care path development efforts. He can be reached at 216.445.1099 or spaldis@ccf.org.
Our Referring Physician Hotline, 855.REFER.123 (855.733.3712), provides 24/7 access to information on Cleveland Clinic Children’s more than 300 pediatric specialists and subspecialists.

**LEADERSHIP TEAM**

Giovanni Piedimonte, MD  
Chairman, Pediatric Institute  
Physician-in-Chief, Cleveland Clinic Children’s  
President, Cleveland Clinic Children’s Hospital for Rehabilitation

Michael McHugh, MD  
Vice Chairman

Vera Hupertz, MD  
Vice Chair, Quality and Safety

Charles Kwon, MD  
Director, Pediatric Residency Program

**STAFF**

Skyler Kalady, MD  
Co-Director, Pediatric Clerkship

Camille Sabella, MD  
Co-Director, Pediatric Clerkship

Wendy Van Ittersum, MD  
Director, Pediatric Fellowship Programs

Gregory Plautz, MD  
Director, Basic Science Research

Katherine Dell, MD  
Director, Clinical and Translational Research

Alec Kulik  
Administrator, Cleveland Clinic Children’s

Julie Niezgoda, MD  
Nelson Riveros, MD  
Shelly-Anne Rodriguez, MD  
Kenneth Saliba, DO  
John Seif, MD  
Wai Sung, MD  
E. Christian Tucker, MD

**AUTISM**

Thomas Frazier, PhD, Director  
Leslie Speer, PhD

**BEHAVIORAL HEALTH**

Michael Manos, PhD, Head  
Joseph Austerman, DO  
Gerard Baney, PhD  
Ethan Benore, PhD, BCB, ABPP  
Cara Cuddy, PhD  
Wendy Cunningham, PsyD  
Kristen Eastman, PsyD  
Kate Eshleman, PsyD  
Thomas Frazier, PhD  
Catherine Gaw, PsyD  
Vanessa Jensen, PsyD

Eileen Kennedy, PhD  
Kathleen Laing, PhD  
Katherine Lamparyk, PsyD  
Amy Lee, PhD  
Alana Lopez, PhD  
Leslie Markowitz, PsyD  
Beth Anne Martin, PhD  
Alison Moses, PhD  
Pamela Senders, PhD  
Sandra Sommers, PhD  
Leslie Speer, PhD

**BRAIN TUMOR AND NEURO-ONCOLOGY**

Erie Murphy, MD  
Violette Recinos, MD  
Tanya Tekautz, MD

**CARDIOLOGY**

Richard Sterba, MD, Interim Chair  
M. Janine Arruda, MD  
Peter Aziz, MD  
Gerard Boyle, MD  
Iqbal Choudhry, MD  
Thomas Edwards, MD  
Francine Erenberg, MD  
Alex Golden, MD  
Richard Lorber, MD  
S. Ken Mehta, MD  
Tamar Preminger, MD  
Lourdes Prieto, MD  
Marcy Schwartz, MD  
Ernest Siwik, MD  
Kenneth Zalika, MD

**CARDIOTHORACIC SURGERY**

Gosta Pettersson, MD, PhD, Chair

**CRITICAL CARE MEDICINE**

Michael McHugh, MD, Interim Chair  
Kshama Dapthary, MD  
Steve Davis, MD  
Federico Fernandez Nieves, MD  
Keshava Gowda Narayana, MD  
Patricia Rairmer, MD  
Sue Sreedhar, MD

**DERMATOLOGY**

Allison Vidiimos, MD, Chair  
Lahel Bedocs, DO  
Douglas Kress, MD  
Joan Tamburo, DO

**DEVELOPMENTAL PEDIATRICS/PHYSICAL MEDICINE AND REHABILITATION**

Douglas Henry, MD, Chair  
Roberta Bauer, MD  
Jeffrey Bolek, PhD  
Carol Delahunty, MD  
Benjamin Katholi, MD  
Virmarie Quinones-Pagan, MD

**ENDOCRINOLOGY**

Douglas Rogers, MD, Chair  
Anzar Haider, MD  
Nouhad Raisoumi, MD  
B. Michelle Schweiger, DO  
Laurie Talianidis, MD

**EPILEPSY**

Ajay Gupta, MD, Head  
William Bingaman, MD  
Tatiana Falcone, MD  
Jorge Gonzalez-Martinez, MD, PhD  
Jennifer Haut, PhD, ABPP-CN  
Patricia Klaas, PhD  
Prakash Kotagal, MD  
Deepak Lachhwani, MBBS, MD  
Ahsan Moosa Nadiwui, MD  
Elia Pestana Knight, MD  
Elaine Wylie, MD

**GASTROENTEROLOGY**

Marsha Kay, MD, Chair  
Naim Alkhouri, MD  
Lisa Feinberg, MD  
Rishi Gupta, MD  
Vera Hupertz, MD  
Barbara Kaplan, MD  
Lori Mahajan, MD  
Jonathan Moses, MD  
Kadakkal Radhakrishnan, MD  
Rita Steffen, MD  
Robert Wylie, MD  
Matthew Wyneski, MD

**GENETICS**

Charis Eng, MD, PhD, Chair  
Rocio Moran, MD, Director, General Genetics  
Marvin Natoicz, MD, PhD  
Vickie Zurcher, MD

**HEMATOLOGY/ONCOLOGY**

Johannes Wolff, MD, Chair  
Aron Flagg, MD  
Lisa Hackney, MD  
Rabi Hanna, MD  
Eric Kodish, MD  
Gregory Plautz, MD  
Tanya Tekautz, MD  
Margaret Thompson, MD, PhD

**HOSPITAL MEDICINE**

Michelle Marks, DO, Interim Chair  
Moises Auron, MD  
Scott Beichner, DO  
Nella Blyumin, MD  
Julie Cernanec, MD  
Eric Kodish, MD  
Julia Frantsuzov, MD  
Amrit Gill, MD  
Denise Greco, DO  
Rakhi Gupta Basuray, MD
CME Events from Cleveland Clinic Children’s

Earn CME credit for live and web-based pediatric CME from Cleveland Clinic’s Center for Continuing Education.

Live CME

Updates in Pediatric Hematology/Oncology
April 4, 2014, 7:30 a.m. to noon
Fairview Hospital, Cleveland, Ohio
Half-day course exploring solid tumor emergencies, novel developments in pediatric oncology, the latest in leukocyte disorders and leukemia, and considerations in the differential diagnoses of sickle cell anemia and hemophilia. To register/RSVP, contact Janet Zaibek at 216.448.6600 or zaibekj@ccf.org.

Perspectives in Pediatrics: From Theory to Practice
May 8-10, 2014
Global Center for Health Innovation, Cleveland Convention Center, Cleveland, Ohio
A collection of evidence-based perspectives on diverse issues in contemporary pediatrics, from immunization controversies to behavioral disorders to dermatology for the pediatrician. Includes two 90-minute workshops on topics of the attendee’s choice. For more information, visit ccfcmc.org/pediatrics (also see back cover of this issue).

20th Annual Pediatric Board Review Symposium
Aug. 25-29, 2014
Renaiiseance Hotel, Cleveland, Ohio
Comprehensive weeklong course featuring board simulation sessions, a case-driven format and an interactive audience response system; Intensive Review of Pediatrics textbook is free to all attendees of the full symposium.

International Pediatric Epilepsy Surgery Symposium
Oct. 5-11, 2014
Cleveland, Ohio
A mix of lectures, interactive sessions, workshops, poster presentations and hands-on simulation lab training focused on pathology-driven approaches to pediatric epilepsy surgery, improving outcomes through surgical treatment, and novel surgical techniques and strategies. For more information, contact Martha Tobin at tobinm@ccf.org or 216.445.3449.

Virtual CME

For a selection of free online CME activities (webcasts and case-based lessons) from Cleveland Clinic Children’s, visit ccfcmc.org and choose “Pediatrics” under “Browse by Specialty.” Topics of current activities include (among others):

- A series in pediatric infectious diseases
- Recurrent fever and autoinflammatory syndromes
- Early detection of autism spectrum disorders

Resources for Pediatricians

24/7 Hospital Transfers/Admissions
Children’s hospital, main campus
216.448.7000 or 866.547.1467
Cleveland Clinic Children’s Hospital
216.448.6400 or 800.635.2417

Pediatric Physician Liaison
For service-related issues or information about our specialists and services, contact Pediatric Physician Liaison Janet Zaibek, RN, at zaibekj@ccf.org or 216.312.6178.

Referring Physician Hotline
For 24/7 access to information on our pediatric specialists and services, call 855.REFER.123 (855.733.3712).

Staff Directory and Services
Visit clevelandclinicchildrens.org/staff to view Cleveland Clinic Children’s staff and services online.

Track Your Patients’ Care Online
Establish a secure online DrConnect account for real-time information about your patients’ treatment at Cleveland Clinic at clevelandclinic.org/drcconnect.

Critical Care Transport Worldwide
To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467. For STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage) or aortic syndrome transfers, call 877.379.8377. CODE (2633). Visit clevelandclinic.org/criticalcarenets to learn more.

Outcomes Data
View Outcomes books for Cleveland Clinic institutes, including Cleveland Clinic Children’s & Pediatric Institute, at clevelandclinic.org/outcomes.

Same-Day Appointments
Cleveland Clinic offers same-day appointments to help your patients get the care they need, right away. Have your patients call our same-day appointment line, 216.444.CARE (2273) or 800.223.CARE (2273).

CME Opportunities: Live and Online
Visit ccfcmc.org to learn about the Cleveland Clinic Center for Continuing Education’s convenient, complimentary learning opportunities.

About Cleveland Clinic
Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a nonprofit academic medical center with a main campus, eight community hospitals, more than 75 northern Ohio outpatient locations (including 16 full-service family health 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.

In 2013, Cleveland Clinic was ranked one of America’s top 4 hospitals in U.S. News & World Report’s annual “America’s Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 14 specialty areas, and the top in heart care for the 19th consecutive year.

Download our new Physician Referral App!
With our free Physician Referral App, you can view all our specialists and get in touch immediately with one click of your iPhone®, iPad®, or Android™ phone or tablet. Download today at the App Store or Google Play.

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

The Cleveland Clinic Way
By Toby Cosgrove, MD,
CEO and President of Cleveland Clinic
Great things happen when a medical center puts patients first. Visit clevelandclinic.org/ClevelandClinicWay for details or to order a copy.
Cleveland Clinic Children’s Locations

Cleveland Clinic Children’s 300+ pediatricians and pediatric subspecialists offer comprehensive medical, surgical and rehabilitative care at more than 40 community locations (dots in map below) throughout Northeast Ohio.

Highlights of our facilities and broad-ranging services include:

› 429 pediatric beds (overall)
› 87 level III NICU beds at our main campus and Fairview and Hillcrest hospitals
› 52 beds at Cleveland Clinic Children’s Hospital for Rehabilitation
› 24/7 pediatric EDs at Fairview and Hillcrest hospitals
› Special Delivery Unit on our main campus
› Pediatric dialysis unit at our Hospital for Rehabilitation
› Diverse subspecialty program offerings at our main campus and Fairview, Hillcrest and Medina hospitals as well as at family health centers across Northeast Ohio

The reach of our care extends beyond Northeast Ohio thanks to Cleveland Clinic Children's Critical Care Transport fleet. To arrange a pediatric transfer from anywhere in the world, call 216.448.7000 or 866.547.1467.
A Symposium Not to Be Missed

Perspectives in Pediatrics: From Theory to Practice
May 8-10, 2014

Global Center for Health Innovation
Cleveland Convention Center, Cleveland, Ohio

The inaugural offering of this comprehensive CME-certified course from Cleveland Clinic Children’s will provide an in-depth, evidence-based review of many of the most challenging clinical issues in contemporary pediatrics. Its content is designed for all pediatric and family medicine providers.

AMONG THE FEATURED TOPICS:

• Immunization update: recommendations and controversies
• Recent articles from MMWR: What they mean for your practice
• Behavioral disorders and ADHD
• Developments in adolescent medicine
• Best practices in current asthma management
• Practice-based dermatology
• Identification of school problems
• Developmental and autism screening
• Sinusitis and otitis media guidelines

SPECIAL FEATURES

❖ Workshops in obesity, sleep apnea, common GI disorders, and UTIs, plus hands-on training simulation in pediatric emergency care (attendees choose two topics)
❖ Thursday evening reception at Cleveland’s singular new Global Center for Health Innovation

Our faculty of nearly two dozen Cleveland Clinic Children’s experts from the full range of pediatric subspecialties is joined by two special guest speakers:

Catherine D. DeAngelis, MD, MPH
Professor of Pediatrics, Emerita,
Johns Hopkins University School of Medicine
Editor in Chief, Emerita, JAMA

Larry K. Pickering, MD, FAAP
Distinguished Consultant,
Centers for Disease Control and Prevention

Visit cfcme.org/pediatrics for full program, to register, and for registration/accommodation information.

For registration questions, email cmeregistration@ccf.org or call 216.448.0777.

This activity has been approved for AMA PRA Category 1 Credit™.