Highlights:

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Cleveland Clinic Children's

Pediatric Perspectives

A Newsletter for Physicians from Cleveland Clinic Children's | 2015-2016

Pancreatectomy with Islet Autotransplant

An Invaluable Option Against Relentless Pancreatitis — and Why Pediatric Patients Can Make the Best Candidates

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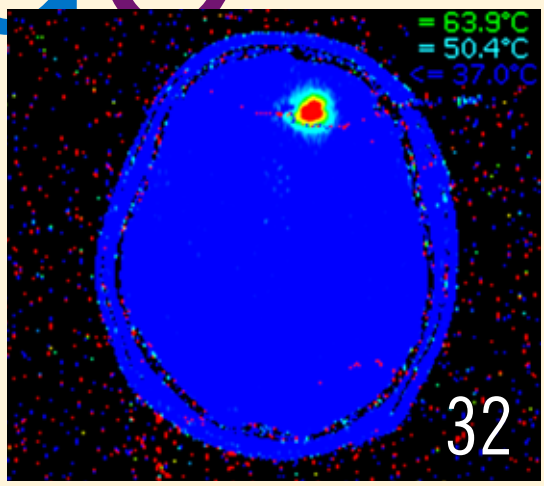

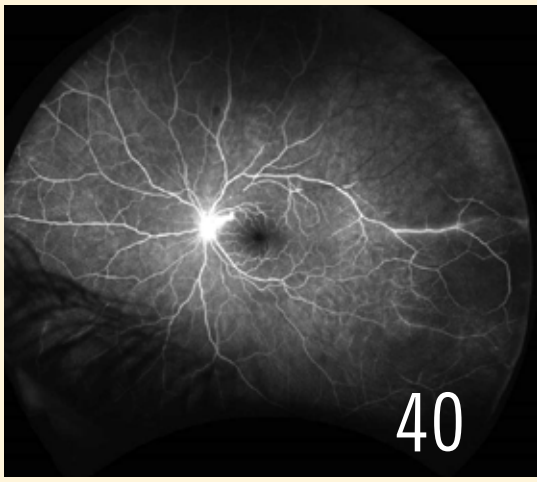

Dear Colleagues,

As pediatricians, we know better than any other clinicians that early interventions can make a world of difference in health outcomes. Yet sometimes even we are struck by just how much of an impact the early timing of a treatment strategy can have.

As I reviewed the contributions of my multidisciplinary colleagues to this issue of Cleveland Clinic Children's *Pediatric Perspectives*, the idea that "earlier is better" surfaced again and again.

On page 10, an investigator from our Center for Autism shares new research showing that the quality of life of families affected by autism starts to decline early — even before the autism diagnosis — suggesting that rapid interventions can provide needed support for the entire family.

On page 16, an author team including one of the nation's leading bariatric surgeons makes a compelling argument that for selected young patients with severe, refractory obesity, intervening with weight-loss surgery early — in adolescence — can yield important lifelong health and psychosocial benefits.

In my own contribution on page 24, I recap our group's recent animal research providing further evidence to suggest that *pre*natal intervention — i.e., focusing on the diet and metabolic health of pregnant women — may be among the most effective ways to combat childhood asthma and obesity.

On page 36, one of our pediatric orthopaedic surgeons reports exciting initial results with a new accelerated recovery protocol for adolescents undergoing spine fusion for idiopathic scoliosis. The clear trend is that an emphasis on early ambulation, promoted through multimodal pain management, is translating to earlier recovery and enabling average length of stay to be reduced by half.

And in our cover story, which profiles how we used total pancreatectomy with islet autotransplantation to provide long-sought relief to a boy with debilitating chronic pancreatitis, the patient's mother shares that her only regret is that the family didn't consider the procedure sooner.

As you peruse these and the other brief reports on Cleveland Clinic Children's latest research and clinical initiatives, let us know if you see opportunities to work together to get an earlier start on a new research initiative or help you introduce a novel early intervention in one of your most challenging cases. Earlier can be better, indeed.

Respectfully,

Giovanni Piedimonte, MD

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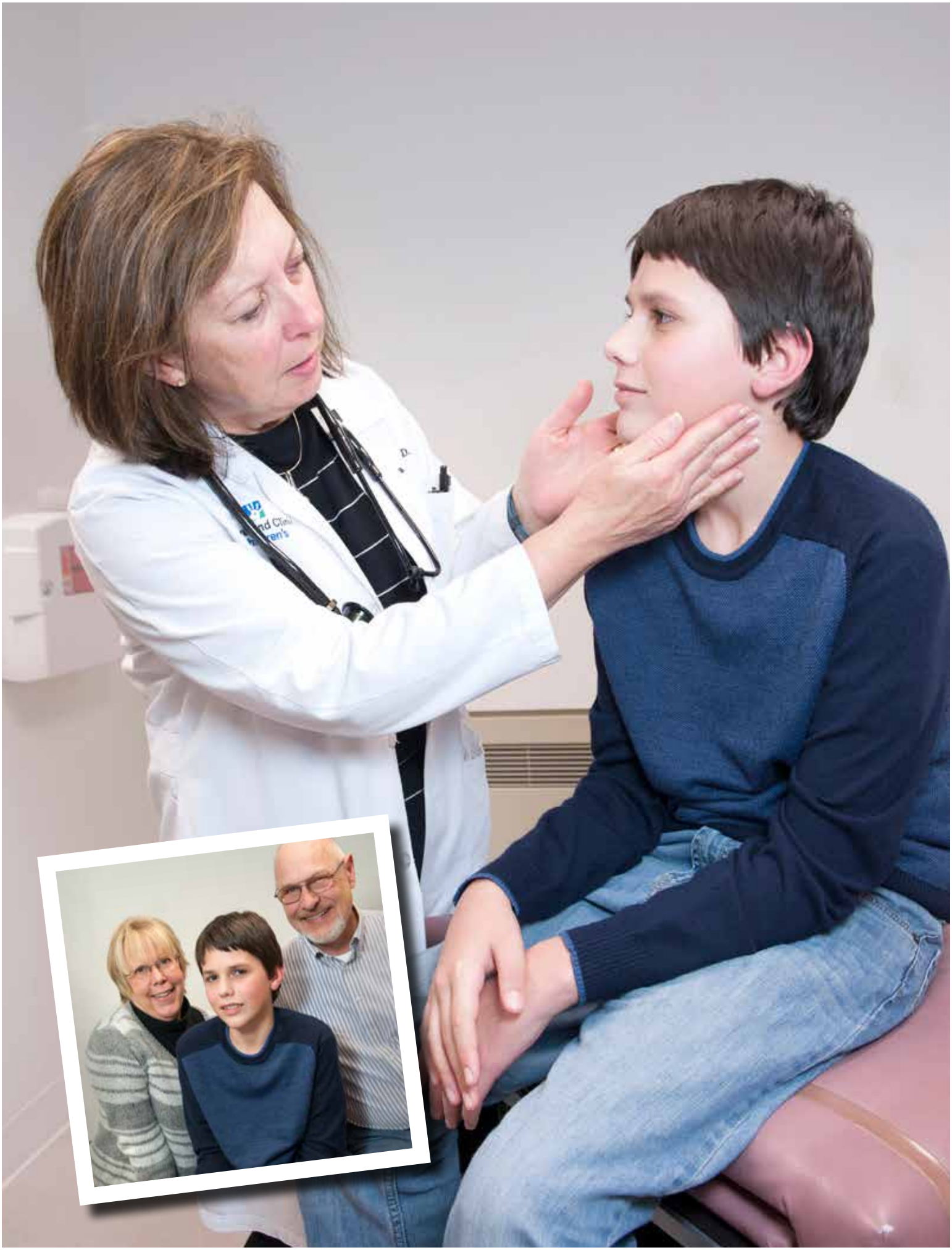

Total Pancreatectomy with Islet Autotransplantation: A Rare but Invaluable Tool for Pediatric Chronic Pancreatitis

By R. Matthew Walsh, MD; Vera Hupertz, MD; and Kadakkal Radhakrishnan, MD

Chronic pancreatitis is uncommon in pediatric patients, but its hallmark recurrent episodes of debilitating abdominal pain can utterly upend a child's quality of life. Frequent emergency room visits and hospitalizations disrupt family life and education, and the need for narcotic pain medication raises concern among parents and providers alike.

Surgical intervention for chronic pancreatitis is infrequent, but when required, surgical approaches are identical in pediatric patients and adults, with an emphasis on disease etiology. Pancreatitis arising from genetic causes will affect the entire gland and will not be cured with isolated pancreatic ductal procedures or local resections since the mutation will cause ongoing pancreatitis in the remnant pancreas.

Total pancreatectomy is rarely indicated for chronic pancreatitis, but when paired with islet cell autotransplantation to mitigate the likelihood of brittle diabetes, it can be of great benefit to selected pediatric patients with the condition. This is particularly true in cases with genetic causes that put the entire pancreas at risk.

Cleveland Clinic is one of the few U.S. institutions with a dedicated multidisciplinary pancreatitis team offering the option of total pancreatectomy with islet autotransplantation. More than 60 patients with chronic pancreatitis have undergone this procedure here as of late 2015, including a dozen pediatric patients.

This article presents a case study of one child who underwent pancreatectomy with islet autotransplant at Cleveland Clinic Children's in 2015. Throughout the case we spotlight teaching points on how, when and why this singular treatment option can offer relief to a pediatric population that may be small in number but is great in therapeutic need.

Case Presentation: Abrupt Abdominal Pain and Vomiting

Michael was a normal, healthy 6½-year-old boy in Northeast Ohio who suddenly developed abdominal pain and vomiting in late 2007. After evaluation and lab tests, he was diagnosed with pancreatitis and admitted to the hospital until the acute attack resolved.

About a year later Michael had two more bouts requiring hospitalization. Over the next several years the frequency of bouts and duration of illness progressively increased, causing him to lose weight from not eating due to severe abdominal pain and miss school due to the pain and frequent hospitalizations.

Early in the course of this progression, a more intensive workup at Cleveland Clinic Children's determined that although there was no family history of pancreatitis, Michael had a form of hereditary pancreatitis. Specifically, he was homozygous for a mutation in the serine protease inhibitor Kazal type 1 gene (*SPINK1*), which normally codes for a trypsin inhibitor.

Hereditary Pancreatitis: A Diverse Genetic Profile

Beyond the *SPINK1* mutation implicated in Michael's case, other gene defects have been identified as causes of hereditary pancreatitis. Mutations in the serine protease 1 gene (*PRSS1*) can present in an autosomal dominant pattern and are associated with up to 80 percent of hereditary pancreatitis cases. Additional mutations, such as in the cystic fibrosis gene (*CFTR*) or the chymotrypsin C gene (*CTRC*), account for other forms of recurrent pancreatitis. Sophisticated and ever-improving genetic panels are exceedingly useful for revealing genetic causes in presumed idiopathic forms of pancreatitis.

Hereditary recurrent pancreatitis is associated with many complications, including poor weight gain and poor quality of life

LEFT — Michael, now 14, at a follow-up visit with his pediatric gastroenterologist, Vera Hupertz, MD, eight months after his pancreatectomy and islet cell autotransplant. He and his parents (inset photo) opted for the procedure to relieve the constant abdominal pain caused by his chronic pancreatitis and to avoid the resulting elevated risk of pancreatic cancer. "He is doing really well," his mother says. "We only wish we had pursued the procedure sooner."

Outcomes of islet autotransplantation are superior in children and adolescents relative to adults. Since disease duration prior to pancreatectomy is shorter in pediatric patients, the mass of islet cells infused is typically greater, with better islet function, in younger patients.

due to chronic pain. Over time, the pancreas becomes very fibrotic and diabetes mellitus is a frequent complication, requiring insulin therapy. Patients with hereditary pancreatitis are also at elevated risk for pancreatic cancer, most likely secondary to the long-term inflammation.

Case Continued: Worsening Course Brings Islet Cell Transplant to the Fore

By late 2013, the pain from Michael's pancreatitis had become constant, significantly impacting his school attendance and requiring a nearly two-month hospitalization at Cleveland Clinic Children's at the end of 2014. During that hospital stay, he developed pseudocysts that ultimately ruptured, causing ascites, peritonitis and other complications.

At this point, Michael's worsening course, his need for opiates to control his pain, the extreme quality-of-life impacts and the long-term risks from pancreatitis prompted discussion with Michael and his family about the possibility of a total pancreatectomy with islet cell autotransplant. We explained that the objectives of the procedure would be to eliminate his pain, get him functioning as a normal teenager and try to prevent diabetes.

Decision-Making Considerations Around the Procedure

It is generally advisable for a child with chronic pancreatitis to be evaluated by a center and pancreatic surgeons capable of rendering all forms of medical and surgical therapy, including total pancreatectomy with islet autotransplant. A host of factors impact the decision about whether to proceed with pancreatectomy, including:

- Pattern and severity of symptoms
- Frequency of recurrence
- Need for persistent narcotics
- Secondary anatomic pancreatic complications
- Overall impact on the child's quality of life

Procedural details of total pancreatectomy with islet autotransplant are outlined in the sidebar on page 7. There are two dominant outcomes for appropriately selected patients who undergo this procedure for chronic pancreatitis — (1) excellent and long-lasting pain control and (2) avoidance of brittle diabetes — and pediatric patients generally have more favorable outcomes than adults in both of these domains.

Specifically, pediatric patients typically have better outcomes than adults in terms of pain relief, return to normal activity and cessation of narcotics. This has led to a general consensus that it is best to proceed with pancreatectomy early in the course of genetic chronic pancreatitis, before chronic pain symptoms and narcotic addiction occur.

Additionally, outcomes of islet autotransplantation are superior in children and adolescents relative to adults. This is because the function of transplanted islets is partially impacted by the number of islets retrieved from the pancreas; since disease duration prior to pancreatectomy is shorter in pediatric patients, the mass of islets infused is typically greater, with better islet function, in younger patients.

For this reason, timing of the surgery is important since having enough islet cells remaining after harvest is necessary for adequate insulin production. Once ingrowth has occurred in the liver, the islets function in that location as they would in the native pancreas, and loss of islet mass over time is thought to be minimal.

Case Concluded: Surgery Brings Freedom from Pain, Return to Normal Life

After Michael underwent a vigorous evaluation, he and his family agreed to proceed with total pancreatectomy with islet autotransplant. The two-part procedure was performed in March 2015, when Michael was 13, and lasted a total of 15 hours, including a break between the pancreatectomy and islet

harvesting/infusion portions to allow for pancreas processing.

Soon after surgery, Michael was able to be weaned off narcotics, his quality of life greatly improved and he is now pain-free. His appetite has returned ("he is happy he can eat regular food," his mother reports), he has resumed regular school attendance, and late in 2015 he even received medical clearance to play football as a kicker (after years of being unable to take part in sports). "He is now living how a child his age should live," his mother says.

Postoperative Insulin Prognosis

Following islet autotransplant, patients are immediately started on insulin to avoid overstressing the islets as they ingrow, and all patients are discharged on a combination of short- and long-acting insulin. Several months of ingrowth are generally required before insulin can be reliably weaned.

The majority of pediatric patients will require a small amount of insulin but will not be brittle diabetics. That has been the case so far for Michael, as he continues to take insulin nine months after his surgery, but his type 1 diabetes remains well controlled.

"We didn't decide to do this to totally avoid diabetes, but to reduce Michael's constant pain, restore a more normal life and reduce future complications," his mother says. "We are so relieved."

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The Surgical Procedure at a Glance

Total pancreatectomy with islet autotransplant is basically a two-stage operation:

- Complete resection of the pancreas/duodenum/gallbladder/distal bile duct
- Islet harvesting and infusion into the liver

The procedure's complexity is dictated primarily by the duration of disease severity, which can affect the peripancreatic vasculature. The goal is to perform the procedure in the absence of acute pancreatic inflammation. If inflammation is minimal, the preferred approach is to leave the spleen and splenic artery and vein.

Following removal, the pancreas is flushed with UW solution and placed in an ice-water bath to improve islet viability. Islets are procured in a designated procurement center under sterile conditions. Liberation of the islets is achieved by both enzymatic and mechanical dissolution of the organ. The pancreatic duct is cannulated and infused with collagenase under pressure to initially disrupt the gland. It is then placed in a sealed chamber with additional collagenase and shaken continuously to allow mechanical disruption aided by enzymatic breakdown. The process of islet isolation takes approximately four hours and may include additional purification steps to isolate fairly pure pellets of islets that are resuspended in albumin solution for reintroduction into the patient.

The islet solution is infused into the patient's portal system via a mesenteric vein, typically the splenic or inferior mesenteric vein. The patient is heparinized before infusion to avoid thrombus in the portal vein, and the pressure of the portal vein is monitored to avoid acute portal hypertension. The islets are then infused into the liver, where they will implant among the hepatocytes (Figure).

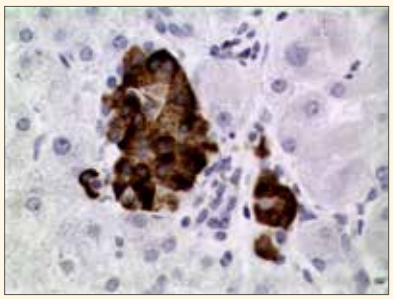

Figure. Islet cells after implantation in the liver.

Eating Disorders in Adolescents: Mounting Research Underscores the Need for Nuance

By Ellen Rome, MD, MPH

Building on its recent pioneering work defining avoidant/restrictive food intake disorder (ARFID),[1] the National Eating Disorder Quality Improvement Collaborative (NEDQIC) is adding nuance to both the diagnostic process and the medical and psychological management of eating disorders in adolescents and young adults (see sidebar). Cleveland Clinic Children's is proud to be a member of this group of 14 adolescent medicine-based eating disorder programs.

This article reviews some essential insights from the NEDQIC's work relating to ARFID and recaps how Cleveland Clinic Children's has built on these insights with a novel study of ARFID in hospitalized adolescents and young adults.

ARFID in Adolescents

Teens with this disorder have insufficient nutritional intake and, like their counterparts with anorexia nervosa (AN), experience significant weight loss or inadequate weight gain. However, whereas the motivation behind food avoidance in AN is to control weight, in ARFID it stems from other reasons.

ARFID's etiology is varied. For instance, it can appear after scoliosis surgery in an adolescent adjusting to a stomach that is suddenly full-size who has to relearn how to eat. It may develop in a teen with a history of vomiting who starts avoiding food because he never wants to vomit again. ARFID can occur in youngsters who fear "getting fat," who have problems with food textures, or who fear choking or believe that eating might hurt. It can likewise arise in teens with food allergies or who have simply been "picky" eaters since childhood.

Pediatricians' Role in Treatment

ARFID can lead to serious medical complications in nutritionally depleted patients, with some requiring hospitalization to acutely stabilize them while refeeding is initiated. Once a child is medically stable, the treatment with the strongest evidence base is family-based refeeding, which involves families taking 100 percent ownership of the feeding process.

Pediatricians play a critical role as consultants to parents, providing medical assessments and treatments as well as guidance and feedback to help families sustain efforts to refeed their child.

Comparing ARFID and Anorexia in an Inpatient Setting

Against the backdrop of this emerging understanding of ARFID, our Cleveland Clinic team performed a retrospective chart review comparing children, adolescents and young adults with ARFID and AN.[2] It is thought to be the first study to assess an inpatient ARFID population.

Among the study cohort of 318 patients ages 9 to 25 years with eating disorders, all hospitalized for acute medical stabilization at Cleveland Clinic between 2008 and 2014, 13 percent (n = 41) met diagnostic criteria for ARFID, and 64 percent (n = 203) met diagnostic criteria for AN. However, ARFID's share of the cases may be an underestimate since many ARFID patients are initially placed on medical services that may not recognize disordered eating.

ARFID patients were demographically and clinically distinct from those with AN and bulimia nervosa. In general, ARFID patients were younger and had fewer eating disorder-related behaviors and less comorbidity, weight loss and bradycardia on admission than did patients with AN. About one in five had generalized anxiety, but they were less likely to have mood disorders (e.g., depression) relative to patients with AN.

During hospitalization, more than two-thirds of patients initially were fed at least 2,000 calories per day. Patients with ARFID were more likely to require enteral nutrition to achieve recommended caloric intake compared with those who had AN. Use of Cleveland Clinic's inpatient nutritional insufficiency care path resulted in similar weight gain in the two groups. ARFID patients had longer hospital stays, with those patients who required enteral nutrition hospitalized twice as long as those who received oral nutrition. Readmission and remission rates were similar across the two diagnoses one year after discharge.

Physiologically, ARFID patients resemble patients with AN with respect to acute and chronic medical consequences of starvation. The challenge in treating ARFID revolves around a potential

need for more specialized interventions, including desensitization to food, treatment of food aversion and other strategies for stress tolerance.

The Imperative of ARFID Recognition

ARFID is a new diagnosis and often unrecognized by pediatricians. Pediatricians can learn to recognize ARFID early and be prepared to treat it or refer to adolescent medicine specialists as needed for acute medical care and to therapists well versed in the Maudsley method or parent-based refeeding. Further research is needed to (1) help answer pediatricians' questions about how best to manage ARFID on both an inpatient and an outpatient basis, (2) determine the optimal approach to refeeding ARFID patients safely and efficiently in inpatient and outpatient settings and (3) identify appropriate long-term therapies to enhance recovery and prevent readmission.

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PERSPECTIVE

Recent Collaborative Contributions to the Eating Disorders Literature

The National Eating Disorder Quality Improvement Collaborative has contributed significantly to the literature on eating disorders in adolescents and young adults, as have our colleagues at the Society for Adolescent Health and Medicine (SAHM). A sampling of our recent publications follows.

Position paper on eating disorders[3]

This paper summarizes SAHM's viewpoint on eating disorders. Among its key positions:

- Eating disorders are life-threatening illnesses and associated with numerous medical complications.
- Medical monitoring and treatment are essential to minimize the significant health impact that follows an eating disorder during adolescence.
- New diagnostic criteria for eating disorders in the DSM-V should increase early identification and treatment of affected adolescents.
- New diagnostic criteria eliminate a low-weight threshold and instead include severity criteria based on clinical symptoms, degree of functional disability and need for supervision.
- Refeeding can be accomplished safely via effective nutritional rehabilitation as a key component of medical care.
- Family-based therapy is a first-line psychological treatment for adolescents with anorexia nervosa.

Update on medical management[4]

This paper reviews changes in the epidemiology of eating disorders and diagnostic criteria along with newer methods of assessing malnutrition, approaches to weight restoration, determination of treatment goal weight and approaches to managing low bone mass. The role of providers at each level of care is also addressed.

Use of psychopharmacologic meds in adolescents with eating disorders[5]

This descriptive study of 635 adolescents with restrictive eating disorders treated at referral centers reported a high rate of psychiatric comorbidity. At presentation, one in five patients was taking medication, while at one year more than half used psychopharmacologic agents, commonly SSRIs/serotonin-norepinephrine reuptake inhibitors. Kids who were depressed or anxious were 10 times more likely to be on medication.

If eating disorders are a manifestation of depression or anxiety — a maladaptive coping habit — psychopharmacologic medicines may help treat the underlying illness. Those with underlying mental health issues may need to be on medications for at least a year, but further study is needed to clarify when and for how long such medication is needed.

Measuring Quality of Life in Families Affected by Autism: Early Reductions Require Rapid Intervention

By Thomas W. Frazier, PhD

A recent study out of Cleveland Clinic Children's Center for Autism has identified reductions in family quality of life even before a child is diagnosed with autism. This finding — made possible by the validated Child and Family Quality of Life questionnaire developed here — highlights the need to collect information about the functioning of the whole family, not just the child. When problems in family life are identified early in the child's life, broad intervention strategies that include the whole family may lead to better outcomes for the child, parents and siblings.

The Importance of Measuring Family Quality of Life

For some time, researchers have known that quality of life is reduced over time in families affected by autism spectrum disorders (ASD).[1] The chronic, severe nature of ASD — which typically involves impairments in one of the most central elements of human life, social interactions — can wear on a family. Tension between parents is common, as new parenting strategies have to be learned and faithfully implemented. Other siblings can be affected when the parents have to devote most of their energy to their child with ASD. Children with ASD also frequently exhibit challenging behaviors, including aggression, self-injury and elopement, which can further impair family relationships and functioning.[2]

Despite these well-documented factors, family quality of life is typically not a focus of initial diagnostic evaluations. As a result, most recommendations are focused on the needs of the child identified with autism and not the remaining family members.

The Questionnaire in Brief

To better understand how early quality of life is impacted in families affected by ASD, we developed a measure — the Child and Family Quality of Life questionnaire (CFQL) — that can be used to assess quality of life of the child, parent, family and external support network.[3] The CFQL includes seven scales to assess quality of life in the following domains:

- Child
- Family
- Parent/caregiver
- Financial
- Partner relationship
- External support
- Coping

Each scale is anchored to determine whether quality of life is low, moderate or high, and the content was developed to be linked to specific actions. For example, low quality of life in the partner relationship domain would signal a possible need for referral to individual or couples counseling.

Findings: Impairments in Quality of Life Start Early

To test the value of the measure and validate it for everyday clinical practice, we administered the CFQL to parents of 212 children suspected of having ASD before their first diagnostic evaluation visit. Of these children, 121 were diagnosed with ASD (mean age, 3.5; range, 1.2-7.2) and 91 were diagnosed with other developmental problems or had no diagnosis (mean age, 3.7; range, 1.1-6.6).

Results showed that the CFQL scales were highly reliable and demonstrated moderate relationships with one another but were unrelated to autism symptom levels or cognitive abilities. Thus, we demonstrated that the CFQL provides a nonredundant, broader measure that can be collected prior to diagnostic evaluation appointments to generate treatment recommendations for the whole family.

Next we demonstrated that parents of children with ASD reported significantly lower family quality of life than did parents of children without ASD (Figure 1). With the exception of external support and partner relationship, there were trends toward lower quality of life for the other CFQL scales in ASD-affected families. This suggests that quality of life is broadly impaired early in the lives of families of children with ASD, even before the children are diagnosed.

Family quality of life is typically not a focus of initial diagnostic evaluations for autism.

Quality-of-Life Patterns Alter Clinical Recommendations

Finally, this research revealed three main patterns of quality of life in families of children at risk for ASD (Figure 2):

- High overall quality of life
- Low financial quality of life with a good partner relationship
- Low partner relationship quality of life with good financial support

The latter two patterns suggest that clinicians should be aware of the types of quality-of-life impairments exhibited in families and develop recommendations that emphasize the strengths while addressing weaknesses. For example, in families with strong partner relationships but weaker financial support, it may make sense to encourage both parents to participate in behavior therapy training and refer them to low-cost government- or insurance-supported treatment programs.

Our future research will further validate and develop norms for the CFQL to enhance its use in evaluations of individuals with or at risk for ASD.

Figure 1. Mean quality-of-life scores across the various CFQL scales in families with and without children diagnosed with ASD. The reduction in the family scale score for ASD-affected families was statistically significant (*$P < .05$). *Reprinted from Markowitz et al[3] as originally published in* Autism.

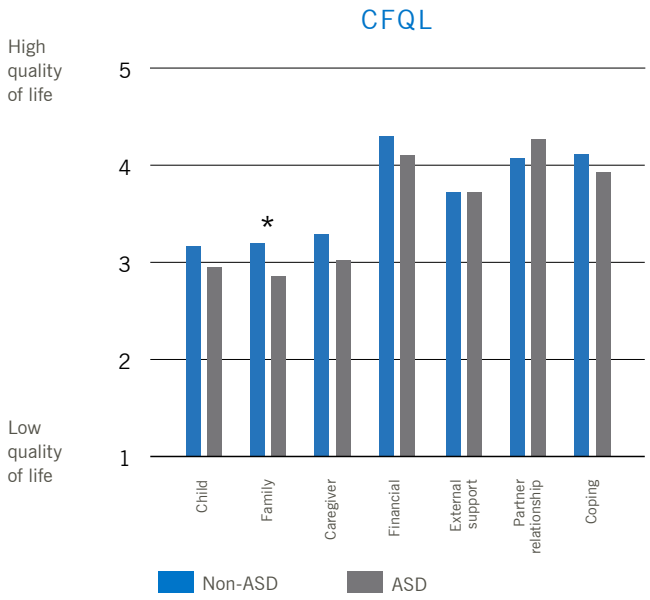
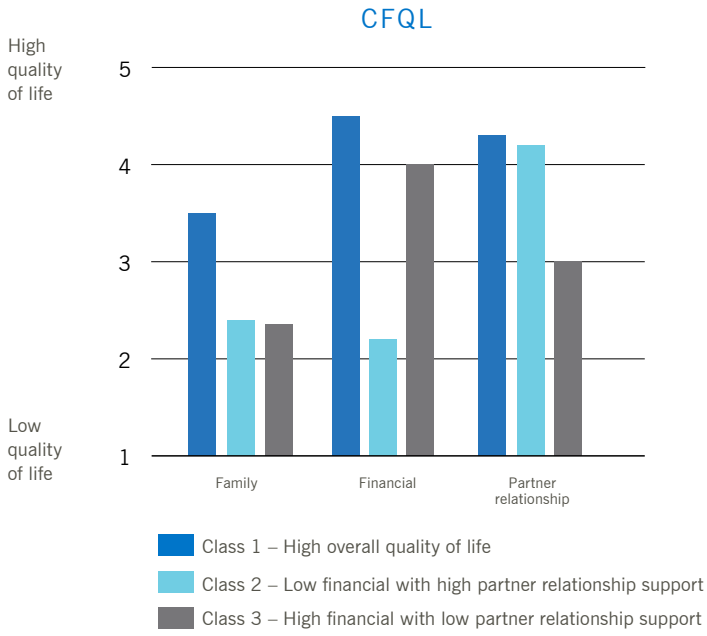


Figure 2. The study revealed three main patterns of quality of life in families of individuals at risk for ASD, as reflected in the three classes detailed in the graph. *Reprinted from Markowitz et al[3] as originally published in* Autism.



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Dose-Response Curves and Predictors of Response to Psychostimulants in School-Age Youths with ADHD

By Michael Manos, PhD; Eric Geyer, BA; Ralph D'Alessio, BA; Kimberly Giuliano, MD; and Michael Macknin, MD

Substantial evidence from clinical trials confirms that psychostimulants improve symptoms in children with attention deficit hyperactivity disorder (ADHD) and that their pharmacokinetic properties are well-documented.[1]

There remains, however, a dearth of information on how behavior changes *during* stimulant titration.

What Influences Dose Response?

The prescribe-and-wait method, in which the physician uses the skill and art of medical practice to determine the best dose, is common and may be informed only by the physician's personal experience with patients.[2] In clinical practice, however, stimulant dose response varies considerably across ADHD subtypes, patient age and gender, type of stimulant, and other variables that have been only peripherally studied.[3]

To date, factors that inform and predict response to stimulants remain elusive. Because the relationship between dose and response tends to be predominantly linear (as dose increases, behavioral improvement increases), clinicians have a tendency to expect this pattern and subsequently may not systematically observe and measure response as it occurs. Response variability often goes unnoticed,[4] and when it is overlooked, optimal treatment can be compromised.

Early clinical practice parameters suggested that dosing should be carried out according to gross body weight, beginning with 0.3 mg/kg in a twice-daily regimen and titrated upward until undesirable side effects emerged or behavior improved. This method was untenable, however, because pharmacological factors such as drug absorption, metabolism and excretion rates produce great interindividual variability.[5]

Six Patterns of Individual Dose Response

Although a *linear dose response* is found consistently at the group level of analysis, individual children vary considerably in behavior change across dose levels.[6] In addition to a linear response, there are five other patterns of response in individuals:

- A *curvilinear response* is incremental improvement at low and moderate doses followed by a decrement at a high dose.
- A *threshold response* is the absence of observed improvement at a low or moderate dose with abrupt therapeutic benefit at a high dose.
- A *variable response* is marked by irregular effects in the wake of dose changes, such as improvement at a low dose, deterioration at a moderate dose and improvement again at a high dose.
- A *placebo response* is when an individual shows equal reaction to medicine and a nonmedicine placebo capsule.
- *No change* may be seen during standard dosing in some individuals who just do not respond to pharmacotherapy.

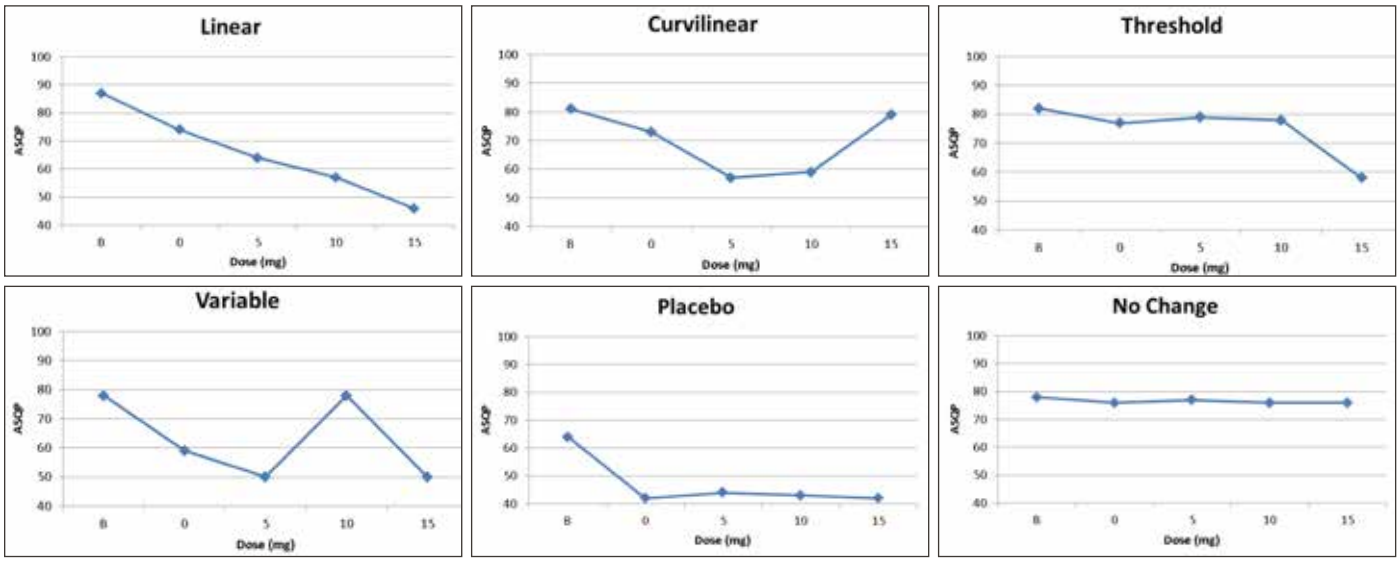
Three curves are predictable in that they tend to yield results in specific regimens and have a readily recognizable course of action. Behavior that improves as dose increases (linear response) indicates to the physician that an optimal dose may be achieved by ramping up the dose. If behavior deteriorates at higher doses (curvilinear response), the best dose is achieved by using the dose just prior to deterioration. If no response is observed at the initial doses, a further increase in dose may still yield optimal response (threshold response).

The remaining three curves, however, are unpredictable and do not help guide the physician's next action during titration. Curves that inconsistently improve response despite increase or decrease in dose (variable response) give little guidance as to the next action, such as to terminate, change or extend the titration. The same case applies when individuals respond to treatment regardless of the medicine or dose (placebo response). Finally, some children do not respond to medicine except at unusual dose levels (no change), and these cases are seldom pursued in primary care. Dose curves are illustrated in the figure.

Real-World Investigation of Dose-Response Patterns

These distinctions describe dose-response patterns that confound titration of psychostimulants during pharmacotherapy for children with ADHD. They also identify characteristic patterns with implications for pediatric practice for ADHD treatment. We investigated these patterns in the Medication Monitoring Clinic of Cleveland Clinic's ADHD Center for Evaluation and Treatment.

Figure. Six dose-response curves from a sample of youths ages 5 to 17 prescribed methylphenidate, mixed amphetamine salts (MAS) or sculpted dosing of MAS (see main text) in Cleveland Clinic's ADHD Medication Monitoring Clinic. A lower score indicates symptom reduction. ASQP = Abbreviated Symptom Questionnaire for parents. The dose response of the 249 youths was as follows: linear, n = 106; curvilinear, n = 65; threshold, n = 18; variable, n = 19; placebo, n = 21; no change, n = 20.



A sample of 249 youths meeting DSM-III or DSM-IV diagnostic criteria for ADHD was evaluated using a four-week, double-blind, placebo-controlled protocol. Physicians prescribed twice-daily dosing of methylphenidate, once-daily dosing of mixed amphetamine salts (MAS) or sculpted dosing of MAS (higher dose in the morning, 5-mg dose at about 3 p.m.) for youths ages 5 to 17 years. Data were collected at baseline and across the pharmacological protocol, which specified four possible dosing sequences (BL = baseline, A = placebo, B1 = 5 mg, B2 = 10 mg, B3 = 15 mg):

- BL, A, B1, B2, B3
- BL, B1, A, B2, B3
- BL, B1, B2, A, B3
- BL, B1, B2, B3, A

Each participant was randomized to one of the four sequences. Teachers and parents rated symptom presence at baseline and at the end of each treatment week using the Conners Abbreviated Symptom Questionnaire for parents.[7]

Children's responses to individual psychostimulant medications varied by age. Predictable dose-response curves (linear, curvilinear and threshold) were associated with younger children (< 10 years), and unpredictable curves (variable, no response and placebo) were associated with older children (> 9 years). The idiosyncratic nature of children's responses to psychostimulants requires close monitoring during titration to optimize treatment. These results underscore the need to use more sophisticated dosing strategies at older ages.

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The Pediatric Heart Network's Normal ECG Project: Redefining the Role of the Pediatric ECG to Help Avert Sudden Cardiac Death

By Elizabeth Saarel, MD

The sudden unexplained death of a young person is rare but catastrophic, its impact on families and society incalculable. While prevention of sudden death in the young may be an achievable challenge, many deaths occur without prior symptoms or a family history of sudden death (or at least without recognition of these and their potential connection to sudden death).

The electrocardiogram (ECG), a cornerstone in the evaluation of children with acquired and congenital heart diseases, has the potential to be a useful tool and the basis of screening to prevent sudden cardiac death in the young. However, realizing that potential will require more reliable reference values for pediatric ECGs and a comprehensively better understanding of the role of the ECG in this setting. The National Institutes of Health-sponsored Pediatric Heart Network is focusing closely on these goals through its Normal ECG Project, for which I am privileged to serve as the primary investigator. This article reviews the rationale for this project and the insights expected from it.

Strengths and Shortcomings of Pediatric Electrocardiography

As a diagnostic tool, the ECG has multiple advantages:

- Ability to detect diverse types of cardiac disease (sometimes with complete precision)
- Low cost
- Potential for accurate automated interpretation
- Digital data storage
- Essentially no risk

At the same time, the current value of ECGs in the identification and monitoring of heart disease in children is limited by the low frequency of disease and a lack of reliable reference values. The amplitude and duration of surface electrocardiography waveforms are affected by cardiac rhythm, age, gender, heart position and the size of cardiovascular structures; ECG data may also be affected by race and body habitus.

A Quest for Relevant Reference Values

Prior studies defining normal ECG values in children have varied widely in terms of methodology, inclusion criteria, number of subjects and population. Available reports were constructed largely from single sites and have not accounted for analog versus digital ECG recording, geographic variations or the influences of gender and race. Indeed, the most commonly used normal value references in the United States today are derived from analog ECGs acquired in French Canadian children more than 40 years ago.[1]

The Normal ECG Project's Charge and Scope

The variation in published data and the challenges of using the ECG to identify significant disease provided a strong motivation to obtain more reliable data and create an infrastructure to redefine the modern role of the ECG in the United States and Canada. The NIH's Pediatric Heart Network (PHN), recognizing the dearth of information about normal pediatric ECGs as well as normal pediatric echocardiograms, has undertaken its Normal ECG Project in the hope of ultimately helping prevent sudden death in the young in North America.

This project has widespread implications in that it will obtain an ECG and echocardiogram from a uniformly and accurately defined group of children (all without heart disease) from 19 centers over a broad geographic area in the United States and Canada. The enrollment target for the PHN Normal ECG Project is 3,600 children from birth to age 18. Findings will be published in 2016.

Does the ECG Figure into Screening for Sudden Cardiac Death Risk?

Significant disagreement exists among experts in the field about the best approach for preventing sudden cardiac death in the young. Some experts support implementation of large-scale cardiovascular screening programs in infants, athletes or all children to identify at-risk individuals in an effort to prevent sudden death. Cardiovascular screening to prevent sudden death typically involves the addition of an ECG to the current standard of care of history-taking and the physical examination. Most who argue against using ECGs for screening in North America cite the lack of reliability of current data to differentiate normal from abnormal children, with unacceptably high false-positive and false-negative rates of detection.

The PHN Normal ECG Project represents a first step toward creating an improved data set from which we can calculate normal ECG values based on race, gender, age, height and weight.

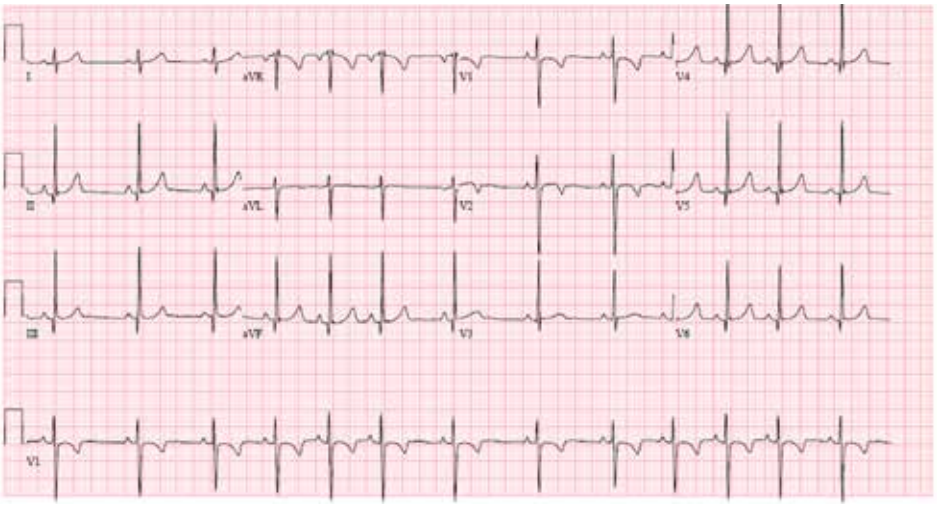

Figure. A normal ECG from a 9-year-old boy without heart disease.

The PHN Normal ECG Project represents a first step toward creating an improved data set from which we can calculate normal values based on race, gender, age, height and weight.

Despite Limitations, an Essential First Step

The current PHN Normal ECG Project is a retrospective study and thus only a first step on the road to creating an accurate map of normal ECG values for U.S. and Canadian children. There are inherent limitations associated with the quality of the waveforms and with self-reported race in a retrospective investigation. Our hope is that the PHN Normal ECG Project, along with other important studies exploring causes of sudden death in the young, will pave the way for future prospective studies documenting high-quality and accurate standards for ECG values among children in the United States and Canada. Such standards are essential for enabling effective screening to prevent unnecessary and tragic sudden death in the young.

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Bariatric Surgery for Obese Adolescents: Perspectives on the Pros, Cons and Special Considerations from a High-Volume Center

By Philip Schauer, MD, and Kathryn Weise, MD, MA

Although use of bariatric surgery for severely obese adolescents has expanded substantially over the past decade, it has not kept pace with the growth in teen obesity. Yet evidence of the benefits of bariatric surgery in this population mounts, most notably in the recent study published by the Teen-LABS Consortium in *New England Journal of Medicine*.[1] This prospective trial demonstrated significant and durable improvements in weight, cardiometabolic health and weight-related quality of life three years after surgery, with complication rates that compare favorably to those in adults.

We believe that in carefully screened and selected adolescents with severe obesity, bariatric surgery is a safe and effective treatment option that offers clinical and psychosocial benefits that can last a lifetime. In fact, because the risk of obesity-related comorbidities increases with the duration of obesity, a strong case can be made that bariatric surgery should be more widely considered for appropriate obese adolescents who fail to respond to multiple nonsurgical weight-loss strategies. Yet many parents' and providers' traditional tendencies to defer weight-loss surgery until patients reach adulthood are understandable.

Cleveland Clinic is home to one of the busiest bariatric surgery programs in the nation, performing 750 to 800 procedures a year — including five to 12 adolescent cases annually for each of the past 10 years. This experience has given us valuable perspectives on the special considerations surrounding bariatric surgery in adolescents — and on the relative merits of earlier versus deferred intervention. We share some of those perspectives in this review.

Similarities Between Adult and Adolescent Procedures Abound …

In many respects, bariatric surgery is the same regardless of whether the patient is an adult or an adolescent. The clinical criteria to qualify as a candidate are similar, the same procedures are used (predominantly Roux-en-Y gastric bypass or sleeve gastrectomy) and virtually all procedures are done laparoscopically. And at Cleveland Clinic, the same bariatric surgeons perform the procedures in both populations, allowing them to apply their volume-based expertise gained in adults to adolescent patients as well.

Moreover, obesity contributes to many of the same consequences in pediatric patients as in adults, including type 2 diabetes, cardiovascular disease, hypertension, dyslipidemia, abnormal kidney function, fatty liver disease, asthma and sleep apnea.

… But Important Adolescent-Specific Issues Remain

Despite these similarities, bariatric surgery in adolescents raises a number of considerations unique to this population, including:

Potential effects on growth and development. Because bariatric procedures aim to reduce caloric intake, concerns about effects on growth in patients who may have not reached skeletal maturity are natural, even if theoretical. While longitudinal studies like the Teen-LABS trial[1] are providing some reassurance about these concerns, our bariatric surgery team works closely with Cleveland Clinic Children's endocrinologists and other pediatric subspecialists to evaluate the physical maturity of candidates and recommend deferral of surgery if needed from a growth/developmental standpoint.

Maturity and need for a stable psychosocial environment. Adolescents often require heightened assessment to confirm they are mature enough to adhere to postop instructions, such as taking vitamins and coming to follow-up appointments. Special vigilance may be needed to ensure they will steer clear of substance abuse and other risky behaviors. To address such concerns, our adolescent bariatric surgery candidates undergo screening and counseling by both a pediatric psychologist and an adult psychologist. The latter meets with the parent/guardian(s) as well, in part to ensure the child has an adequate support system at home.

Need for both assent and consent. Bariatric surgery in patients under 18 involves obtaining both the legally required informed consent of a parent/guardian and the assent of the child to demonstrate that he/she understands and accepts the potential risks and benefits.

Other special ethical questions. It's essential that adolescents understand the permanency and long-term consequences of bariatric surgery and recognize the major lifestyle changes required. Ethics and psychological consults must include an assessment of emotional and intellectual maturity and ensure that adolescents don't unrealistically view the procedure as a quick fix.

Other considerations may make a case for earlier intervention rather than deferring surgery until adulthood. These include:

Curbing obesity's immediate and long-term health effects. The earlier we intervene in patients refractory to nonsurgical treatments, the greater the chance of reducing obesity-related comorbidities or attenuating their long-term effects.

Reducing psychosocial stigma and deferred opportunities. Adolescence and young adulthood are highly formative years. Enabling patients to shed excess weight and improve their health at an earlier point in those crucial years may yield significant and enduring payoffs in self-esteem, social development, quality of life, and college and job prospects.

Resilience of youth. Even among the severely obese, adolescents are generally healthier than adults (even young adults) and thus may face low complication rates, as suggested by the Teen-LABS study,[1] and the prospect of quicker recovery.

Who's a Candidate?

Intensive weight-management programs (such as those offered by Cleveland Clinic Children's Be Well Kids Clinic) can be successful for obese teens. However, for those who fail to reach weight-loss targets despite repeated attempts, few options exist because most weight-loss medications are not approved for use in children.

Requests for evaluation for bariatric surgery typically come from the teen's parents (many of whom have had bariatric surgery themselves) or primary care pediatrician. Coexistent type 2 diabetes often triggers referral from pediatric endocrinologists as well. At Cleveland Clinic Children's, adolescent surgical candidates and their families meet with a multidisciplinary team consisting of a bariatric surgeon, pediatric and adult psychologists, an adolescent medicine specialist, a bioethicist and other pediatric subspecialists as dictated by comorbidities. Dedicated bariatric nurses and pediatric dietitians also are involved in the preop workup and postop care.

Cleveland Clinic Children's follows American Academy of Pediatrics guidelines[2] in qualifying adolescent patients for weight-loss surgery. These focus on patients' BMI (morbid obesity is the general threshold) and obesity-related health issues, the duration and adequacy of previous physician-supervised weight-loss attempts, and the attainment/near attainment of physiologic and skeletal maturity. The guidelines also underscore the need to rule out underlying medical issues (e.g., thyroid deficiency) that could be treated nonsurgically.

Defining Success: More than Weight Loss

Bariatric surgery in adolescents may be seen as having multiple objectives. In the strictest sense, success is defined as sustained loss of a majority of the patient's excess weight over five years (after which the weight is unlikely to be regained). Yet success should also be conceived in terms of overall well-being. If a teen achieves meaningful and enduring weight loss that translates to improved overall health and quality of life, that is a worthwhile result even if less than 50 percent of excess weight was lost.

Success is also measured in terms of eliminating or improving obesity-related comorbidities. Key among these is type 2 diabetes, which figures in up to 30 or 40 percent of our adolescent bariatric surgery cases. In the STAMPEDE study of adult diabetics, our group showed that bariatric surgery resulted in glycemic control (hemoglobin A1c $\leq$ 6 percent) in significantly more patients than did intensive medical therapy,[3] and we have observed similarly positive effects on glycemic control in our adolescent diabetic patients to date. In fact, findings from the Teen-LABS study led those investigators to hypothesize that adolescents may have a greater potential than adults for reversal of the cardiometabolic consequences of obesity.[1]

While hypotheses like this require confirmation in future trials, it is clear that bariatric surgery can put young patients on a path to improved lifelong health — and that the case for intervening as early as during adolescence looks increasingly compelling.

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Breath Testing in the Pediatric Gastroenterology Clinic: Moving Beyond Liver Disease to a Host of Other Conditions

By Elizabeth Collyer, MD, and Naim Alkhouri, MD

Noninvasive screening tests are becoming increasingly important in pediatrics. A test that could distinguish between various disease states with minimal invasiveness and good specificity would be ideal. We are in the preliminary stages of working to develop such a test in Cleveland Clinic Children's Department of Pediatric Gastroenterology.

Need for Discrimination Between Disease States

Many of the diseases that pediatric gastroenterologists encounter have similar presenting symptoms, such as abdominal pain and diarrhea. Wouldn't it be helpful to be able to distinguish among these illnesses without subjecting children to painful blood draws and even more invasive tests like endoscopy? Enter the breath test.

Why Breath Testing?

The human body emits a wide array of volatile organic compounds (VOCs) in the breath; each individual's distinctive mixture of these compounds can be considered his or her characteristic "breath print." Various disease states can lead to the production of new VOCs or a change in VOCs — and thus can have distinctive breath prints as well. Advances in mass spectrometry have made it possible to identify hundreds of VOCs in the breath. Use of this technology has made breath testing a noninvasive, quick, painless procedure that can help in characterizing and distinguishing various disease states.

Methods in Brief

After our group's initial work demonstrating the potential of breath VOC analysis as a noninvasive tool for detecting pediatric nonalcoholic fatty liver disease[1] (as reported in this publication two years ago), we were motivated to assess this method's diagnostic utility for other pediatric gastrointestinal conditions.

Patients with three commonly encountered diseases — irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and celiac disease — were recruited from Cleveland Clinic Children's pediatric gastroenterology clinics, and comparable healthy controls were recruited from our institution's general pediatric clinics. Breath testing was performed on both groups of children using selective ion flow tube mass spectrometry. The children completed a mouth rinse with water prior to exhaled breath collection to eliminate sources of mouth 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 (Figure). The bag was taken to the laboratory, and analysis for a wide array of VOCs was completed using the mass spectrometry machine.

Results: IBS, IBD and Celiac Disease Have Unique Breath Prints

We found distinctive breath prints among the children with IBS and IBD, and results are promising in patients with celiac disease as well.

Among our patients with IBS, significant differences were noted relative to controls in levels of benzene, dimethyl sulfide, 1-octene and 3-methylhexane. Discriminant analysis of five mass scanning ion peaks was able to accurately distinguish IBS patients from healthy controls with an excellent area under the curve (AUROC) of 0.99.[2]

In our analysis of IBD, 21 VOCs were found to correctly classify patients as having IBD or as healthy controls ($P < .0001$). Additionally, three known compounds — 1-octene, 1-decene and (E)-2-nonene — were shown by multivariable analysis to be able to correctly classify subjects as IBD patients or as healthy controls with an AUROC of 0.96.[3]

In preliminary analyses of patients with celiac disease, multiple unknown compounds were found to differ significantly between the existing-diagnosis patients and new-diagnosis patients. Discriminant analysis was performed and was able to correctly classify all but three of 40 patients.[4]

We found distinctive breath prints among children with irritable bowel syndrome and inflammatory bowel disease, and results are promising in patients with celiac disease as well.

Figure. Dr. Alkhouri assists as a patient exhales into the collection bag used for breath analysis via selective ion flow tube mass spectrometry. Cleveland Clinic Children's is studying the technology as a promising noninvasive means of detecting a growing number of gastrointestinal diseases in children.

Next Steps

Now that we have established on a small scale the possibility of a unique breath print for each of these diseases, we will be working toward comparing the various groups to one another and expanding our sample sizes. Cleveland Clinic Children's is one of few centers across the country with the capability of performing exhaled breath analysis at this time, and we will be looking to expand and externally validate many of our findings.

The Overall Goal: Reliable Noninvasive Testing

Exhaled breath analysis shows promise as a noninvasive and painless method for detecting various gastrointestinal diseases encountered in the gastroenterology clinic. We hope our findings will ultimately enable children to be evaluated for these diseases without the need for invasive testing.

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First Randomized Trial of a Plant-Based Diet to Attenuate Pediatric Cardiovascular Risk Paves the Way for Larger, Longer Studies

By Michael Macknin, MD

The beneficial health effects of plant-based (PB) diets have been established in adults, but whether these benefits extend to children is not known. To shed light on this question, a team of clinician researchers from Cleveland Clinic Children's recently conducted the first randomized trial[1] to determine whether cardiovascular risk is reduced in children following a PB, no-added-fat diet compared with children following the American Heart Association (AHA) diet.

Do Adult Findings Apply to Children?

Cardiovascular disease is known to frequently begin in childhood, and the need for effective lifestyle modifications that target the growing group of obese children with dyslipidemia is clear. Studies in adults have suggested that a low-fat, vegan diet (no animal products) may promote weight loss, reduce body mass index (BMI), improve lipoprotein profiles and insulin sensitivity, and possibly prevent cardiovascular disease. Those who follow a vegetarian diet (no animal products except for dairy and/or eggs) typically have lower cholesterol levels and a lower risk for coronary heart disease than do nonvegetarians. Additionally, vegan and vegetarian diets have been shown to not only prevent but also reverse heart disease in adults.

To assess whether similar effects may be seen in children, we conducted a four-week randomized trial comparing a PB, no-added-fat diet (only plants and whole grains, limited avocado and nuts) with the AHA diet in a group of 30 children ages 9 to 18 years and one of each child's parents. All children were obese (BMI > 95th percentile for age and sex) and had hypercholesterolemia (total cholesterol > 169 mg/dL). Similar to the PB diet, the AHA diet[2] encourages fruits, vegetables, whole grains and low sodium intake but permits non-whole grains, low-fat dairy, selected plant oils, and lean meat and fish in moderation. Our aim was to determine whether either or both of these diets would significantly change anthropometric measures and/or biomarkers of inflammation and cardiovascular risk after a four-week intervention with weekly two-hour classes on nutrition education in these children at elevated risk for cardiovascular disease.

Key Study Findings

After the four-week intervention, statistically significant ($P < .05$) beneficial changes from baseline (mean decreases) were observed in 9 of 17 clinical measures assessed among children in the PB diet group and in 4 of 17 measures among children in the AHA diet group (Table). The only significant change favoring the AHA diet was a 1 percent difference in children's waist circumference. Among parents, statistically significant ($P < .05$) beneficial changes from baseline were observed in seven clinical measures for those on the PB diet and in two clinical measures for those on the AHA diet.

Implications and Limitations

The only significant problem in diet acceptance reported by our middle-class study population was difficulty purchasing food. Notably, cost may be an additional barrier to adherence to a PB diet in populations with lower socioeconomic status. In another study (conducted among adults), the only identified barrier to adherence was the effort required.[3] If the PB diet is to achieve wider adoption, barriers to easy, affordable access to plant-based, no-added-fat foods will need to be reduced.

The major limitations of our study are its small size, short duration and restriction to middle-class subjects, as well as the use of less than completely reliable adherence measures and no direct health outcome measures. Moreover, although the AHA is considered a standard of care and was used as a comparison group, there was no placebo group.

There is also concern that long-term adherence to the PB diet could be problematic, especially given the difficulties expressed by families in finding food to purchase for the diet in our study and the efforts required to follow a PB diet in a previous study.[4] At the same time, other studies describe good acceptability of and compliance with a PB diet.[3,5-7]

PB diets are generally recognized as safe for children and adolescents as long as the intake of key nutrients is monitored and appropriate supplements are provided. The results of our study suggest that the documented benefits of PB diets in adults — including a reduction in overweight/obesity and a decrease in cardiovascular risk — most likely would be seen in children. These benefits, especially given the known onset of cardiovascular disease in childhood, could improve the lifetime health of populations that adopt a PB diet in childhood.

Table. Clinical Measures Showing Statistically Significant Improvements from Baseline by Diet Group*

Children on Plant-Based Diet	Children on AHA Diet
BMI z-score (–0.14) ($P < .05$)	Weight (–1.55 kg) ($P < .01$)
Systolic blood pressure (–6.43 mm Hg) ($P < .05$)	Waist circumference (–2.96 cm) ($P < .05$)
Weight (–3.05 kg) ($P < .01$)	Mid-arm circumference (–1.14 cm) ($P < .05$)
Mid-arm circumference (–2.02 cm) ($P < .01$)	Myeloperoxidase (–69.23 pmol/L) ($P < .01$)
Total cholesterol (–22.5 mg/dL) ($P < .01$)	
LDL cholesterol (–13.14 mg/dL) ($P < .05$)	
High-sensitivity C-reactive protein (–2.09 mg/L) ($P < .01$)	
Insulin (–5.42 μU/mL) ($P < .05$)	
Myeloperoxidase (–75.34 pmol/L) ($P < .01$)	

* Values are mean reductions from baseline.

Larger and Longer Studies Now in the Works

Our future research efforts are focused on answering some questions this preliminary study left unanswered. Our initial study was powered to detect within-group differences before and after intervention. The benefits of dietary intervention were so large that we were able to demonstrate many significant improvements in markers of cardiovascular risk despite studying only 30 patients with a brief four-week intervention. Our future studies are designed with sample sizes large enough to detect statistically and clinically significant differences between PB and AHA diet interventions and will also include a Mediterranean diet group.

Our future studies will also be designed to help patients easily locate the food they need to purchase for their diets, will have improved methods of measuring diet compliance, and will be at least a year in duration to help determine the sustainability and one-year effects of these diets. By simultaneously studying the three major diet types highlighted in the 2015 U.S. dietary guidelines — AHA, Mediterranean and PB — we hope to provide insight on the comparative advantages and disadvantages of these diets in children and their parents for preventing cardiovascular disease.

ACKNOWLEDGMENT

Portions of this article were excerpted from reference 1 (Macknin et al, *Journal of Pediatrics*), ©2015, with permission from Elsevier.

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Boosting Effectiveness of Radiation Against Childhood Cancers: Pursuing New Medicines and Paradigms

By Peter Anderson, MD, PhD

Osteosarcoma is the most common primary malignancy of the bone in children, adolescents and young adults. As osteosarcoma is a bone-forming tumor, bone formation in the specimen is the hallmark that clinches the pathologic diagnosis of this cancer by light microscopy. New bone formation also results in high uptake of the ^{99m}Tc-MDP tracer on standard bone scans, and bone-seeking radiopharmaceuticals provide opportunities for targeted therapy.

Bone-Seeking Radiopharmaceuticals as Alpha Particle Therapy

These opportunities stem in part from multicenter studies I have been involved with for more than a decade. Our group showed that a 30× dose escalation of the bone-seeking radiopharmaceutical samarium (^{153}Sm-EDTMP) was possible — if cryopreserved stem cells were given two weeks later — and that many patients had excellent responses.[1] Gemcitabine, a radiosensitizer, subsequently increased the response rate further.[2]

Because ^{153}Sm is a lower-energy beta (electron) emitter that causes single-stranded DNA breaks that are easy for cancer cells to repair (Figure 1), relapses were common within 6 to 18 months. Instead of continuing with samarium, a new kid on the block, the alpha-emitting radiopharmaceutical 223-radium (^{223}Ra), was studied.

Since alpha particles are much more massive and energetic than beta emitters but act at shorter distances (0.1 mm), resistance to ^{223}Ra should be less frequent and collateral damage to normal marrow much less than with samarium (Figure 1). Our group recently completed a study that escalated the ^{223}Ra dose in osteosarcoma to 100 kBq/kg, which is twice as high as the level used for this agent's FDA-approved indication for prostate cancer. Findings included:

- The first demonstration of activity against brain metastasis
- Clinical benefit in over half the patients (less pain, and improvement in scans)

The Na^{18}F PET-CT was the most sensitive and specific scan to determine response. These results were presented at the 47th Congress of the International Society of Paediatric Oncology (SIOP) in Capetown, South Africa, Oct. 9, 2015.[3] Future studies are planned to determine use of this "designer drug" for osteosarcoma with current chemotherapy.

Our recent study of 223-radium for osteosarcoma showed clinical benefit in over half of patients and the first demonstrated activity against brain metastasis.

Lymphocytes Are Important Survival Predictors in Childhood Cancers

The speed and extent of recovery of lymphocytes after chemotherapy (improved absolute lymphocyte count) is associated with superior survival in childhood cancers including Ewing sarcoma, osteosarcoma and even acute lymphoblastic leukemia (ALL). Recovery of absolute lymphocyte count has been shown to be a more powerful independent predictor of survival than percent necrosis of osteosarcoma surgical specimens; it is also an independent and significant predictor compared with more complicated and expensive flow cytometry tests of minimal residual disease in ALL.

Inflammation associated with cancer and cancer therapy can result in increased expression of PD-1 and CTLA4, immune checkpoint molecules associated with a (mal)adaptive downregulation of lymphocyte function (Figure 2). Antibodies against PD-1 and CTLA4 have offered new hope for patients, releasing the lymphocytes to function better and sometimes even resulting in out-of-field (abscopal) responses after radiotherapy (RT)[4] (Figure 2). With greater precision now possible using stereotactic body RT, proton RT, and more precise RT with image guidance, RT should not only cause less inflammation but also

become a potential tool to induce "vaccine effects."

We have submitted a grant to study how using RT with checkpoint inhibitors could result in better immune function — i.e., "making lemonade out of lemons." We think it is indeed possible that in the future, radiation will become something to be desired, instead of feared, in a childhood cancer therapy plan — and this may help RT act like a cancer vaccine.

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Figure 1. Depiction of the mechanism of action of radiation therapy (DNA breaks) caused by beta particles and conventional photon radiotherapy versus protons and alpha particles. Beta particles and conventional radiotherapy are characterized by low mass and ionization potential, with rest mass energy of 0.5 MeV. In contrast, alpha particles and protons are characterized by high mass and ionization potential, with rest mass energy of 3,800 and 938 MeV, respectively.

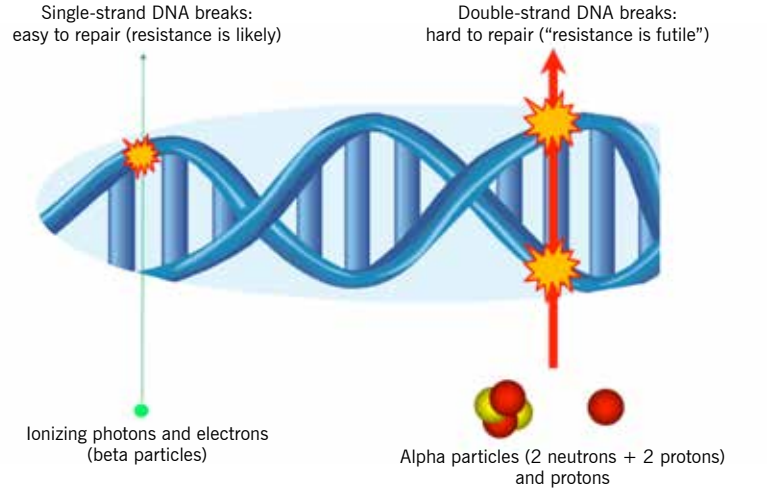
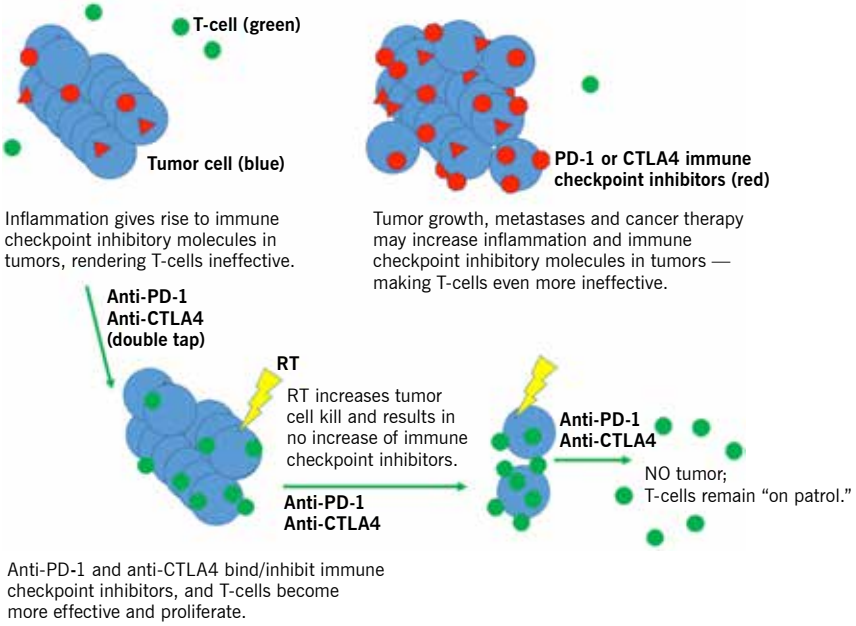


Figure 2. Schema of how inflammation causes a (mal)adaptive immune response. In cancer, however, PD-1 and CTLA4 (red triangles and octagons) can inhibit lymphocyte function. Tumor growth and cancer may increase the (mal)adaptive immune response and increase PD-1 and CTLA4. The combination of anti-PD-1, anti-CTLA4 and radiotherapy (RT) may release immune checkpoint inhibition and allow T-cells to proliferate and more effectively kill tumor cells (bottom), resulting in better local control and possible out-of-field (abscopal) responses.



Maternal Nutrition in Pregnancy Affects Metabolic and Respiratory Outcomes in Offspring: Time to Sharpen Focus on Health Practices in Pregnancy?

By Giovanni Piedimonte, MD

The prevalence of both obesity (17 percent) and asthma (9.6 percent) in children continues to rise in the United States.[1] While pathophysiologic links between obesity and asthma have been proposed, such linkage remains controversial.[2]

Nutrition's Role in the Asthma-Obesity Link

My colleagues and I previously demonstrated in a study of 18,000 school-age children that those with asthma tend to have higher serum triglyceride levels and higher rates of insulin resistance, regardless of body mass.[3] This finding brought forth a potentially game-changing idea: Early abnormalities of lipid and glucose metabolism may be associated with the development of asthma, confounding asthma's epidemiologic link to obesity.

Building on this population-based correlation, we subsequently undertook an animal study to determine whether maternal nutrition in pregnancy affects postnatal metabolic and respiratory outcomes in offspring. The study, recently published in *Pediatric Research*[4] and funded in part by a grant from the National Institutes of Health, was fueled by the likelihood that both obesity and asthma begin in utero and in early childhood. Therefore, nutritional factors — especially prenatal and early infant diet — may play a role in the pathogenesis of both conditions.

In this follow-on study, we sought to determine if fetal exposure to a maternal high-fat hypercaloric diet (HFD) — even in the absence of maternal obesity prior to pregnancy — could result in a predisposition to pathological airway responses to environmental challenges.

Increased availability of nutrients to the placenta was associated with airway inflammation and hyperreactivity during pups' development.

Study Highlights

Using a rat strain without a genetic predisposition to obesity, we fed dams an HFD or a control diet (CD) during pregnancy and lactation. We compared the offspring in terms of:

- Metabolic profiles
- Inflammatory status
- Neurotrophic pathways
- Lung function in early versus adult life

The offspring of the HFD and CD dams also were exposed to the most common respiratory pathogen in infancy, respiratory syncytial virus (RSV), to evaluate the interactions between maternal and environmental factors on postnatal lung function.

Our findings included the following:

- Pups born from HFD dams developed *measurable postnatal metabolic abnormalities that persisted throughout development.*
- Cytokine expression analysis of lung tissues from newborns born to HFD dams revealed a *strong proinflammatory pattern.*
- Gene expression of neurotrophic factors and receptors was upregulated in lungs of weanlings born to HFD dams.
- HFD dams delivered pups that were prone to develop more severe RSV disease following infection.

Based on these findings, we concluded that maternal nutrition in pregnancy is a critical determinant of airway inflammation and hyperreactivity in offspring.

Take-Home Points

This study demonstrated that changing to an HFD in a normal-weight dam during gestation leads to offspring with abnormal metabolic profiles, chronic airway inflammation and increased susceptibility to RSV infection. Pups born to mothers fed an HFD during pregnancy had hypertriglyceridemia and increased body fat without a corresponding change in body weight.

One of the most important findings of this study is that increased availability of nutrients to the placenta was associated with airway inflammation and hyperreactivity during development.

A greater focus on the diet and metabolic health of pregnant women could have a significant impact on the global epidemics of childhood obesity and asthma — more so than other, more expensive postnatal prevention strategies or therapies.

Because this was an animal study, we were able to analyze the lung mechanics without obesity as a mechanical confounder, which allowed us to confirm our previously described population-based association of abnormal pulmonary function with elevated triglycerides.[3]

This study did have limitations, including the fact that we did not investigate variables related to maternal metabolism, such as gestational weight gain. In addition, since the dams were on the HFD prior to delivery for only about three weeks, we had to use a diet that would be considered extreme for humans.

Clinical Implications: Early Interventions Look More and More Compelling

In this study, we developed a new model of airway inflammation and hyperreactivity induced by prenatal dietary imbalance. While we cannot ethically achieve this same model in clinical research, the clinical implications are clear, especially in light of our earlier population-based study:[3] A greater focus on the diet and metabolic health of pregnant women could have a significant impact on the global epidemics of childhood obesity and asthma — more so than other, more expensive postnatal prevention strategies or therapies.

When considered with our earlier population-based study in school-age children,[3] the results of this animal study clearly suggest that public health interventions must occur as early in life as possible — especially in pregnant women and young children. Enormous resources are currently spent on treating the manifestation of diseases, yet the only way to stop them efficiently is to deal with them at the source. The consequences of a mother's health — including nutrition — during pregnancy are not only important, but long-lasting.

At Cleveland Clinic, we have two programs in place focused on early nutritional and other health interventions that could serve as models for other centers. Our **Healthy Expectations** program gives women the support and information they need to optimize their weight and health before and during pregnancy, as well as after delivery. And Cleveland Clinic Children's **Be Well Kids Clinic** brings together a comprehensive team of clinicians and researchers with expertise in childhood weight management to help children and families develop strategies and create plans for healthy lifestyle changes.

Our continuing research will focus on maternal and early-life nutrition as well as additional studies predicated on the notion that indoor and outdoor pollution (e.g., tobacco smoke, fine particles), bacterial or viral infections, psychological or physical traumas, or anything else a mother encounters in the environment during gestation can affect the well-being of a fetus or child and also have long-term health consequences in adulthood.

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Between a Rock and a Hard Place: Insights on Preventing Necrotizing Enterocolitis While Maintaining Growth in VLBW Infants

By Taylor Rice, RD, and Jalal Abu-Shaweesh, MD

Over the past 30 years, Cleveland Clinic's Fairview Hospital — home to one of three level III NICUs in the Cleveland Clinic Children's network — has maintained a very low incidence of necrotizing enterocolitis (NEC) in infants with very low birth weight (VLBW). Specifically, among 1,992 VLBW infants admitted during this period, the incidence of NEC has been 0.6 percent, ranging from 0 to 2 percent annually. This compares favorably to the 5.6 percent mean incidence reported in the Vermont Oxford Network database over the past five years.

Reducing NEC Risk Through Slow-Advance Feeding

This low risk of NEC has been attributed to a distinctive feeding strategy, which we call the Fairview slow-advance feeding protocol, instituted at Fairview Hospital in 1986. As our Fairview Hospital colleagues reported in a 20-year experience review published nearly a decade ago,[1] the protocol differed from previously published protocols by providing late-onset, slow, continuous-drip enteral feeding.

This protocol was shown to decrease the incidence of NEC without an increase in long-term morbidity;[1] however, use of the protocol was associated with an adverse effect on growth. Between 2006 and 2010, the incidence of VLBW infants with discharge weight below the 10th percentile was 70 to 80 percent annually. Moreover, the incidence of a head circumference below the 10th percentile at discharge was 30 to 45 percent during the same period.

A Closer Look at the Effect on Growth Rate

In response to these findings, in 2012 we evaluated feeding tolerance, growth rate and short-term outcomes in 85 VLBW infants admitted to the Fairview NICU during 2011. Average gestational age was 28.7 $\pm$ 2.1 weeks; average birth weight was 1,090 $\pm$ 279 g. Feeds were started at day of life 3.5 $\pm$ 2.6, and full fortified feeds were achieved by 24.1 $\pm$ 8.8 days. The most impressive finding was that once started, feeds were interrupted for only 0.7 $\pm$ 1.6 days, signifying dramatic feeding tolerance. Infants regained their birth weight by 10.6 $\pm$ 4.1 days. The major factor associated with accelerated growth rate was reaching full fortified feeds. Whereas the growth rate was 8.2 $\pm$ 5.9 g/day before full fortified feeds were reached, it was a significantly higher 25.8 $\pm$ 6 g/day afterward ($P < .001$).

Complications traditionally associated with slow feedings — including cholestasis, bone disease and sepsis, including central line-associated bloodstream infections (CLABSIs) — were low. Cholestasis (direct bilirubin > 1 mg/dL) occurred in nine infants and resolved in all by discharge, while six infants had a maximum alkaline phosphatase level above 500 U/L. The incidence of any late infection was 2.2 percent, which compares favorably to the 14.2 percent in the Vermont Oxford Network database. The incidence of CLABSIs was 0.7 per 1,000 line days.

We concluded that the slow-advance feeding protocol is effective in preventing NEC without increased short-term complications but is associated with poor growth. This led to the first revision of our protocol in 20 years, which was adopted with some modification by all Cleveland Clinic NICUs. Table 1 summarizes our current feeding protocol.

Boosting Early Protein Intake to Spur Growth

To reduce rates of growth failure at discharge, we introduced an aggressive early nutrition initiative in VLBW infants that consisted of starting parenteral nutrition with protein intake of 3.2 g/kg/day in the first day of life, followed gradually by maintaining parenteral protein intake of at least 3 g/kg/day in the first week.

We then evaluated the effect of this initiative on growth parameters at discharge in 70 VLBW infants. There was a gradual decrease in the incidence of infants with discharge weight and head circumference below the 10th and 3rd percentiles between 2011 (before and during implementation of the aggressive early nutrition initiative) and 2012 (after the initiative), and also as compared with historical data (Table 2).

Average protein intake in the first week of life was found to be significantly lower in infants with head circumference below the 10th percentile at discharge relative to those with circumference above the 10th percentile: 2.9 $\pm$ 0.5 vs. 3.2 $\pm$ 0.4 g/kg/day ($P < .05$). While higher protein intake was associated with significantly higher blood urea nitrogen at 24 hours (28 $\pm$ 10 vs. 18 $\pm$ 6 mg/dL; $P < .01$), the difference disappeared after 24 hours and no infants developed long-term renal insufficiency. We concluded that higher protein intake in the first week of life is associated with better head growth at discharge in VLBW infants.

Table 1. Current Fairview Feeding Protocol for VLBW/Premature Infants

Birth weight (g)	500-750	751-999	1,000-1,250	1,251-1,375	1,376-1,500	> 1,500 and < 34 wk
NPO days	1-2	1-2	0-1	0-1	0-1	0-1
Trophic feed days	3-5	3-5	3-5	2-3	1-2	0-1
Trophic volume, Q 3-6 hr	0.5 mL	0.5 mL	1 mL	1 mL	1 mL	2 mL
Advancing feeds, day 1	0.5 mL/hr	0.5 mL/hr	0.5 mL/hr	0.5 mL/hr	1 mL/hr	20 mL/kg/day
Advance by	0.5 mL/hr	0.5 mL/hr	0.5 mL/hr	0.5 mL/hr	1 mL/hr	20 mL/kg/day
Advance	Q 4 days	Q 3 days	Q 2 days	Daily	Daily	Daily

Table 2. Mean Incidence of Growth Failure at Discharge vs. Vermont Oxford Network (VON) Database

	Fairview 2011	Fairview 2012	VON Database
Discharge weight			
< 3rd percentile	35.2%	14.9%	29.5%
< 10th percentile	67.0%	47.3%	53.7%
Discharge head circumference			
< 3rd percentile	6.8%	1.4%	12.9%
< 10th percentile	19.3%	8.4%	29%

How Crucial Is the First Week of Life?

We noted, however, that the difference between groups could have been related to changes in intake beyond the first week of life. We therefore evaluated the effect of nutritional factors *throughout hospitalization* on growth parameters at discharge in 103 VLBW infants admitted to Cleveland Clinic's regional NICUs between January 2013 and May 2014. Median [Q1, Q3] birth weight was 1,189 [900, 1,345] g, and median gestational age was 29 [28, 31] weeks.

The incidence of weight and head circumference below the 10th percentile was 22.3 percent and 18.4 percent at birth and 41.7 percent and 15.5 percent at discharge, respectively. Head circumference was categorized into six percentile ranges (< 3rd, 3rd-10th, 10th-50th, 50th-90th, 90th-97th, and > 97th), and the change in category from birth to discharge was computed. For example, a change from category 4 (50th-90th) to category 2 (3rd-10th) represented a category change of –2. Head circumference percentile category at discharge was significantly and positively associated with:

- Weight and head circumference category at birth ($P < .001$)
- Weekly head circumference gain ($P < .001$)
- Weight at discharge ($P < .001$)
- Protein intake in first week of life ($P = .012$)

At discharge, 50 percent of babies with head circumference below the 10th percentile had fallen in percentile category since birth. Notably, average protein intake > 3.5 g/kg/day was associated with improved percentile category at discharge compared with intake < 3.5 g/kg/day ($P = .016$). After adjusting for head circumference at birth, each 1 g/kg/day increase in protein intake in the first week of life was associated with a 0.41 increase in head circumference percentile category. Caloric intake had no effect on percentile category change.

Bottom Line: Focus on Protein to Promote Growth While Curbing NEC Risk

In summary, the slow-advance feeding protocol as used across Cleveland Clinic Children's is well tolerated and associated with very low incidence of NEC in VLBW infants. While it is associated with poor growth, especially before full fortified feeds are achieved, growth can be improved by optimizing parenteral nutritional intake. Protein intake throughout hospitalization — but especially during the first week of life — should be emphasized to promote brain growth and prevent head growth failure.

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New Quantitative MRI Measures Open a Door to Clinical Trials in Autosomal Recessive Polycystic Kidney Disease

By Katherine Dell, MD

Autosomal recessive polycystic kidney disease (ARPKD) is a rare, potentially fatal, inherited disease that occurs in approximately 1 in 20,000 children. Half of all patients will progress to end-stage renal disease (ESRD) during childhood and require dialysis or kidney transplantation. ARPKD also affects the liver, causing congenital hepatic fibrosis.

No disease-specific therapies for ARPKD are clinically available. Treatment is directed at medical and/or surgical management of the kidney and liver disease complications. While studies of novel therapies show encouraging results in slowing kidney or liver disease progression in animal models of ARPKD, development of human trials of these therapies is hampered by a lack of safe and sensitive noninvasive measures of kidney and liver disease progression to assess therapeutic impact.

Quantitative MRI techniques have the potential to measure parenchymal changes over time without need for ionizing radiation or gadolinium contrast agents, but they have not been applied to the study of ARPKD — until now. As part of an ongoing NIH-funded research program, investigators at Cleveland Clinic Children's and Case Western Reserve University have, for the first time, developed and validated two quantitative MRI measures of kidney and liver progression in an ARPKD animal model.[1] These MRI techniques, including T1 relaxometry of the liver (Figure 1), were able to not only measure progression over time but also assess the impact of novel therapies. These investigations, which are being translated to human studies in patients with ARPKD, may provide the missing elements needed to design and implement clinical trials of novel therapies in ARPKD patients.

ARPKD: One Disease, Two Pathologies and Multiple Mutations

Most children with ARPKD are diagnosed before birth, when enlarged echogenic (bright) kidneys are seen on prenatal ultrasonography. ARPKD kidney disease is characterized by diffuse microscopic dilatations of the collecting tubules, which are often too small to detect as cysts by ultrasonography but are reflected in the large, bright kidneys also evident by MRI (Figure 2). ARPKD liver disease is a developmental bile duct abnormality characterized by bile duct dilatation and proliferation with accompanying fibrosis of the portal tracts.

As the genetics of ARPKD have unfolded, it is now recognized that the disease can present later in life, even in adulthood. This smaller subset of ARPKD patients develops clinically evident hepatic complications (such as hepatosplenomegaly and bleeding varices related to portal hypertension), and the PKD component is discovered only incidentally when the patients undergo abdominal imaging.

ARPKD is caused by mutations in the *PKHD1* (polycystic kidney and hepatic disease 1) gene, which is located on chromosome 6 and encodes for fibrocystin, a very large protein of unclear function. ARPKD is clinically, histologically and genetically distinct from the more common autosomal dominant PKD (ADPKD).

Despite Improved Survival, Challenges Remain

ARPKD was once considered uniformly fatal in affected newborns. With modern neonatal care, about 70 percent of ARPKD patients now survive beyond the newborn period, and over 80 percent of those survivors will live beyond 10 years.

However, the kidney and liver disease complications remain substantial for affected children and their families. Kidney complications include hypertension and chronic kidney disease (CKD), and about 50 percent of patients progress to ESRD by age 15 years. Liver complications include portal hypertension and its sequelae of bleeding gastrointestinal varices, splenomegaly, thrombocytopenia, ascites and, rarely, ascending cholangitis (severe bile duct infection). Although liver complications may not become severe until late childhood or early adulthood, liver involvement is likely to grow in importance as more patients survive to adulthood. Notably, liver disease may be a significant cause of mortality in ARPKD patients who have already undergone kidney transplantation.

Novel Therapies Emerge

Although ADPKD and ARPKD are distinct, they are part of the family of disorders called "ciliopathies" that share important pathophysiologic features. These include localization of the gene products on or near the primary cilia, growth factor/receptor

overexpression, increased cell proliferation and upregulation of cyclic AMP. Several novel therapies tested in ADPKD animal models have been shown to be effective in ARPKD animal models (and vice versa). Data on two of these novel PKD therapies, octreotide and tolvaptan, were so compelling that clinical trials in adults with ADPKD have been undertaken, and early results are very encouraging.

However, clinical trials in ARPKD patients have not been possible due to the lack of measures to detect a treatment effect during the course of a typical clinical trial. Standard clinical measures of kidney disease progression — i.e., measured glomerular filtration rate (GFR) and urine protein excretion — have not been rigorously studied in ARPKD. To address this, we examined rates of GFR decline in ARPKD subjects currently participating in the NIH-sponsored multicenter Chronic Kidney Disease in Children (CKiD) study. Unfortunately, we found that annualized changes in GFR were relatively small (with large variation) and that proteinuria was minimal, suggesting neither measure would be useful in monitoring kidney disease progression.[2]

MRI-based kidney volume measures that have been used in the ADPKD treatment trials are not useful in ARPKD, where kidney volumes stabilize over time despite disease progression. Similarly, many clinical assessments of liver disease (such as bilirubin or transaminases) are normal in most patients with ARPKD liver disease, even those with advanced disease. Taken together, these factors highlight the need for markers to detect and monitor disease progression and/or responsiveness to therapy in ARPKD.

MRI Biomarkers of ARPKD Are at Hand

As part of an ongoing NIH-funded study, we have sought to identify MRI markers of kidney and liver disease progression and response to therapy in an ARPKD animal model. The quantitative imaging techniques do not require gadolinium contrast, which is contraindicated in patients with advanced CKD and is thus not appropriate for an ARPKD study. We have identified T2 and T1 relaxation time assessments as valid measures to detect kidney and liver disease, respectively, in this model. We have further found that these measures can detect response to novel therapies that impact kidney and/or liver disease progression. Importantly, these kidney and liver MRI assessments are immediately translatable to studies in ARPKD patients. As a result, we anticipate being able to initiate clinical studies of these MRI biomarkers in ARPKD patients in the near future. Successful application of these noninvasive MRI measures to ARPKD patients would supply the crucial element needed to begin developing clinical trials of novel therapies for ARPKD patients.

Figure 1. Representative liver T1 maps (top row) and Masson's trichrome stained sections (bottom row) for two 3-month-old PCK rats and one age-matched Sprague-Dawley (SD) control rat. One of the PCK rats exhibited cholangitis associated with more severe ARPKD liver disease, as observed periodically in ARPKD patients. Stained sections assess periportal fibrosis (blue) and biliary dilatation (asterisks). *Reprinted from Gao et al,[1] ©2015, John Wiley and Sons.*

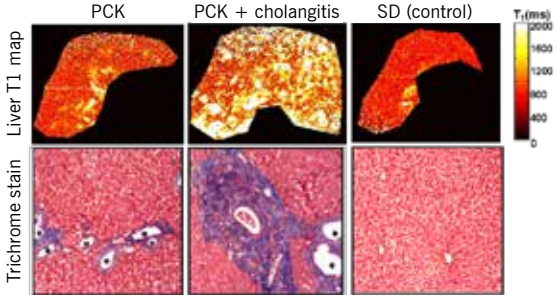
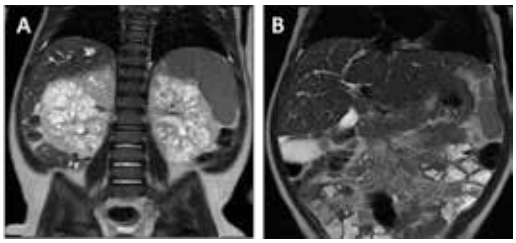


Figure 2. Coronal T2-weighted kidney (A) and liver (B) images from a 2-year-old patient with ARPKD. Note the substantial hyperintense renal cysts and expanded liver bile ducts typical of ARPKD kidney and liver disease.



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Collaborative Clinical Trial to Provide First Assessment of Ketamine in Patients with Rett Syndrome

By Thomas W. Frazier, PhD; Sumit Parikh, MD; and the Rett Ketamine Study Investigative Team

Researchers from Cleveland Clinic and Case Western Reserve University are conducting an exploratory human study of low-dose ketamine for use in the treatment of the complex neurodevelopmental disorder known as Rett syndrome. The investigation — the first of its kind — is being funded by a grant from the Rett Syndrome Research Trust. If the study is successful, a multicenter phase 2 trial will follow.

Rett Syndrome Essentials

Rett syndrome results from loss-of-function mutations in *MECP2*, the gene encoding methyl-CpG binding protein 2, a transcriptional regulatory protein. After a period of apparently normal early development, affected individuals develop a spectrum of symptoms that generally includes the following:

- Loss of acquired speech
- Head growth deceleration
- Motor, respiratory and autonomic dysfunction
- Stereotypic hand movements
- Anxiety
- Increased risk of seizures

Patients with Rett syndrome also experience behavioral symptoms similar to those of autism spectrum disorder, including difficulties with social interaction and repetitive behaviors. As a result, Rett syndrome is one of the most debilitating genetic neurodevelopmental syndromes associated with autism-like features.

Rett syndrome is one of the most debilitating genetic neurodevelopmental syndromes associated with autism-like features. Treatments that directly influence its pathology are desperately needed.

Rett syndrome is diagnosed in 1 of 10,000 female births. Treatment focuses on improving the physical and behavioral manifestations. Common treatment modalities are physical, occupational, speech and behavior therapy, along with feeding assistance. Medications can be used to provide some symptomatic relief and to control seizures in some patients, but there is no cure. Treatments that directly influence the pathology of Rett syndrome are desperately needed.

Why Ketamine?

The use of ketamine as a treatment strategy is modeled on the recent success of low-dose ketamine for treating major depressive disorder and obsessive-compulsive disorder. In these studies, IV infusion of ketamine has been shown to acutely reverse symptoms, with relief lasting up to a week or more in some cases.

Ketamine has a long history of safe use as an anesthetic, mostly for dental procedures, and more recently for pain management. It is also known as a drug with potential for abuse at higher doses. However, human studies in psychiatric disorders have focused on low, subanesthetic doses that have shown modest side effects relative to substantial benefit. These subanesthetic doses are the focus of our current Rett syndrome trial.

Potential for Acute Rescue of Neurological Function in Rett Syndrome

The therapeutic potential of ketamine for treatment of Rett syndrome was first demonstrated by Katz and colleagues, who found that treatment of *MECP2*-mutant mice with a subanesthetic dose of ketamine acutely reverses or improves several disease symptoms, including abnormalities in brain activity, cognitive function, breathing and locomotion.[1,2] Even more recently, chronic administration of ketamine was also found to improve symptoms and extend life span in *MECP2*-mutant mice.[3]

In other disease models, ketamine treatment has been shown to rapidly stimulate dendritic growth, brain-derived neurotrophic factor (BDNF) translation and expression of key synaptic proteins through activation of mTOR signaling, which is deficient in *MECP2*-mutant mice.

In addition to acute rescue of neurological function, ketamine has the potential to induce long-term synaptic repair by enhancing structural and functional brain connectivity in Rett syndrome.

Taken together, these findings suggest that, in addition to acute rescue of neurological function, ketamine has the potential to induce long-term synaptic repair by enhancing structural and functional brain connectivity in Rett syndrome.

Trial Design and Next Steps

Approximately 30 patients with Rett syndrome will be enrolled in our exploratory trial (co-principal investigators are David M. Katz, PhD, and Daniel Sessler, MD — see Acknowledgment below). Each participant will be randomized to receive three of five possible doses of ketamine plus a placebo dose. Each dose will be administered intravenously at one of four consecutive monthly visits while safety and efficacy outcome measures are carefully tracked.

The primary aim of the study is to determine the safety and tolerability of single-dose subanesthetic ketamine. Secondary aims are to evaluate potential efficacy, including improvements in breathing, behavioral symptoms, brain function (assessed by EEG and auditory evoked potentials) and overall clinical severity. The study's within-subjects design allows each patient to be his or her own control and may enable determination of potential dose-safety and dose-efficacy relationships.

If the trial is successful, the next step will be to plan for a large-scale, multisite phase 2 trial of ketamine in patients with Rett syndrome. We may also explore the efficacy of an oral ketamine formulation as an alternative to the IV infusion used in the current trial.

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ACKNOWLEDGMENT

In addition to Drs. Frazier and Parikh, the Rett Ketamine Study Investigative Team includes David M. Katz, PhD, Professor of Neurosciences and Psychiatry, Case Western Reserve University (co-principal investigator), and Daniel Sessler, MD, Chair of Outcomes Research at Cleveland Clinic (co-principal investigator).

Combining Robotic SEEG with Laser Ablation: A Minimally Invasive Approach for Difficult-to-Localize Pediatric Epilepsy

By Jorge Gonzalez-Martinez, MD, PhD, and Ahsan N.V. Moosa, MD

Laser ablation guided by real-time MRI, initially described in 2006 as a treatment for metastatic tumors, has shown promising results in the treatment of multiple intracranial pathologies including primary and metastatic lesions, epileptogenic foci and radiation necrosis.

Advantages of Laser Ablation

The use of laser ablation for treatment of epileptogenic areas such as tubers (in tuberous sclerosis) and in mesial temporal sclerosis (via selective laser amygdalohippocampotomy), focal cortical dysplasias, hamartomas and post-stroke epilepsy has been described in the literature. The advantages of laser ablation are attributed to several factors:

- The small opening required to accommodate the probe
- The precision related to the probe's final location
- The relatively short ablation time associated with each treatment (< 5 minutes, on average, after placement of the laser catheter)

All these attributes result in a potentially safer, more cost-effective and more efficient treatment option than other approaches for pediatric patients with medically intractable focal epilepsy. Additionally, laser ablation provides access to areas where surgical treatment using conventional therapies would be contraindicated.

Pioneering Integration of SEEG with Laser Therapy

While Cleveland Clinic's Epilepsy Center has previously published cases of laser ablation of epileptogenic lesions, the use of the robotic stereoelectroencephalography (SEEG) technique in combination with laser ablation to disrupt a specific epileptic network in patients with nonlesional epilepsy has not been reported. We have been performing this innovative work in adult and pediatric patients for more than a year, with promising results in terms of seizure control and safety. We share here an illustrative case report of a pediatric patient.

Representative Case Description

Epilepsy history. A 17-year-old male presented with a history of intractable epilepsy since age 9. He described his seizures as a "cold chill down the whole body" followed by partial awareness of subsequent events. His caregivers reported that the seizures began with a stare, changes in facial expression and pouting of the mouth, accompanied by changes in breathing pattern. He often walked aimlessly or made quick "robotic" movements. His seizures ended with a scream that startled anyone nearby and disrupted his social life. Although the seizures lasted only 15 to 20 seconds, they occurred as frequently as 20 times a day, and almost hourly during sleep.

The patient presented to Cleveland Clinic after failure to respond to eight different antiepileptic drugs and vagal nerve stimulation. His neurologic examination was normal.

Presurgical noninvasive workup. Video EEG evaluation suggested a diagnosis of left frontal epilepsy based on interictal spikes and ictal patterns in a few seizures. Several other seizures, however, were poorly localized, with bifrontal involvement. A 3T MRI of the brain did not reveal any lesion. FDG-PET showed focal hypometabolism in the left frontal region. Ictal single-photon emission computed tomography (SPECT) also showed hyperperfusion in the left anterior medial frontal region. Magnetoencephalography confirmed epileptiform discharges in the same region (Figure 1).

The absence of a lesion on brain MRI and localization in the dominant frontal lobe led to consideration of invasive monitoring with SEEG. This procedure was performed to map the epileptogenic zone and determine the margins of the resection.

Invasive monitoring with robotic SEEG. During SEEG monitoring, the electrode in the left anterior mesial frontal area (L′, contacts 2, 3 and 4) showed focal and persistent repetitive spikes throughout the evaluation (Figure 2). All recorded seizures also arose from the same region (Figure 2). This was concordant with presurgical suspicions. Stimulation of the same regions elicited habitual seizures, further reinforcing the hypothesis. After discussion with the patient and his family, we elected to perform laser ablation of the focus at the time of removal of the SEEG electrodes.

Laser ablation. With the patient under general anesthesia, a small lesion centered at the previous location of the L′ electrode (left mesial frontal area, contacts 2, 3 and 4) was created, approximately 1 cm^3 in volume (Figure 3). The treatment period, from insertion of

Figure 1

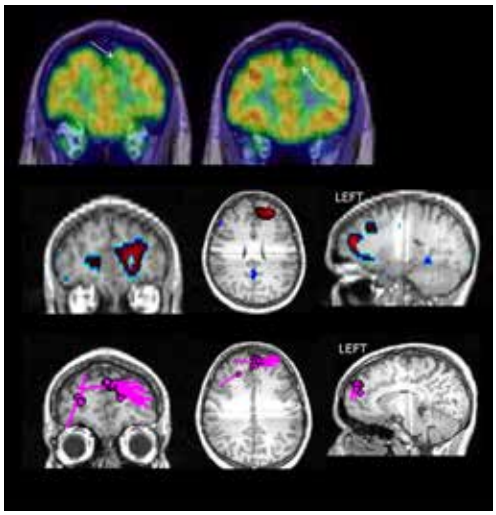

Figure 2

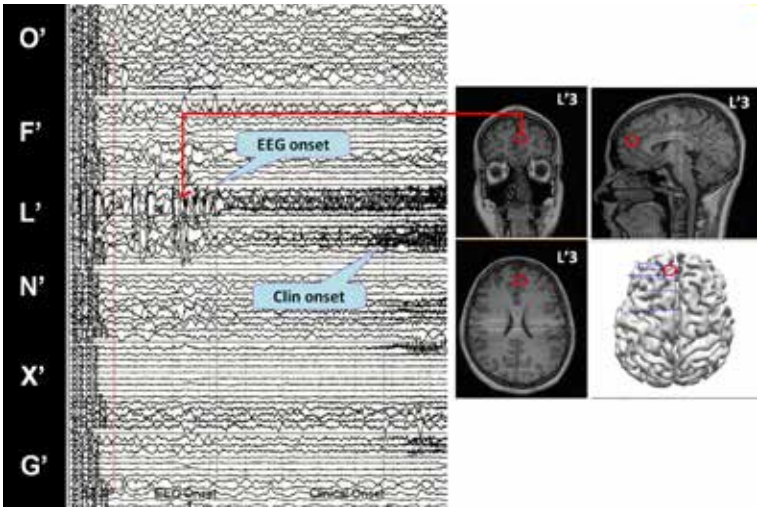

Figure 3

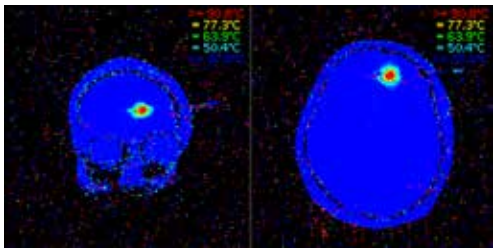

Figure 1. Left frontal localization supported by noninvasive testing with FDG-PET (top), ictal single-photon emission computed tomography (middle) and magnetoencephalography (bottom).

Figure 2. Localization of ictal onset to the left anterior mesial superior frontal gyrus (L′ 2-4) as confirmed by intracranial SEEG.

Figure 3. Intraoperative coronal and axial thermograms during MRI-guided laser ablation of the left mesial frontal area.

the laser probe to the end of the lesioning phase, was five minutes. Afterward, the probe was removed, the incision was closed with one stitch and anesthesia was reversed. The patient was discharged from the hospital the next morning.

Outcome. At three-month postoperative follow-up, the patient was seizure-free. He has had no change in personality or memory. However, his family reports a new "problem": "Since surgery, we don't know if he is at home or not!" they relate (because his seizure-associated screams have ended).

Conclusions: A Promising Diagnostic-Therapeutic Combination

Our preliminary experience with the described method clearly illustrates the feasibility of a unique combination of robotic SEEG, laser ablation and intraoperative MRI in the management of pediatric patients with difficult-to-localize epilepsy. While further study is needed, the success of this procedure allows the possibility of a diagnostic-therapeutic combination unparalleled in its minimal invasiveness, reduction of treatment time and brevity of recovery time — all apparently without compromising efficacy.

SUGGESTED READING

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Combating Retinopathy of Prematurity: Can Stabilizing Hypoxia-Inducible Factors Prevent Hyperoxia-Induced Retinal Damage?

By Jonathan E. Sears, MD, and George Hoppe, MD, PhD

Recent data from two randomized prospective trials[1,2] have defined the central paradox of oxygen therapy in severely premature infants — i.e., that oxygen is necessary to prevent mortality in these children but is simultaneously toxic to premature tissues such as the retina and the lung.

The discovery of hypoxia-inducible factors (HIFs) and their oxygen-dependent regulation through HIF prolyl hydroxylases offers a possible translational pathway for the growth and protection of blood vessels relevant to a broad range of diseases. These include anemia, stroke, myocardial infarction, skeletal muscle ischemia — and especially retinopathy of prematurity (ROP).

Our research team within Cleveland Clinic's Cole Eye Institute is pursuing investigations that build on this work by raising the prospect of using low-dose, systemic, intermittent drug delivery to alleviate the hyperoxia-induced retinal damage of ROP. This article briefly reviews the basis for this work and the road ahead.

ROP's Growing Impact

ROP is the most common cause of childhood blindness worldwide, and its incidence grows as severely premature infants are resuscitated at increasingly lower birth weights and younger gestational ages. Each year about 500,000 children are born prematurely in the U.S. and 13 million worldwide. In children born at less than 28 weeks' gestation, the incidence of ROP can be as high as 75 percent.

The simplicity of targeting a central visceral organ might justify angioprotection in diseases like ROP that require only a brief window for therapy.

The Underlying Science

ROP is a vasoproliferative disease that affects neonates with very low birth weight and early gestational age. The fetus develops in relative hypoxia in utero, a physiologic state that is disrupted by premature birth and worsened in susceptible tissues by supplemental oxygen.

The presence of excess oxygen, which corresponds to the hyperoxic phase I of ROP, causes the prolyl hydroxylase domain protein (PHD) to target key proline residues within the oxygen-dependent degradation domain (ODD) of the HIF-1α subunit for degradation by the ubiquitin-proteasome pathway. Two proline residues are targets of HIF PHD within the ODD and can interact independently with the von Hippel-Lindau tumor suppressor protein (pVHL). PHDs are a family of conserved enzymes with at least three mammalian homologues (PHD1-3) that regulate HIF activity through post-translational modification and therefore quickly respond to hyperoxia by downregulating HIF. Absence of HIF-1α results in halted downstream angiogenic pathways, including the reduction of VEGF secretion associated with oxygen-induced vascular obliteration.

Rodent Models Direct Attention to Hepatic Targeting

Our lab has definitively proven that systemic injection of the HIF activator and nonselective inhibitor of HIF PHD, dimethyloxalylglycine (DMOG), in two separate rodent models of ROP resulted in a dramatic inhibition of oxygen-induced retinopathy that was recapitulated by systemic PHD2 ablation.[3-5]

Surprisingly, hepatic HIF-1α protein levels after DMOG injection in mice were dramatically upregulated compared with levels in the brain, retina and kidney. Organ lysate obtained from DMOG-treated mice expressing a transgene of luciferase fused to the ODD confirmed that the highest luciferase activity is in the liver.[4]

This unusual finding of liver-specific HIF-1α activation and subsequent protection of retinovasculature initiated the hypothesis that the liver could be stimulated to protect retinal capillary beds via hepatic PHD inhibition. The simplicity of

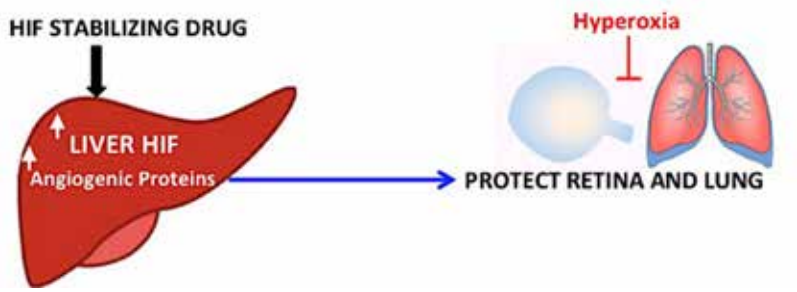

Figure. Many hypoxia-inducible factor (HIF)-stabilizing small molecules can induce the liver to protect remote capillary beds such as in the lung and the retina. This creates the possibility of using low-dose, intermittent drug delivery to systemically alleviate hyperoxia-induced damage to various developing tissues in neonates born prematurely.

targeting a central visceral organ might justify angioprotection in diseases that require only a brief window for therapy, such as ROP.

Confirming Remote Protection

This concept of remote protection — stimulating the liver to protect distal capillary beds — was then definitively proven using selective ablation of hepatic HIF-1α.[6] This remarkable finding suggested that using a systemic agent to protect against retinal disease might simultaneously prevent hyperoxic damage to the lung, thereby improving gas exchange and decreasing supplemental oxygen requirements (Figure).

End Goal: A Small Molecule to Induce Normal Tissue Growth

A recent National Eye Institute-supported investigation by our lab using systems pharmacology has demonstrated that different small molecules can target the liver, the eye or both. The latter pathway is especially valuable because it raises the possibility of using low-dose, intermittent drug administration to vulnerable neonates to minimize the chance of drug toxicity. We envision the use of a soluble small molecule, given intravenously once or twice a week in the first few weeks of life until corrected gestational age of 30 weeks, to gently induce the normal coordinated growth of retinal blood vessels and possibly other organ systems negatively impacted by hyperoxia.

ACKNOWLEDGMENTS

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Additional references are available by contacting Dr. Sears (searsj@ccf.org).

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New Protocol Uses Multimodal Pain Management to Shorten Length of Stay for Idiopathic Scoliosis Patients Undergoing Spine Fusion

By Ryan C. Goodwin, MD

Spine fusion for progressive deformity due to idiopathic scoliosis remains the gold standard for definitive treatment. It is a reliable technique for preventing progression as well as the long-term cardiopulmonary sequelae that progressive curves produce when severe.

Unfortunately, fusion is historically accompanied by significant perioperative morbidity and prolonged hospital stays for these otherwise predominantly healthy patients. Hospital stays averaging nearly seven days are common in some centers and are typically required for adequate pain control and mobilization.

A Multimodal Approach to Improve Pain Management

Recent radical changes in postoperative pain management protocols for these cases at Cleveland Clinic Children's have resulted in a significant reduction in perioperative morbidity, pain and ultimate length of stay for patients undergoing spine fusion for deformity. A more aggressive approach to pain management and mobilization has cut our average length of stay nearly in half.

Our new protocol, patterned after a successful pilot at Children's Healthcare of Atlanta, employs a multimodal approach to aggressive pain management and mobilization with physical therapy during the patient's hospital stay:

- Preoperative and postoperative oral gabapentin
- Narcotics-only epidural analgesia placed by the surgeon
- Generous use of local anesthetics applied by the surgeon
- High-dose IV and oral ketorolac
- IV and oral narcotics
- Early mobilization

These modalities have excellent perioperative analgesic properties, which allow early mobilization and, ultimately, more timely discharge home. Selected components of the protocol are outlined in the table.

Other additions to the protocol that have helped decrease length of stay include:

- Sitting or standing with a few steps on postoperative day 0
- Gum chewing and early dietary advancement for gastrointestinal recovery
- No postoperative bracing

Other perioperative techniques for reducing blood loss and allogeneic blood transfusions also show promise. The use of tranexamic acid, hypotensive anesthesia and intraoperative cell salvage has reduced our use of allogeneic blood transfusion to almost zero.

Data Collection Underway — and Promising So Far

We are in the process of collecting specific data on this protocol, but the results since its inception in 2014 are promising. With the institution of this new protocol, average length of stay was reduced to 3.3 days in the first six months of 2015, with 67 percent of patients going home in three days or less.

Integration of the protocol into the electronic medical record has helped make the transition seamless, and all three surgeons performing pediatric scoliosis surgery — including Thomas Kuivila, MD, and David Gurd, MD — are using the protocol essentially 100 percent of the time. Cost data are not yet available, but we anticipate a significant reduction in total hospital expenses through use of this protocol with no change in ultimate outcomes.

Preliminary patient satisfaction data are likewise promising, and we have seen no increase in emergency department visits for pain control following discharge. We also see no differences in perioperative complications. We anticipate no differences in fusion rates as well, although long-term data — which are not yet available — will be required.

While this protocol is in its infancy at our institution, it has significantly improved the efficiency of postoperative care delivery in this subset of patients. Further dedicated prospective studies on defined clinical outcomes and cost are forthcoming.

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Table. Selected Components of the Accelerated Recovery Protocol

	Day of Surgery	Postop Day 1	Postop Day 2	Postop Day 3
PT/OT activity	Therapy in p.m. if tolerated. Sit with PT. Stand if tolerated.	Therapy BID. Log roll every 2 hours. Up in chair TID. Ambulate TID.	Therapy BID. Log roll on own. Up in chair TID. Ambulate TID. Begin stairs.	Therapy in a.m. Log roll on own. Up in chair TID. Ambulate TID. Master stairs.
Nutrition and GI	Clear liquid diet.	Assess bowel sounds. Gum chewing. Advance diet.	Assess bowel sounds. Gum chewing. Regular diet.	Gum chewing. Regular diet.
Pain management	Per pediatric anesthesia pain management. Patient-controlled epidural analgesia, IV and oral analgesics, ketorolac, benzodiazepines as needed.	Gabapentin 5 mg/kg orally (max 1,200 mg) every 8 hours. Transition to oral pain meds.	Gabapentin 5 mg/kg orally (max 1,200 mg) every 8 hours. Discontinue epidural catheters.	Gabapentin 5 mg/kg orally (max 1,200 mg) every 8 hours. Oral regimen only.
Discharge planning		Assess home health and transportation needs.		Ensure home health and transportation resources are available.

Post-Protocol Results to Date

Average length of stay ⬇ to **3.3 days**

67% of patients discharged in **3 days** or less

Airway Epithelial Barrier Dysfunction in Response to Respiratory Syncytial Virus: Readying the Research for Animal Model Replication

By Fariba Rezaee, MD

Respiratory syncytial virus (RSV) is the most important virus causing acute lower respiratory infection in young children. RSV infects airway epithelial cells and is thought to cause tissue pathology by inducing expression of proinflammatory mediators, but the effect of RSV infection on airway epithelial barrier structure and function has not been well understood.

I have been part of a research team focused for a number of years on basic aspects of viral pathogenesis, airway epithelial biology and epithelial barrier immunology, with a particular interest in RSV. We are deeply interested in exploring mechanisms that regulate the structure and function of airway epithelial apical junctions, and a focus of our work has been establishing comprehensive in vitro and in vivo models to identify the signaling pathways that change the integrity of apical junctional complexes (AJCs) following RSV infection.

With my recent arrival at Cleveland Clinic Children's, I am pleased to be continuing this research here, with the long-term goal of better understanding how to modify the involved mechanisms to restore barrier integrity and dampen inflammatory responses. This article reviews a few of my group's findings in this area to date and some of our leading research priorities moving forward.

How RSV Induces Airway Barrier Disruption

The airway epithelium forms a barrier to the outside world and is made up of the surface mucous layer as well as AJCs that regulate paracellular permeability. Our group has revealed that infection with RSV leads to airway epithelial barrier dysfunction in the absence of cell death. A defect of epithelial barrier allows greater luminal influx of environmental allergens, toxicants and microbes into the subepithelial space, where they may encounter dendritic cells and other immune sentinels.

Early studies in our lab showed that administration of polyinosinic:polycytidylic acid, a mimic of viral double-stranded RNA, induces barrier dysfunction, AJC disassembly and remodeling of the apical actin cytoskeleton.[1] This involved a cell-intrinsic signaling mechanism dependent in part on toll-like receptor 3. We subsequently showed that RSV infection of airway epithelial cells also results in sustained decreases in airway resistance and increased paracellular permeability. The barrier-disruptive effects of RSV were not associated with cell cytotoxicity.

Role of Tight Junctions in the Epithelial Barrier

Most asthma exacerbations in children are caused predominantly by respiratory infections. Virus-induced epithelial permeability may facilitate the translocation of inhaled aeroallergens and may help explain the association between respiratory viral infection and allergen sensitization in asthma. A colleague and I recently summarized various barrier-disrupting agents in a review article.[2] We elucidated how disruption of barrier integrity enhances outside-in translocation of inhaled particles into the subepithelial space, where these particles encounter innate immune cells and lead to airway inflammation and immune responses (Figure 1).

Mechanisms of RSV-Induced Airway Barrier Disruption

Our group has also found that RSV-induced disassembly of AJCs occurs in a protein kinase D (PKD)-dependent manner.[3] Originally known as PKCμ, this molecule was renamed because its structure and substrate specificity differ from those of other PKC family members. PKD regulates cell shape and motility in part by controlling actin dynamics, and in support of a role for cytoskeletal remodeling, we found that RSV infection induces phosphorylation of the actin binding protein cortactin (Figure 2). Taken together, these studies suggest that PKD could be more broadly involved in barrier dysfunction caused by respiratory viruses, which will be an interesting area for future studies.

Next Research Step: Animal Model Replication

The next step in our research will be to see if these observations can be replicated in an animal model. We currently have a limited understanding of how AJCs function in vivo in the normal lung. The RSV murine model offers advantages for studying the immunopathogenesis of RSV-induced long-term airway disease. Eventually, our research will focus on human studies to investigate the effect of viral infection on the airway barrier of patients suffering from asthma relative to nonasthmatic subjects.

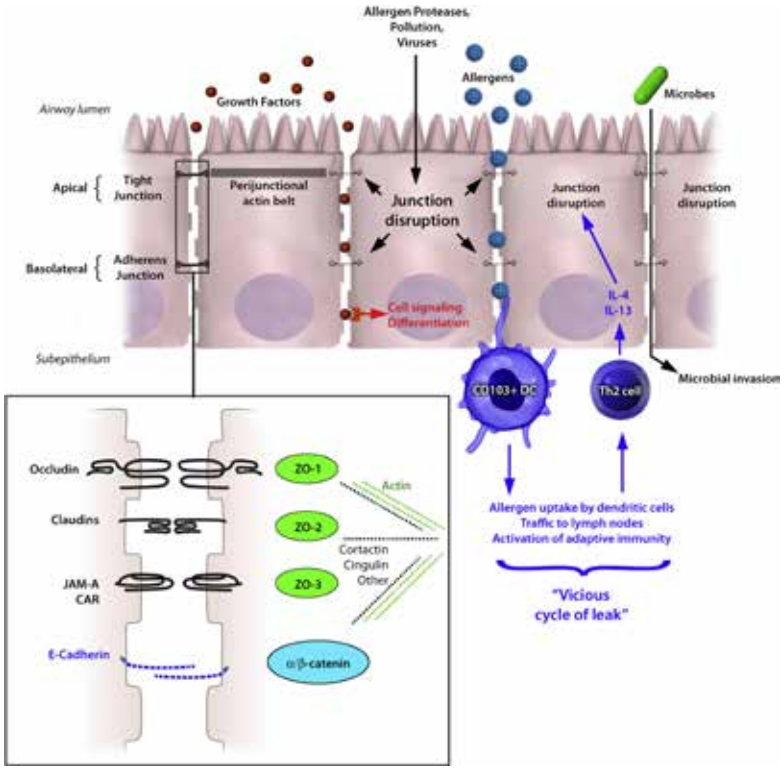

Figure 1. Illustration of airway epithelial cells indicating junctional structures, including tight junctions (black) and adherens junctions (blue), which are intimately linked with perijunctional actin filaments. The inset shows an enlarged schematic of protein-protein interactions in tight (black text) and adherens (blue text) junctions, including the ability of zonula occludens (ZO) proteins to interact with intracytoplasmic domains. Inhaled allergens, air pollutants and respiratory tract viruses can cause dysfunction of the epithelial junction, resulting in greater outside-in permeability. Barrier dysfunction will also allow greater sampling of luminal allergens (blue stars) by intraepithelial dendritic cells. Allergen-induced Th2 responses can induce a vicious cycle of leak because Th2 cytokines perpetuate junctional dysfunction. Another consequence of leaky epithelial barriers is increased microbial invasion, which might predispose susceptible patients to exacerbations or lung infections. *Reprinted from reference 2, ©2014, with permission from American Academy of Allergy, Asthma and Immunology.*

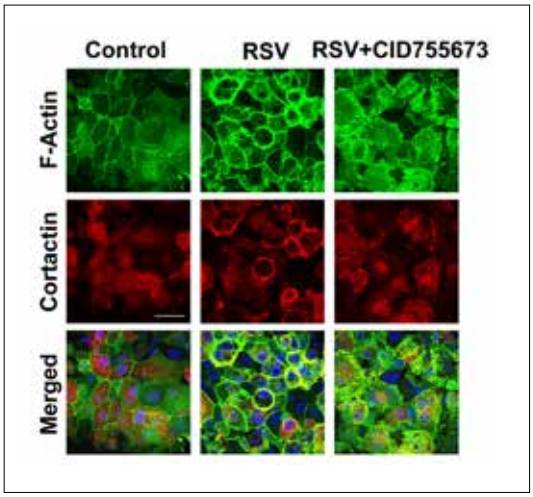

Figure 2. Confocal images showing marked redistribution of cortical actin fibers into intracellular vesicles and recruitment of cortactin to perijunctional actin filaments in RSV-treated epithelial cells, which was also inhibited by a pharmacological inhibitor of PKD (CID755673). Bottom row (yellow staining) shows increased co-localization of actin and cortactin in response to RSV infection. *Reprinted from reference 3, ©2013, American Society for Microbiology.*

Our findings collectively provide new insights into the regulation of the epithelial barrier by a clinically significant virus with a poorly understood pathogenesis. Improved understanding of the mechanisms involved will not only enhance our knowledge of basic biology but also aid in the design of agents that could specifically target virus-mediated pathology. Such agents would have positive impacts on the well-being and quality of life of both children and adults suffering from respiratory illness.

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Susac Syndrome: Giving a Newly Appreciated Autoimmune Disease the Attention It Requires in Children and Adolescents

By Robert Rennebohm, MD; Divya Yadav, MD; and Sunil Srivastava, MD

Pediatric rheumatologists around the world encounter patients with symptoms and signs that should prompt consideration of Susac syndrome (SuS), yet information on SuS remains relatively scarce. Through an array of initiatives centered on SuS — including the International Collaborative Study of Susac Syndrome and a related international registry for the disease — Cleveland Clinic is leading efforts to help change that, with its Center for Pediatric Rheumatology playing a central role.

Not as Rare as Perceived

First described by Dr. John Susac in 1979, SuS primarily affects young women between ages 20 and 40, but it also affects men, children and adolescents. Of the 313 cases reported in the worldwide medical literature to date, 34 (about 11 percent) have been children or adolescents, predominantly older adolescents.

Because many cases have not been reported, it is likely that SuS is considerably more common than the above numbers suggest. Moreover, SuS is commonly misdiagnosed, usually as atypical multiple sclerosis or atypical acute disseminated encephalomyelitis (ADEM).

Although SuS is relatively rare, the clinical scenarios in which it is a relevant consideration are quite common. Specifically, SuS must be considered in the differential diagnosis of any patient who presents with one or more of the following: (1) unexplained encephalopathy, (2) unexplained retinal vasculopathy and (3) unexplained hearing loss.

The Clinical Profile — and Treatment — of SuS

SuS is a chronic immune-mediated microvascular endotheliopathy that partially or completely occludes the microvasculature in the brain, retina and inner ear, resulting in varying degrees of ischemic injury to these tissues. Clinically, it is characterized by the triad of:

- Encephalopathy (chiefly headaches and cognitive dysfunction, but there can be a variety of other neurologic manifestations)
- Branch retinal artery occlusion (BRAO), as well as vessel wall hyperfluorescence and leakage (Figure 1)
- Hearing loss (often with tinnitus and vertigo) (Figure 2)

This triad is typically accompanied by the distinctive MRI finding of "snowball" lesions in the central portion of the corpus callosum (Figure 3). The immunopathogenesis of SuS appears to be quite similar to that of dermatomyositis, which is also an immune-mediated, occlusive microvascular endotheliopathy. In its most severe form, SuS threatens to cause dementia, blindness, deafness and severe lifelong physical and mental disability.

Fortunately, experienced and prompt use of aggressive, sustained immunosuppression (typically corticosteroids, IV immunoglobulin, and mycophenolate or cyclophosphamide) can markedly improve outcomes. In severe cases, cyclophosphamide, rituximab and/or plasma exchange may be considered.

Addressing SuS on Multiple Fronts

Timely diagnosis of SuS is extremely important to ensure appropriate treatment before irreversible harm to the brain, retina and inner ear occurs. Few clinicians are highly experienced with this disease. The care of patients with SuS requires a team of experts familiar not only with the condition but also with its mimics to ensure an accurate diagnosis and workup.

In response to these needs, Cleveland Clinic has established an array of SuS-specific clinical services and research/educational initiatives that are directed out of its Department of Rheumatic and Immunologic Diseases and Cleveland Clinic Children's Center for Pediatric Rheumatology. These include:

- **The Susac Syndrome Consultation Clinic**, designed to comprehensively evaluate patients with definite or suspected SuS. The clinic is staffed by a multidisciplinary team of specialists (from adult and pediatric rheumatology, neurology, ophthalmology, neuro-otology, otolaryngology and neuroradiology) who have particular expertise in inflammatory diseases affecting the brain, eye and inner ear. To date, 50 patients from 23 states and three countries have been evaluated in this clinic.
- **The International Susac Syndrome Consultation Service**, which serves patients with SuS (and their providers) who cannot travel to Cleveland Clinic. It includes the Susac Syndrome MyConsult Program, a secure online second opinion service involving review of a patient's medical records

and associated imaging studies, a team-generated expert opinion on diagnosis and treatment, and options for ongoing expert consultation on patient management. Our team also fields physician and patient questions about SuS, responding to email or phone inquiries related to 120 individual patients from 29 states, 25 countries and six continents to date. Of these patients, 16 have been children or adolescents. In addition to benefiting patients and their providers, this service has substantially advanced our understanding of SuS.

- **The International Collaborative Study of Susac Syndrome**, an IRB-approved investigation launched by Cleveland Clinic to prospectively and retrospectively study the presentation, course, treatment, long-term outcomes and immunopathogenesis of SuS. Any patient in the world is eligible to participate.
- **The International Disease Registry for Susac Syndrome**, a key component of the above study designed to collect essential basic information on as many patients with SuS as possible from around the world.
- **An educational website, clevelandclinic.org/susac**, which provides extensive information on the condition, the International Collaborative Study and much more for both providers and patients.

Meeting SuS Challenges Through Collaboration

Because SuS is a relatively newly recognized entity with potential to cause devastating harm to the brain, retina and inner ear, we need broad-based efforts to detect it, manage it appropriately and understand it better. At the patient level, that means taking a collaborative, multidisciplinary approach to its evaluation and management across pediatric and adult subspecialties. At the international level, it means pooling experience and expertise through initiatives like those outlined above.

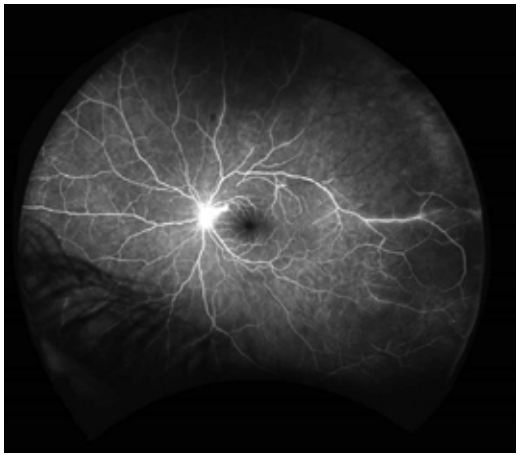


Figure 1. Fluorescein angiography showing partial branch retinal artery occlusion (BRAO) and segmental hyperfluorescence and leakage in a patient with Susac syndrome.

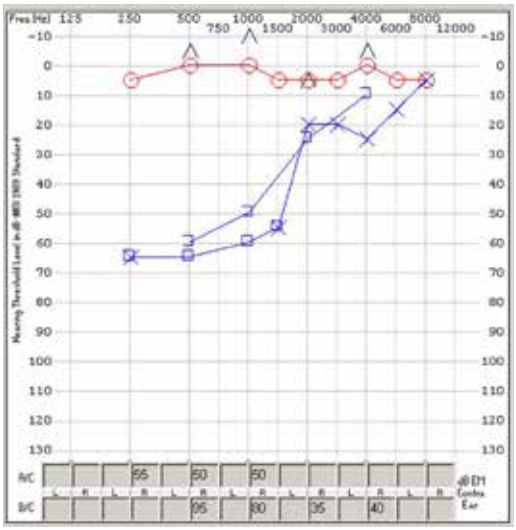
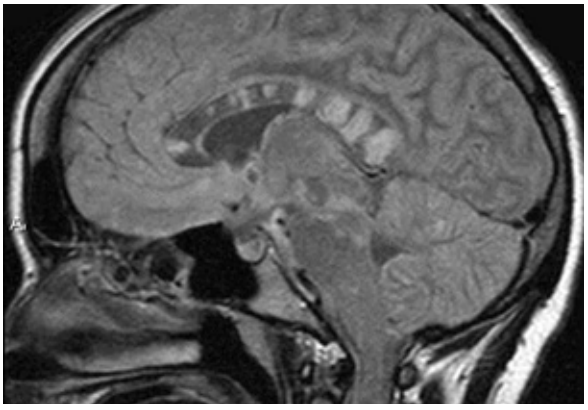


Figure 2. Audiogram from a patient with Susac syndrome showing typical low-frequency sensorineural hearing loss in the left ear (indicated by X's) with normal hearing in the right ear (indicated by O's).

Figure 3. Sagittal T2-weighted FLAIR image (MRI) showing four particularly large "snowball" lesions in the posterior half of the corpus callosum in a patient with Susac syndrome. *Reprinted from* Journal of the Neurological Sciences, *vol. 299, Rennebohm et al, "Susac's syndrome — update," p. 87. Copyright 2010, with permission from Elsevier.*



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First Pediatric Robotic Partial Nephrectomy at Cleveland Clinic Demonstrates Safety in a Well-Selected Patient

By Audrey Rhee, MD

The robotic approach in pediatric urologic surgery is constantly under scrutiny. That's because many reconstructive procedures can be performed in less operative time using an open approach, with similarly small sum-total incisions. Pediatric patients who undergo open urologic procedures rarely remain hospitalized more than two days postoperatively unless they are older and more muscular. Thus, both patient selection and the procedure performed must justify the cost and approach in robotic cases.

This article briefly reviews the first pediatric robot-assisted partial nephrectomy performed at Cleveland Clinic and discusses some insights gained from the case.

Case Presentation and Evaluation

The patient, a 9-year-old girl, initially presented with epigastric pain. She was ultimately diagnosed with chronic pancreatitis, but imaging incidentally revealed a complex left upper pole cystic lesion. This T1 and T2 hypointense, nonenhancing lesion measured 1.6 × 1.1 × 0.9 cm and was consistent with a renal cyst in the superior pole of the left kidney. Septations and calcifications were present (Figures 1 to 3).

Notably, the patient had a duplex collecting system on the left kidney; however, this was not associated with a dysplastic upper pole or dilated ureter. Nor did it appear to be consistent with a calyceal diverticulum.

The Decision to Proceed Robotically

After extensive counseling, we offered the patient's parents the options of watchful waiting or excision of the lesion. Given the complexity of the lesion, the parents were interested in pursuing excision but were not keen on an open approach. Our pediatric urology and minimally invasive teams reviewed the patient's medical imaging and determined that the procedure could be performed robotically.

The Procedure in Brief

Retrograde pyelograms confirmed the duplex collecting system and that the upper pole lesion was not merely a dysplastic upper pole. An open-ended ureteral catheter was left in place in the lower pole ureter for identification purposes.

The robot was docked using a 12-mm camera port, 8-mm standard robotic arm ports and a 12-mm assistant port. We carefully defatted the left kidney and dissected the hilum. A laparoscopic ultrasound confirmed our preoperative findings. We applied a bulldog clamp to the renal artery and excised the renal lesion in its entirety. The renorrhaphy was closed in a running horizontal mattress fashion. Total warm ischemia time was 13 minutes.

A Good Outcome Two Years Out

The patient did well after surgery and was discharged the next day with a stable complete blood count. The pathology report confirmed a benign renal cortical cyst.

The patient obtained a follow-up ultrasound that demonstrated a healthy left kidney with no residual lesions. Two years postoperatively, her images are consistently unchanged (Figure 4). Her small abdominal incisions are well-healed and well-concealed.

Key Takeaway: Proper Patient Selection Is Imperative

Heminephrectomies have been reported in the pediatric patient population. However, blood loss is markedly less in a nonfunctioning upper pole than in a potentially vascular and malignant lesion. Partial nephrectomies are less common, and few are managed minimally invasively.

This case demonstrates that in addition to reconstructive procedures, such as pyeloplasty or reimplants, extirpative robotic procedures are also a safe option in the pediatric population. Had this child undergone an open approach, her recovery would likely have been much longer, given her age and size. Additionally, her incision would have been much larger.

Proper patient selection is the cornerstone of success in robot-assisted cases.

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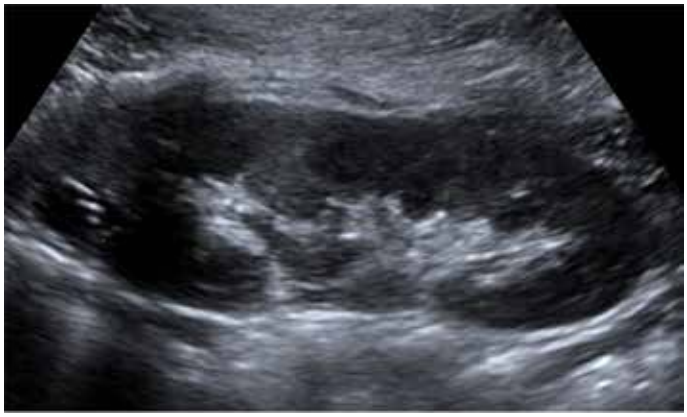


Figure 1. Preoperative ultrasound of the patient's left kidney (sagittal view) showing a 1.6 × 1.1 × 0.9-cm cystic lesion in the upper pole. There is increased echogenicity within the periphery, which may reflect calcifications.

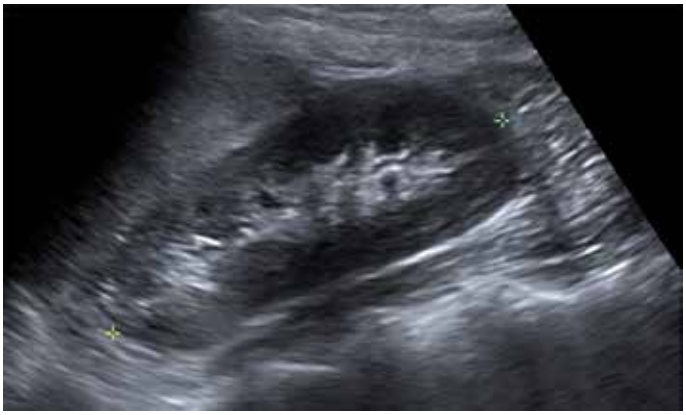
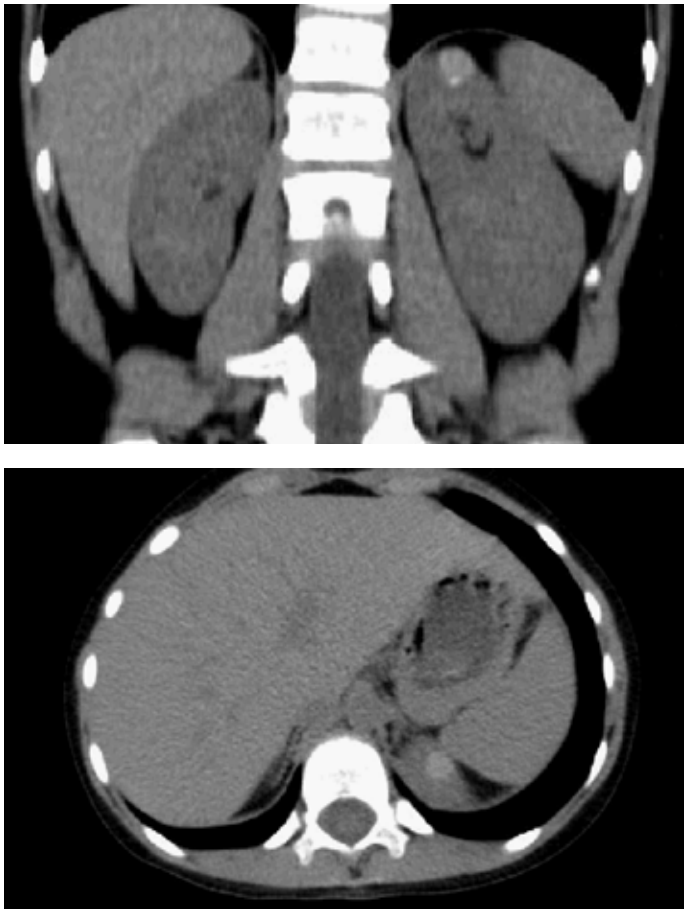


Figure 4. Ultrasound of the patient's left kidney (sagittal view) two years after surgery. The previously noted cystic lesion is no longer seen at the superior pole, and there is no evidence of hydronephrosis.



Figures 2 and 3. Preoperative CT images (coronal and axial views) showing a 9 × 9 × 12-mm hyperdense (80 HU), round endophytic lesion in the upper pole of the patient's left kidney, with a 3-mm peripheral calcification inferiorly. No layering fluid levels are seen within the lesion.

This case demonstrates that in addition to reconstructive procedures, such as pyeloplasty or reimplants, extirpative robotic procedures are also a safe option in the pediatric population. Had this child undergone an open approach, her recovery would likely have been much longer.

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Physician Referral App
Download today at the App Store or Google Play.

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

Critical Care Transport Worldwide
To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467.
clevelandclinic.org/criticalcaretransport

Staff Directory and Services
Visit clevelandclinicchildrens.org/staff to view our staff and services online.

Same-Day Appointments
To help your patients get the care they need, right away, have them call our same-day appointment line, 216.444.CARE (2273) or 800.223.CARE (2273).

Outcomes Data
View Outcomes books at clevelandclinic.org/outcomes.

CME Opportunities
Visit ccfcme.org for convenient learning opportunities from Cleveland Clinic's Center for Continuing Education.

Executive Education
Learn about our Executive Visitors' Program and two-week Samson Global Leadership Academy immersion program at clevelandclinic.org/executiveeducation.

Cleveland Clinic Way Book Series
Lessons in excellence from one of the world's leading healthcare organizations.

- *The Cleveland Clinic Way*
  Toby Cosgrove, MD
  President and CEO, Cleveland Clinic
- *Innovation the Cleveland Clinic Way*
  Thomas J. Graham, MD
  Former Chief Innovation Officer, Cleveland Clinic
- *Service Fanatics*
  James Merlino, MD
  Former Chief Experience Officer, Cleveland Clinic

Visit clevelandclinic.org/ClevelandClinicWay for more details or to order.

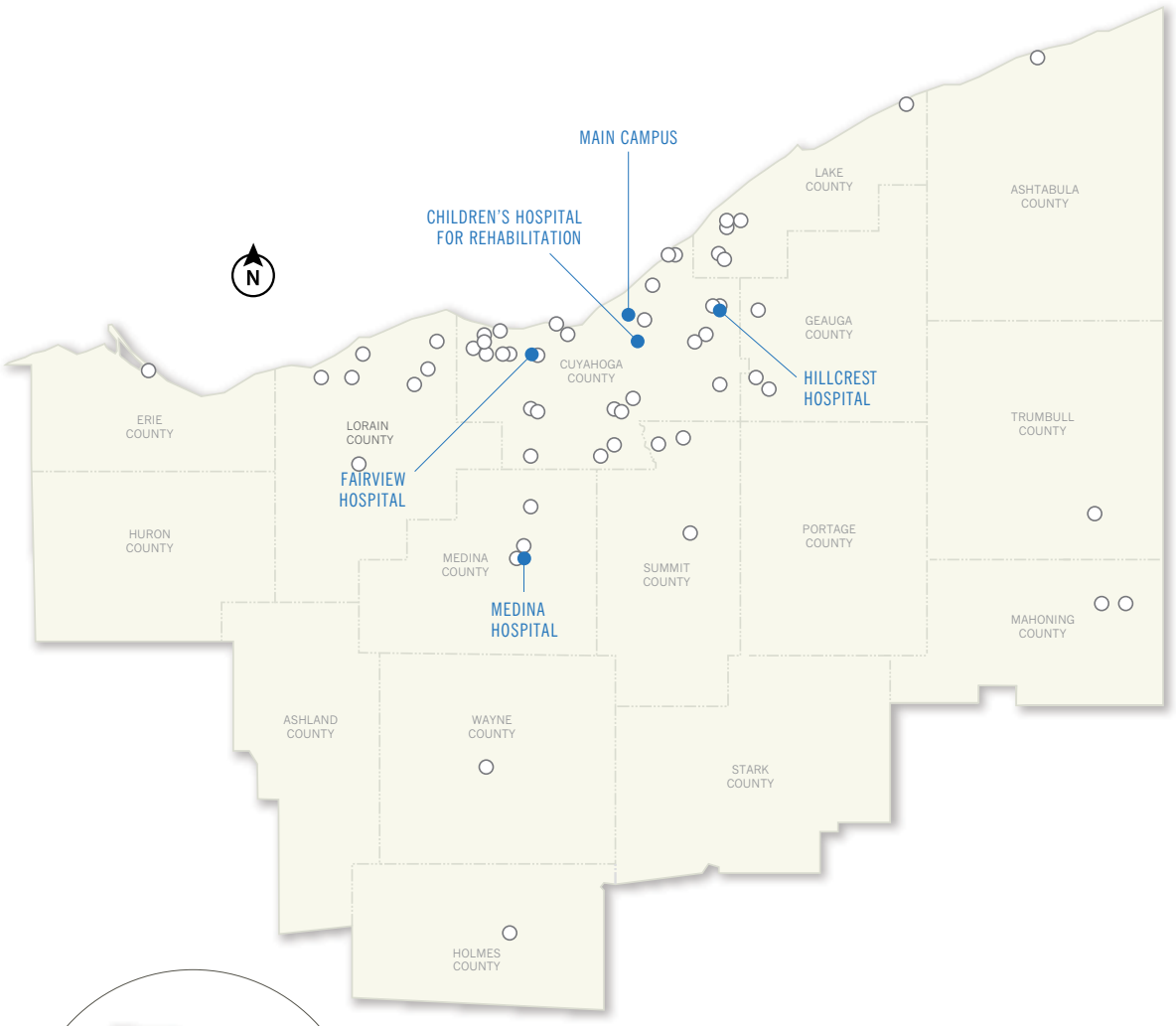
About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,200 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 90 northern Ohio outpatient locations (including 18 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 2015, Cleveland Clinic was ranked one of America's top five hospitals in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care for the 21st consecutive year.

Cleveland Clinic Children's Locations

Cleveland Clinic Children's 300+ pediatricians and pediatric subspecialists offer comprehensive medical, surgical and rehabilitative care at more than 50 community locations (dots on map below) throughout Ohio.



Highlights of our facilities and broad-ranging services:

- 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 Children's Hospital for Rehabilitation
- Diverse subspecialty offerings at our main campus, our Fairview, Hillcrest and Medina hospitals, and our family health centers across Northeast Ohio

The reach of our care extends beyond 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.

Cleveland Clinic Children's

The Cleveland Clinic Foundation
9500 Euclid Ave. / AC311
Cleveland, OH 44195

MEMBER CHILDREN'S HOSPITAL ASSOCIATION
Champions for Children's Health

MAGNET RECOGNIZED

CLEVELAND CLINIC (MAIN CAMPUS)
FAIRVIEW HOSPITAL
HILLCREST HOSPITAL

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2015-16

Cleveland Clinic Children's is honored to be recognized for top care in all 10 of the 10 specialties ranked by *U.S. News & World Report* in its "Best Children's Hospitals" rankings for 2015-16.

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CANCER 2015-16

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CARDIOLOGY & HEART SURGERY 2015-16

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT DIABETES & ENDOCRINOLOGY 2015-16

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT GASTROENTEROLOGY & GI SURGERY 2015-16

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT NEONATOLOGY 2015-16

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BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT ORTHOPEDICS 2015-16

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT PULMONOLOGY 2015-16

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT UROLOGY 2015-16

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