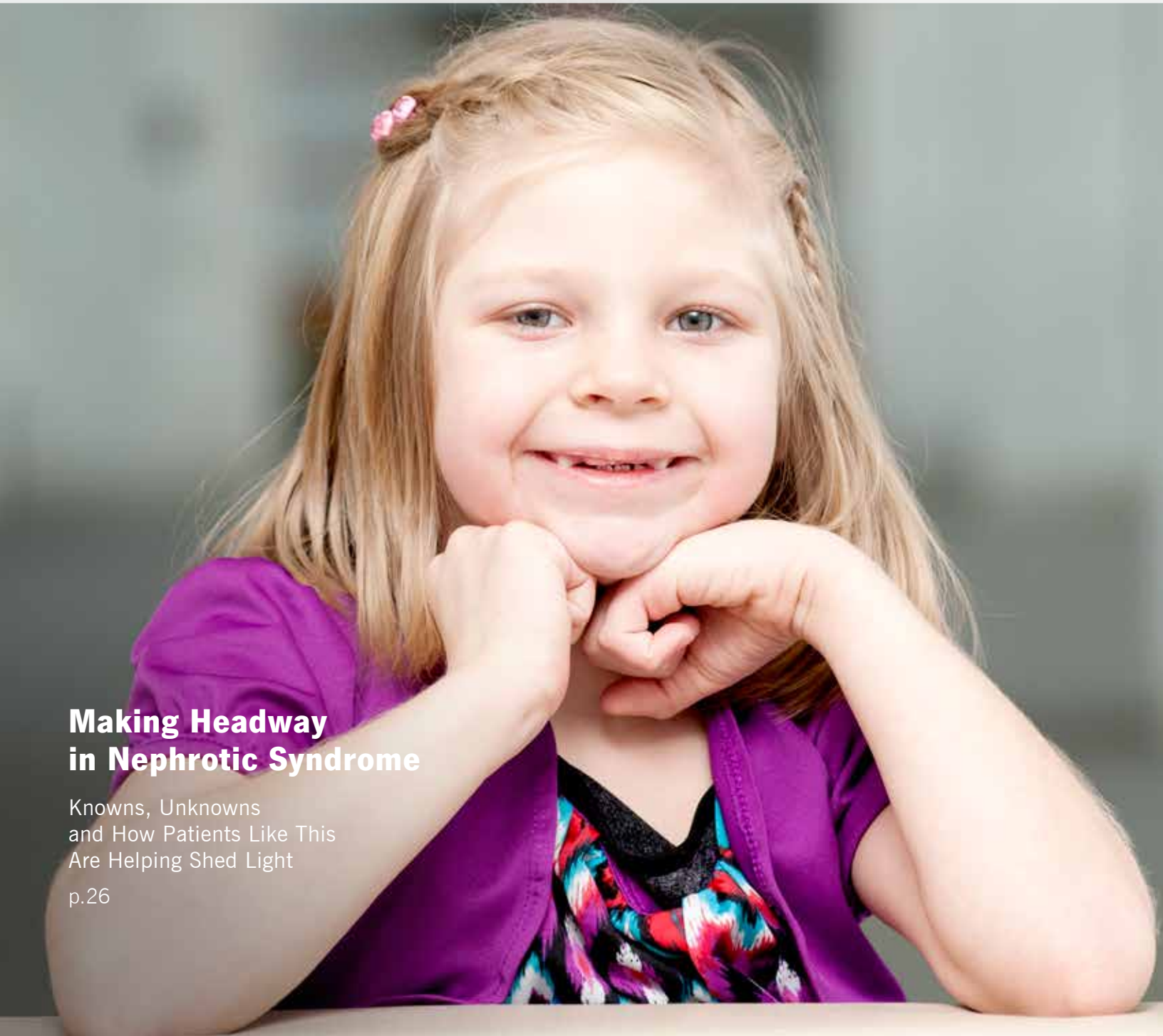
Highlights:

Full contents on inside cover

Cleveland Clinic Children's

Pediatric Perspectives

A Newsletter for Physicians from Cleveland Clinic Children's | 2014-2015



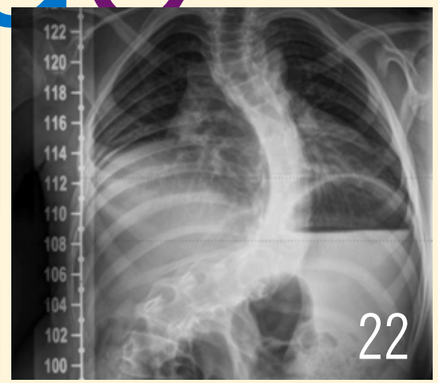
Making Headway in Nephrotic Syndrome

Knowns, Unknowns and How Patients Like This Are Helping Shed Light

p.26

Pediatric Perspectives 2014-2015

Inside



Dear Colleagues,

We hear all the time that healthcare is a team sport. That's undoubtedly true, but how do we go beyond that truism to build better teams? At Cleveland Clinic Children's, we're focusing on factors that make teams really work and that can even infuse our practice with the special magic that marks the most unified sports teams.

This issue of our *Pediatric Perspectives* publication is full of snapshots of how we're increasingly collaborating across boundaries to build teams to better meet young patients' needs. One recurring theme is that the best teams are sometimes those that bring together seemingly unlikely teammates. Just like a kids' pickup basketball game can spark collaborative mojo between two players previously unknown to each other, we can sometimes benefit from combining our expertise with that of specialists from seemingly remote disciplines.

That's part of the secret behind the success of our Vascular Anomalies Program (p. 12) combining the acumen of pediatric dermatologists, cardiologists and scores of other specialists.

It's also a foundational principle of our new Center for Pediatric Integrative Medicine, which brings together broad clinical teams for the most complex cases, like the one profiled on p. 22.

And the network of 12 different specialties we rely on for managing the genetic neurological disorder known as *CDKL5*-related disease is a key reason we've been designated one of the nation's three CDKL5 Centers of Excellence (p. 30).

Similarly, our Center for Pediatric Rheumatology is teaming with colleagues in Cleveland Clinic's Department of Quantitative Health Sciences to build predictive models to guide future treatment decisions (p. 36). This is just one of several cases where our clinicians are starting to harness the power of big data to benefit our young patients. Similar efforts in pediatric oncology and infectious diseases are profiled on pp. 18 and 20, respectively.

Finally, we recognize that teamwork must extend beyond the walls of one's own institution. That's why Cleveland Clinic Children's continues to expand its participation in multicenter trials. Several articles here provide updates from major multisite investigations, including our cover story on pediatric nephrotic syndrome (p. 26) and contributions on investigations in pediatric interventional cardiology (p. 8) and type 1 diabetes (p. 14).

I hope you enjoy this issue, and we invite your feedback on how Cleveland Clinic Children's can team with you or your organization, be it on the care of an especially complex case or through collaboration on a multisite study or clinical initiative.

Respectfully,

Giovanni Piedimonte, MD

Chairman, Pediatric Institute | Physician-in-Chief, Cleveland Clinic Children's
President, Cleveland Clinic Children's Hospital for Rehabilitation
piedimg@ccf.org

New Study Shows That for HPV Vaccination Rates, Gender Matters in More Ways Than One

By Ellen Rome, MD, MPH

Despite long-standing FDA approval of the human papillomavirus (HPV) vaccine for youths ages 9 to 26 (since 2006 for girls, and since 2009 for boys), HPV vaccination rates in the U.S. remain stubbornly low. Neither 10+ years of safety data on the vaccine nor the administration of approximately 70 million vaccine doses in the U.S. has had much effect on HPV vaccination rates.

According to the Centers for Disease Control and Prevention, only 53.8 percent of U.S. girls received at least one dose of the three-dose HPV vaccine series in 2012, and only one-third completed all three doses.[1] Despite widespread efforts to increase vaccination, these rates remained flat compared with the prior year. Rates in U.S. boys were considerably lower, although they did show an increase from 2011 to 2012 — from 8.3 to 20.8 percent for the first vaccine dose, and from 1.3 to 6.8 percent for the full series.

Why Vaccination Matters

HPV is the most common sexually transmitted infection in the U.S., and the majority of the 6.2 million new infections each year occur in young people (ages 15 to 24).[2] HPV types 6 and 11 account for 90 percent of genital warts,[3] and types 16 and 18 cause 70 percent of cervical cancers and a majority of vulvar, vaginal, anal, penile and oropharyngeal cancers.[4,5]

Australia, where HPV vaccine uptake is well above 80 percent, offers an instructive example of the benefits of widespread vaccination, as reductions in cervical abnormalities and genital warts have already been observed in Australian youths,[6,7] with reductions in HPV-related cancers expected over the longer term. As long as the U.S. continues to lag woefully behind Australia and other developed countries in its HPV vaccination rates, we are needlessly forgoing some of these public health benefits.

First Study of Vaccination Rates by Provider Characteristics

At Cleveland Clinic Children's, we are striving to reach the federal government's Healthy People 2020 goal of 80 percent HPV vaccination for both boys and girls. While previous studies have evaluated barriers to HPV vaccination — including lack of knowledge about the vaccine, assumptions about parental attitudes and misconceptions about when vaccination is appropriate[8-11] — we recently undertook the first study to look at provider characteristics and practice location (urban vs. suburban) with respect to HPV vaccination rates.

Our study assessed HPV vaccination rates among more than 5,000 patients ages 13 to 26 presenting for well-care visits to 15 suburban family health centers and three urban care sites across the Cleveland Clinic health system in 2010. We specifically analyzed vaccination rates among these patients according to site, patient gender and provider gender.[12]

We found that across the overall group of Cleveland Clinic sites studied, HPV vaccination rates exceeded the national rates noted above. Specifically:

- Nearly two-thirds of girls (62 percent) received the first dose in the vaccine series, and 47 percent completed the full three-dose series.
- Among boys, 19 percent received the first dose and 8 percent completed the full series.

Notably, male providers were significantly less likely than female providers to administer the vaccine to their male patients (11 percent vs. 30 percent, $P = .002$) (Figure 1). Additionally, providers at the suburban sites were less likely to vaccinate both boys and girls than providers at urban sites (18 percent vs. 41 percent for boys, $P = .005$; 58 percent vs. 81 percent for girls, $P = .003$) (Figure 2).

Surprises, Confirmations — and an Impetus for More Education

Our finding of higher vaccine uptake in our urban practices was not unexpected, as it reflects our previous findings from a survey regarding intention to vaccinate among mothers of children under age 10. In that study,[13] urban parents were more likely to know someone who was infected with HPV or to be aware that their adolescent child might engage in sexual activity in high school, leading them to view vaccination more favorably. Suburban parents, on the other hand, were more likely to view adolescent sexuality as "something that happened to other people's children," and to view the HPV vaccine as "too new."

In contrast, our finding of the discrepancy in vaccination rates for boys between male and female providers was a surprise. It is particularly intriguing that the male providers' lower vaccination rates for boys did not carry over to girls. These discrepancies in HPV vaccination by provider gender are worthy of further exploration in different and larger groups of providers.

Figure 1. Vaccination rates by provider gender

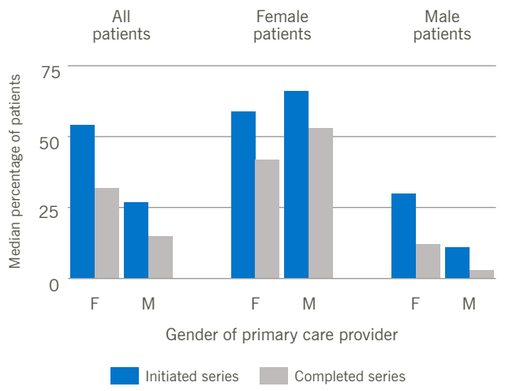
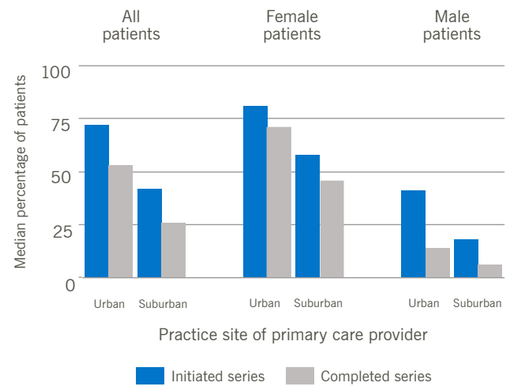


Figure 2. Vaccination rates by practice site



Our findings identify a window of opportunity to target interventions to improve HPV vaccination rates among male providers caring for male patients and among suburban providers regardless of provider or patient gender. More than 10 years of outcomes data now show that the rate of adverse outcomes associated with the HPV vaccine — six events for every 1 million doses administered — is in fact lower than the eight events per 1 million doses associated with other common childhood vaccines, per data from the CDC, which adds that no deaths have been attributed to the HPV vaccine.[14]

With education focused on this safety record — as well as on the HPV vaccine's availability and public health benefits for both boys and girls — we may yet achieve the national goal of 80 percent vaccination for youths of both genders.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among adolescents aged 13-17 years — United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2013;62(34):685-693.
2. Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. *Perspect Sex Reprod Health.* 2004;36(1):6-10.
3. Greer CE, Wheeler CM, Ladner MB, et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. *J Clin Microbiol.* 1995;33(8):2058-2063.
4. Muñoz N, Castellsagué X, de González AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. *Vaccine.* 2006;24(suppl 3):S3/1-10.
5. Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers — United States, 2004-2008. *MMWR Morb Mortal Wkly Rep.* 2012;61:258-261.
6. Gertig DM, Brotherton JM, Budd AC, et al. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med.* 2013;11:227.
7. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ.* 2013;346:f2032.
8. Saraiya M, Rosser JI, Cooper CP. Cancers that U.S. physicians believe the HPV vaccine prevents: findings from a physician survey, 2009. *J Womens Health (Larchmt).* 2012;21(2):111-117.
9. Javanbakht M, Stahlman S, Walker S, et al. Provider perceptions of barriers and facilitators of HPV vaccination in a high-risk community. *Vaccine.* 2012;30(30):4511-4516.
10. Perkins RB, Clark JA. What affects human papillomavirus vaccination rates? A qualitative analysis of providers' perceptions. *Womens Health Issues.* 2012;22(4):e379-e386.
11. Quinn GP, Murphy D, Malo TL, et al. A national survey about human papillomavirus vaccination: what we didn't ask, but physicians wanted us to know. *J Pediatr Adolesc Gynecol.* 2012;25(4):254-258.
12. Strandjord SE, Abdullah N, Chen C, McCully J, Marino M, DeMarsh S, Singh H, Worley S, Giuliano K, Rome ES. Provider characteristics associated with human papillomavirus vaccination rates. Submitted for publication.
13. Gillespie LA, Hicks CW, Santana M, Worley SE, Banas D, Holmes S, Rome ES. The acceptability of human papillomavirus vaccine among parents and guardians of newborn to 10-year-old children. *J Pediatr Adolesc Gynecol.* 2011;24(2):66-70.
14. Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination coverage among adolescent girls, 2007-2012, and postlicensure vaccine safety monitoring, 2006-2013 — United States. *MMWR Morb Mortal Wkly Rep.* 2013;62(29):591-595.

ABOUT THE AUTHOR

Dr. Rome (romee@ccf.org; 216.444.3566) is Head of the Center for Adolescent Medicine in the Department of General Pediatrics.

PTEN Mutations and Autism: The Search for Individualized Treatments Gets Underway

By Thomas W. Frazier, PhD

New research[1] out of Cleveland Clinic Children's Center for Autism has focused on a genetic subgroup of children with autism spectrum disorder (ASD) — those with mutations of the *PTEN* gene — to identify a unique pattern of brain abnormalities and cognitive deficits. We are now building on these insights with new investigations that promise greater understanding of the biological mechanisms causing autism — and that ultimately may lead to individualized treatments.

Turning to a Genetic Subgroup for Answers

Disorders along the autism spectrum are frequently debilitating and lead to lifelong impairments in social interaction coupled with inflexible behavior. Research has identified a strong genetic component to autism, but identifying effective treatments has been difficult due to high variability in the underlying biology.

One approach to this problem is to study genetic subgroups of autism. Our group applied this strategy to individuals with *PTEN* mutations who also have autism (PTEN-ASD). The *PTEN* gene was identified as a tumor suppressor gene by Charis Eng, MD, PhD, Chair of Cleveland Clinic's Genomic Medicine Institute and my close colleague and scientific mentor. Dr. Eng also noticed that parents with mutations in the *PTEN* gene were having a disproportionately high number of children with autism and very large heads, a feature consistent with brain overgrowth.

Together, Dr. Eng and I led a group that recruited 17 children with PTEN-ASD (mean age, 11.5 years) and compared them to patients with autism with no known genetic cause and to healthy controls. The primary goal was to identify specific patterns of brain abnormalities and thinking skills unique to PTEN-ASD. The secondary goal was to determine whether these patterns are linked to the molecular effects of *PTEN* mutations.

Findings: Useful Clinical Signals Emerge

Our study found that patients with PTEN-ASD had overgrowth of the white matter connections as well as spots where white matter development was clearly abnormal (Figure 1). These brain changes correlated with cognitive problems, such as reductions in information processing speed and memory, and motor difficulties in the PTEN-ASD group relative to both other study groups. These findings enabled us to determine that reduction in the PTEN protein drives brain overgrowth and white matter abnormalities that, in turn, drive these patients' cognitive and behavioral impairment (Figure 2).

At a practical level, these data suggest that any child presenting with large head size and developmental or cognitive delays should receive genetic counseling and possible testing for a *PTEN* mutation. Such testing is particularly important because individuals with PTEN-ASD may have increased cancer risks due to the role of *PTEN* as a tumor suppressor and regulator of cell growth and proliferation.

Our findings also suggest that therapists treating patients with PTEN-ASD should speak slowly and clearly, with frequent repetition and attention questions, to ensure that children understand the information being communicated. Given the high rate of motor difficulties seen in patients with PTEN-ASD, patients also should be regularly referred for occupational and, in many cases, physical therapy.

Other Proteins Apparently Not Implicated

Interestingly, we did not find that other proteins related to *PTEN* were abnormal, suggesting that *PTEN* mutations cause reductions in PTEN protein levels but do not seem to cause changes in the typical PTEN biological pathways. This may indicate that reductions in PTEN protein levels are working through other mechanisms, such as interactions with mitochondrial or metabolic pathways or other noncanonical biological routes.

In the Works: A Longitudinal Study and Medication Trial

Future research is needed to pin down the exact molecular effects of PTEN protein loss and develop additional treatment targets. However, based on the low PTEN protein levels observed in this study, Dr. Eng and I have received funding as part of a consortium examining rare genetic causes of autism to longitudinally follow patients with PTEN-ASD over two years and begin a medication trial. The latter is especially exciting because it was designed based on knowledge of *PTEN* and associated pathways and would represent one of the first attempts to develop an individualized gene-based treatment approach for children with autism.

Figure 1. Brain scans showing white matter abnormalities in PTEN-ASD subjects but not in healthy controls. These types of imaging findings from our study suggest that reduced PTEN protein (strongly observed in PTEN-ASD subjects) seems to drive white matter abnormalities that, in turn, lead to IQ reductions.

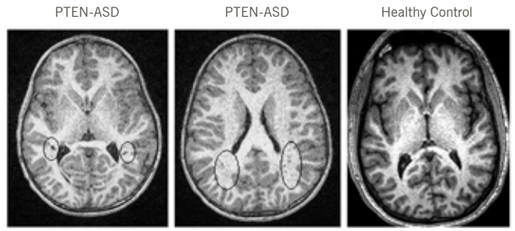
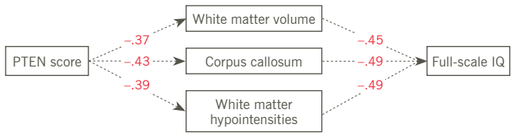


Figure 2. Mediational models displaying how PTEN protein levels drive white matter abnormalities that then drive cognitive deficits in patients with PTEN-ASD. *Adapted from Frazier et al,[1] ©2014 Macmillan Publishers Limited.*



We hope to build on the findings reported here by using processing speed, memory and brain white matter changes as outcomes to provide more-sensitive treatment targets than those used in typical medication trials focused on autism symptoms or other behavioral aspects that often require long periods for changes to be detectable.

Ultimately, we believe this study and the planned follow-up research we are just beginning represent a new paradigm for autism research: Find the gene or set of genes causing autism, comprehensively study and follow patients with those genetic changes, and use the knowledge gained to develop individualized treatments.

REFERENCES

1. Frazier TW, Embacher R, Tilot AK, Koenig K, Mester J, Eng C. Molecular and phenotypic abnormalities in individuals with germline heterozygous *PTEN* mutations and autism. *Mol Psychiatry.* 2014 Oct 7 [Epub ahead of print].
2. Frazier TW, Thompson L, Youngstrom EA, Law P, Hardan AY, Eng C. A twin study of heritable and shared environmental contributions to autism. *J Autism Dev Disord.* 2014;44(8):2013-2025.
3. Frazier TW, Georgiades S, Bishop SL, Hardan AY. Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. *J Am Acad Child Adolesc Psychiatry.* 2014;53(3):329-340.

PERSPECTIVE

More Findings of Note

In addition to these *PTEN* studies, Cleveland Clinic Children's Center for Autism has been pursuing pacesetting research in other aspects of autism. Below are profiles of two other significant 2014 publications by the center's researchers.

Largest-ever study of clinically ascertained ASD in twins

In this study[2] we compared concordance in 568 monozygotic (identical) and dizygotic (fraternal) twin pairs, of whom 471 were affected with ASD, and identified a strong genetic component to ASD. Among the key findings:

- Shared environment was not supported as a causative factor, whereas genetic influences were strong.
- Social interaction and repetitive/inflexible behaviors appear to be driven by highly overlapping genetic influences.

This research supports the search for genetic influences on autism and suggests that environment may play only a minor role.

Largest-ever study of behavioral characteristics of females with ASD

This study,[3] supported by the Simons Foundation Autism Research Initiative, analyzed data from 304 females and 2,114 males with ASD. It found that females had:

- Lower levels of restricted interests but greater irritability and externalizing behavior
- Weaker social communication skills, lower overall cognitive ability and poorer daily living skills

Our findings suggest that ASD may be underidentified in females and that this underidentification may be due to a focus on male-centric representations of autism in diagnostic instruments or to genetic or developmental protective factors.

ABOUT THE AUTHOR

Dr. Frazier (fraziet2@ccf.org; 216.448.6440) is Director of the Center for Autism.

Interdisciplinary Pediatric Pain Rehabilitation Program Yields Measurable Improvements in Chronic Daily Headache with Migraine

By Ethan Benore, PhD; Gerard Banez, PhD; and David Rothner, MD

The literature supporting rehabilitation for children with chronic pain and functional disability has begun to specifically demonstrate utility for children whose pain involves chronic daily headache with migraine. Rehabilitation seems most appropriate for severely affected children and adolescents with headache who have not responded well to outpatient therapies and medications and who require a multidisciplinary setting that addresses medical, psychological, environmental and lifestyle factors concurrently and intensively.[1,2] A recent review found that children with chronic migraine reported less pain and improved mood following pediatric rehabilitation.[3]

These findings align with our experience treating chronic daily headache with migraine in Cleveland Clinic Children's Pediatric Pain Rehabilitation Program. Here we present encouraging outcomes from 111 children with chronic daily headache with migraine treated in our program during the past seven years.

The Program in Brief

At Cleveland Clinic Children's, we evaluate approximately 350 children each year with a diagnosis of chronic daily headache with migraine. Approximately 20 are treated each year in our multidisciplinary Pediatric Pain Rehabilitation Program, an intensive program designed to improve the functional quality of life of children and their families. Ours is the nation's only pediatric specialty interdisciplinary pain rehabilitation program to be accredited by the Commission on Accreditation of Rehabilitation Facilities.

The program supports children with chronic daily headache with migraine by increasing strength and endurance, assisting a return to daily life activities and promoting use of appropriate self-directed coping and pain management skills.

Children are typically enrolled for three weeks — two weeks of inpatient care and one week of daytime hospital care. The program blends rehabilitation therapies (physical therapy, occupational therapy, recreational therapy), psychological services, medical subspecialty care, alternative therapies (aromatherapy, acupuncture, biofeedback and reiki) and school.

On average, patients spend seven to eight hours in treatment each day, with services scheduled hourly from 8 a.m. to 5 p.m.

Rehabilitation therapy takes place in groups and individually, using both land-based and aquatic forms of therapy three hours per day. Patients receive three individual/family psychological treatment sessions per week, on average, and take part in a cognitive-behavioral skills training group three times weekly. They participate in a school program one to two hours each day and in recreation or music therapy groups at least one hour daily.

Since severe pediatric headache typically affects the patient's whole family, parents are involved in a separate part of the program focused on parent support and wellness, and parents and siblings participate in recreational therapy.

Experience Shows Improvements Across Multiple Measures

Our Pediatric Pain Rehabilitation Program has shown clinically significant improvements in the lives of the 111 children with chronic daily headache with migraine (and their families) who completed the program over the past seven years. These patients' mean pre-enrollment duration of headache was three years.

Child quality of life. As shown in Figure 1, children and parents both reported a sharp improvement in the child's quality of life that continued through 12 months of postdischarge monitoring. Scores at 12 months were close to a previously reported average for "healthy children"[4] (Cleveland Clinic child report = 73.9; healthy child report = 83.84) (Cleveland Clinic parent-proxy report = 64.2; healthy child parent-proxy report = 82.7).

Pain. Interestingly, but not unexpectedly, pain level was reduced but not eliminated during the 12 months following discharge (Figure 1). This is consistent with our program's philosophy and with findings in related literature — that the primary goal for chronic pain management in these families is to increase independent functioning despite pain. At each time point, between 4 and 11 percent of children reported no pain that day.

Emotional functioning. Given the link between pain and emotional functioning, we also reported notable reductions in both anxiety and depressed mood in children and their parents following the program (Figure 2). Scores are reported as a percentage of total symptom severity for the respective scales. This result underscores the link between emotional and physical functioning, providing further support for an interdisciplinary approach that addresses the spectrum of a child's well-being.

Absenteeism. Finally, outcomes from the program translated into reduced school and work absences related to the child's headache (Figure 3). When children are physically conditioned and learn coping skills to maintain high levels of functioning despite the presence of headache, they are less likely to miss school (due to headache or doctor appointments). In turn, their parents can return to a regular workweek. These outcomes are a marker for the impact of chronic pain and the benefit of intensive multidisciplinary rehabilitation.[5]

Figure 1. Self-reported headache pain rating (0-10) and child quality of life as rated by PedsQL™ child and parent-proxy reports.

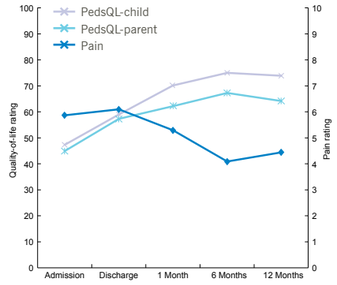


Figure 2. Raw symptom scores of parent depression and anxiety rated on the Bath Adolescent Pain–Parent Impact Questionnaire, and raw symptom scores of child depression and anxiety rated on the Bath Adolescent Pain Questionnaire. Scores are reported as a percentage of total symptom severity.

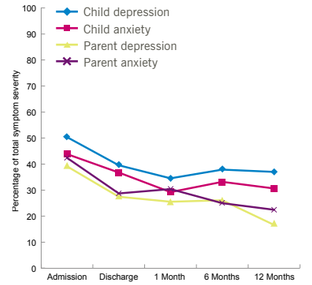
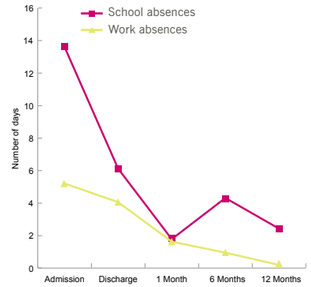


Figure 3. Rates of child absences from school (per month) and parent absences from work (per month) related to the child's chronic daily headache with migraine.



An Additional Outcome: Hope

Chronic daily headache with migraine poses a serious threat to a child's well-being and profoundly impacts his or her family. Our Pediatric Pain Rehabilitation Program is measurably improving the lives of these children, and our updated outcome results provide hope for patients and families alike.

REFERENCES

1. Sieberg CB, Huguet A, von Baeyer CL, Seshia S. Psychological interventions for headache in children and adolescents. *Can J Neurol Sci.* 2012;39(1):26-34.
2. Pistoia F, Sacco S, Carolei A. Behavioral therapy for chronic migraine. *Curr Pain Headache Rep.* 2013;17(1):304.
3. Eccleston C, Palermo TM, de C Williams AC, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev.* 2012;12:CD003968.
4. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes.* 2007;5:43.
5. McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain.* 2008;9(9):771-783.

ABOUT THE AUTHORS

Dr. Benore (benoree@ccf.org; 216.448.6253) is a pediatric psychologist and associate staff member in the Center for Pediatric Behavioral Health.

Dr. Banez (banezg@ccf.org; 216.448.6253) is a pediatric psychologist and Clinical Director of the Pediatric Pain Rehabilitation Program.

Dr. Rothner (rothned@ccf.org; 216.444.5514) is a pediatric neurologist, Chairman Emeritus of the Section of Child Neurology and Director of the Pediatric/Adolescent Headache Program.

As Covered Stents Come to the Catheterization Lab, Interventional Pediatric Cardiologists Should Sleep Better at Night

By Lourdes R. Prieto, MD

Therapeutic interventions for congenital cardiac lesions are becoming increasingly complex at the same time that larger numbers of patients can be treated via transcatheter techniques instead of open heart surgery. As these new technologies enter the clinical realm, they must compare well against surgical interventions in both efficacy and safety. For every new procedure performed in the catheterization laboratory, the ability to treat potential complications is just as important as the ability to perform the procedure itself.

One of the most dreaded complications of transcatheter therapeutic interventions is vessel rupture. Occurrence of a rupture in a great vessel, such as the aorta or the pulmonary artery, can be lethal if not treated within a very short time frame.

Balloon-expandable covered stents large enough to treat such complications are not yet approved by the FDA but are currently being evaluated in the United States in multi-institutional trials. Cleveland Clinic Children's is one of the participating institutions, which enables us to contribute to the data necessary for eventual approval and, importantly, to use the covered stents in our patients when needed. We profile two of these ongoing trials below.

COAST: Covered Stents Show Promise for Aortic Narrowing

The Coarctation of the Aorta Stent Trial (COAST) allows use of the Cheatham-Platinum stent covered with an expandable fluoropolymer sleeve (Covered CP Stent™, NuMED, Hopkinton, N.Y.) in two different scenarios for patients with coarctation (congenital narrowing) of the aorta:

- For patients who have suffered an aortic rupture during treatment of coarctation with a conventional (uncovered) stent
- For preventive use in patients at high risk of rupture

These groups include patients with extremely severe aortic narrowing, in whom the minimal diameter is 3 mm or less (Figures 1 to 3), and those with conditions that confer a higher risk of rupture, including previous aortic wall injury, age greater than 65 years or a connective tissue disease affecting the aortic wall.

To date, Cleveland Clinic has enrolled six patients in COAST: two due to acute rupture, three for severe narrowing (≤ 3 mm) and one for age greater than 65. Both patients with rupture had their aortic tear successfully treated by the covered stent and had no neurologic or other sequelae. All six patients have had excellent relief of their coarctation and have required no further procedures.

Ours is one of 29 institutions participating in COAST nationwide, and we are hopeful that approval of this potentially lifesaving device will make it available to all pediatric catheterization labs in the near future.

PARCS: Providing Reassurance During Melody Valve Placement

The Pulmonary Artery Repair with Covered Stents (PARCS) trial allows use of the same Covered CP Stent in two groups of patients:

- Those who suffer acute injury to the conduit connecting the right ventricle to the pulmonary artery during conduit preparation for, or placement of, the Melody® Transcatheter Pulmonary Valve (Medtronic, Minneapolis, Minn.)
- Those found to have a pre-existing conduit injury at the time of Melody valve implantation

To date, we have implanted 47 Melody valves at Cleveland Clinic Children's and have been fortunate not to have yet encountered a conduit injury requiring use of the covered stent. We do, however, ensure that every patient taken to the catheterization lab for Melody valve implantation undergoes informed consent for potential use of the covered stent should it become necessary.

In the near term, the availability of these covered stents allows us to sleep better the night before a case. In the longer term, if these studies continue to produce reassuring results, they should soon make it possible for many more patients to undergo safer percutaneous correction of congenital heart anomalies.

CARDIOLOGY

For every new procedure performed in the catheterization laboratory, the ability to treat potential complications is just as important as the ability to perform the procedure itself.

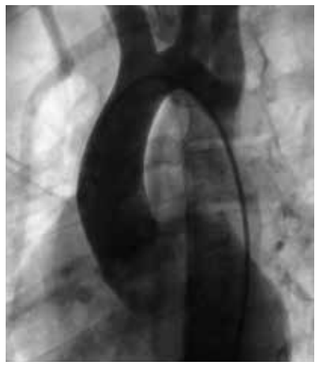


Figure 1. Ascending aorta angiogram demonstrates a severe aortic coarctation with no contrast visible in the descending aorta.

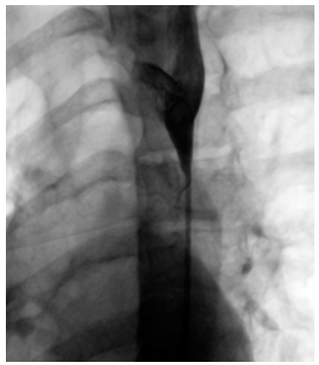


Figure 2. Descending aorta angiogram just above the coarctation shows a minimal amount of flow around the 6-French catheter, demonstrating that the minimal diameter is just about 2 mm.

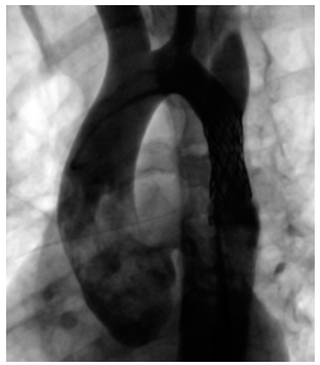


Figure 3. Ascending aorta angiogram after placement of a covered stent shows excellent relief of the coarctation with no residual obstruction and no aortic wall complications.

Dr. Prieto and a colleague perform coarctation stent placement in a leading-edge pediatric cardiac catheterization laboratory equipped with biplane and rotational (three-dimensional) angiography. Rotational angiography allows selection of the best angiographic angles for interventions like coarctation stent placement.

ABOUT THE AUTHOR

Dr. Prieto (prietol@ccf.org; 216.445.3865) directs the pediatric catheterization laboratory in the Center for Pediatric and Congenital Heart Disease.

Defining Functional Nutritional Requirements in Critically Ill Children: New Research Brings Some Guidance on Parenteral Methionine Needs

By Leticia Castillo, MD

Nutrients play far more than just nutritional and metabolic roles. They are active compounds that intervene in multiple functions, and their availability is known to influence immunity, function, behavior and even epigenetic changes — thereby defining pediatric origins of adult diseases.

Despite the essential role of nutritional support in the management of critically ill infants, specific amino acid requirements in parenterally or enterally fed patients are not known. Research evaluating these requirements is a high priority, as the enteral or parenteral nutrition support currently provided to patients is based on limited data. Moreover, septic children exhibit marked metabolic differences from healthy children, and nutrient utilization is different when nutrition support is provided via the enteral vs. the parenteral route. Therefore, nutritional recommendations for healthy infants may not be applicable to the sick infant.

My work as a researcher in pediatric nutrition biochemistry has recently included a focus on determining the parenteral requirements for a specific sulfur amino acid — methionine — in critically ill septic children. My colleagues and I are interested in methionine for the multiple relevant functions that it and its metabolites perform in this population.

Why Methionine Matters

The functional importance of sulfur amino acids is particularly relevant in the pediatric population, where growth and development are actively ongoing, and even more so in the setting of critical illness, where protein synthesis is increased for immune function and repair.

Methionine, an indispensable sulfur amino acid, is necessary for biosynthesis of proteins, polyamines, choline, creatine, and DNA and RNA intermediates. But its work doesn't stop there. It also serves as a major methyl group donor for methylation reactions involved in signal transduction, protein repair, chromatin regulation and gene silencing.

Methionine is metabolized via three major pathways — transmethylation, remethylation and transsulfuration — that yield functionally active intermediate metabolic products. Through the transsulfuration pathway, methionine serves as a precursor for the amino acid cysteine. Under physiologic conditions, cysteine is the rate-limiting step in the synthesis of the tripeptide glutathione, a major antioxidant with detoxifying and signaling properties that play a key role in control of apoptosis and inflammation. Altered oxidative processes and apoptosis are prevalent mechanisms in the inflammation and multiorgan system dysfunction frequently observed in the pediatric ICU.

Rationale for Studying Methionine Needs in Critically Ill Children

Parenteral amino acid formulas are devoid of cysteine and taurine, both of which are important amino acids found in regular diets. Hence, commercially available total parenteral nutrition (TPN) formulas contain large amounts of methionine, with the expectation that methionine will be metabolized to cysteine via transsulfuration. However, methionine, like all the essential amino acids, can be toxic when supplied in large amounts and can be associated with hepatic and neurologic toxicity.

Furthermore, previous studies conducted at my laboratory have found that the synthesis rates of glutathione are decreased in critically ill septic children,[1] suggesting that these patients' ability to support an antioxidative response is limited.

These factors have driven our ongoing research on parenteral requirements of methionine in critically ill septic children, which I initiated at my prior institution and have continued with colleagues at Cleveland Clinic since late 2013.

A Glimpse of Our Findings on Parenteral Methionine Requirements

Using the indirect indicator amino acid oxidation technique with L-[1-^{13}C]-labeled leucine as the indicator amino acid, together with state-of-the-art mass spectrometric methods, we have defined parenteral methionine requirements in 55 critically ill septic infants 1 to 3 years of age. As detailed in the figure, we determined

CRITICAL CARE MEDICINE

Figure. Graphs showing relationships between methionine intake and the indicator amino acid leucine in 55 septic children. **Left:** Breakpoint between rates of leucine oxidation and graded levels of methionine intake. **Right:** Breakpoint between rates of leucine balance and graded levels of methionine intake.

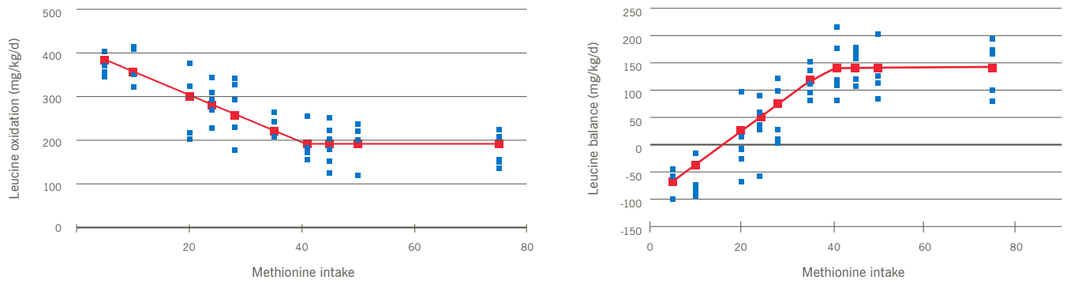


Table. Breakpoints and Related Findings from Studies of Leucine Oxidation and Balance with Varying Levels of Methionine Intake in Septic Children

Variable	Breakpoint (EAR) for methionine (mg/kg/d)	95% CI below breakpoint (mg/kg/d)	95% CI above breakpoint (RDI) (mg/kg/d)	EAR for total sulfur amino acids* (mg/kg/d)	RDI for total sulfur amino acids* (mg/kg/d)
Leucine oxidation **	40.26	30.65	49.87	55.26	64.87
Leucine balance **	38.96	33.97	43.97	53.96	58.97

* "Total sulfur amino acids" refers to methionine plus cysteine.
** For all measures, differences in values obtained by leucine oxidation were not significantly different from those obtained by leucine balance.
EAR = estimated average requirement; RDI = recommended dietary intake

breakpoints between graded levels of methionine intake and rates of leucine oxidation (left graph) and rates of leucine balance (right graph).

As detailed in the table, the "breakpoint," or estimated average requirement (EAR), between methionine intake and leucine oxidation was found at methionine intakes of 40.26 mg/kg/d. The safe population intake (recommended dietary intake; RDI), based on the breakpoint's upper 95 percent confidence limit, was determined to be 49.87 mg/kg/d. The total sulfur amino acid requirements (methionine plus cysteine) were determined to be 55.26 mg/kg/d in terms of EAR and 64.87 mg/kg/d in terms of RDI.

We also determined EAR and RDI values based on rates of leucine balance, as detailed in the table. There were no statistical differences between the values obtained by leucine oxidation and leucine balance.

Conclusion: Current Methionine Intakes Appear Excessive

Our data suggest that the current standard parenteral intakes of methionine for 1- to 3-year-old critically ill septic children — i.e., 100 to 120 mg/kg/d — are approximately *double the required levels*. This excessive amount of methionine, and the corresponding lack of cysteine, may contribute to TPN cholestasis and oxidative injury, particularly in children who require long-term TPN.

We are preparing these findings for full peer-reviewed publication soon. Stay tuned for more details in the continuing quest to better define functional amino acid requirements for critically ill children.

REFERENCE

1. Lyons J, Rauh-Pfeiffer A, Ming-Yu Y, et al. Cysteine metabolism and whole blood glutathione synthesis in septic pediatric patients. *Crit Care Med.* 2001;29(4):870-877.

ABOUT THE AUTHOR

Dr. Castillo (castill@ccf.org; 216.444.6022) is Chair of the Department of Critical Care Medicine.

First Known Application of the SCAMP Paradigm in Pediatric Dermatology

Infantile hemangioma outcomes benefit from a standardized clinical assessment and management plan for propranolol use

By Alex Golden, MD; Joan Tamburro, DO; and Allison Vidimos, MD

Since the utility of propranolol for treatment of infantile hemangiomas was serendipitously identified in 2008,[1] the nonselective beta-adrenergic blocker has gained increasing acceptance as a first-line treatment for this indication. Use of propranolol in children is associated in the literature with rare adverse effects, most notably hypotension, bradycardia and hypoglycemia. Nonetheless, this beta-blocker has been used in pediatric cardiology for over 40 years with a favorable safety profile, even in high-risk populations such as preterm neonates and patients with complex congenital heart disease.

Optimal Propranolol Use Takes a Team

Since 2009, Cleveland Clinic Children's Vascular Anomalies Program has used propranolol to treat more than 150 children with infantile hemangiomas, with 100 percent success and no major side effects requiring therapy discontinuation. We believe treatment of infantile hemangiomas with propranolol is most safely and effectively accomplished by a multidisciplinary team, with input from pediatric dermatologists, plastic surgeons, radiologists, ophthalmologists, otolaryngologists and cardiologists. Appropriate coordination of care among these subspecialties is indispensable for successful treatment.

The diversity of presentation of infantile hemangiomas, the range of subspecialties involved in patient care and the challenge of assessing for cardiac risk were important considerations when we began to use propranolol as a treatment at Cleveland Clinic. Given the importance of systematizing the approach in order to allow an organized assessment of outcomes and any adverse events, we adopted the standardized clinical assessment and management plan (SCAMP) paradigm.

Standardizing the Team Approach with a SCAMP

SCAMPs have been used successfully in multiple medical specialties, including pediatric cardiology, to reduce variation in clinical practice and resource utilization while optimizing patient care.[2] Intrinsic to the approach is the ability to continuously revise the standardized treatment plan as new data emerge. This allows protocols to benefit from continuous improvement while preserving the ability to carefully measure and assess outcomes. The SCAMP method is an important tool in efforts to drive therapeutic innovations from theory to practice in a timely manner without compromising patient safety.

Drawing on the SCAMP methodology, Cleveland Clinic Children's Vascular Anomalies Committee developed a standardized protocol for initiating treatment with propranolol in the outpatient setting. The protocol was established with three initial goals:

- Patient safety, with careful pretreatment cardiovascular evaluation and initiation of treatment under supervision of an experienced pediatric cardiologist
- Facilitation of multidisciplinary involvement in patient care
- Careful documentation of methods and results to foster continuous quality improvement

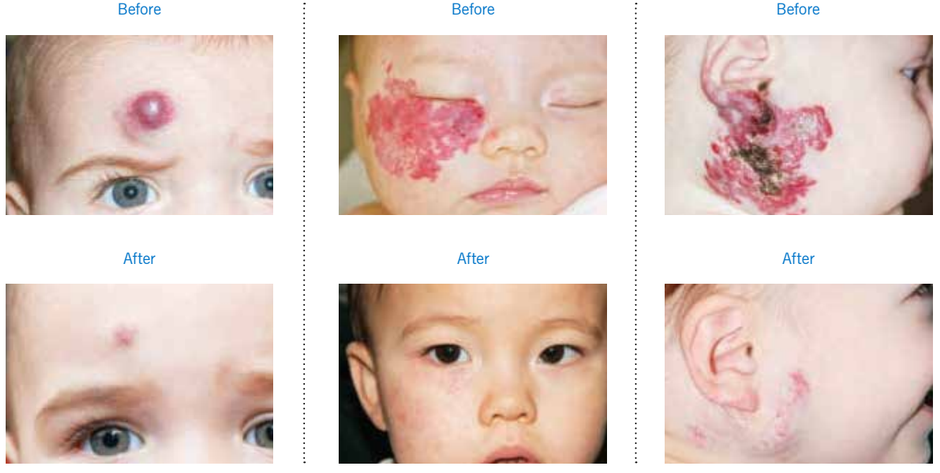
As our experience with propranolol use for this indication increased, we improved dosing protocols, expanded and updated parent education materials, incorporated professional medical photography to monitor and document treatment response, and improved surveillance for comorbidities such as PHACES syndrome, among other updates.

Outcomes Speak for Themselves

What resulted from application of the SCAMP, in its multiple and continuously improving iterations, was a tremendously successful experience in treating our pediatric patients with infantile hemangioma. A full 100 percent of patients had arrest of hemangioma growth from the very first dose, and all cases saw significant shrinkage of the lesions over time, usually in the first few weeks of therapy.

Treatment of the vast majority of patients was started in the outpatient setting, with monitoring of vital signs two hours after the first dose. The only patients who began treatment as inpatients were premature infants with very low birth weight already being cared for in the neonatal ICU and patients already admitted for another indication, such as one child with stridor due to an infantile hemangioma of the airway.

Photos from representative cases of infantile hemangioma managed under the SCAMP paradigm for propranolol treatment in Cleveland Clinic Children's Vascular Anomalies Program. **Left:** Forehead hemangioma with deep and superficial components at presentation at 6 months of age (note brow distortion) and after seven months of treatment. **Middle:** Facial lesion at presentation at 1 month of age and after 16 months of treatment. **Right:** Ulcerated hemangioma at presentation at 2 months of age (note distortion of the right cheek and jawline) and after 14 months of treatment.



No patient had any side effect requiring therapy discontinuation. One patient with a severe retro-ocular infantile hemangioma causing compression of the optic nerve and vein had a prior history of reactive airway disease and developed chronic cough. Adjustment of his pulmonary medication regimen allowed successful continuation of propranolol therapy.

An Unprecedented SCAMP Application

To our knowledge, this is the first-ever application of the SCAMP paradigm in a pediatric dermatology setting. The SCAMP has helped our Vascular Anomalies Program bridge the central multidisciplinary aspects of effective care and communication. The SCAMP has been modified many times to date, including such changes as converting from three-times-daily to twice-daily dosing schedules after the age of 6 months, eliminating standard pre-treatment echocardiography, and continuously improving the patient instructions given to families. The above photos present a few examples of our program's results.

REFERENCES

1. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med.* 2008;358(24):2649-2651.
2. Rathod RH, Farias M, Friedman KG, et al. A novel approach to gathering and acting on relevant clinical information: SCAMPs. *Congenit Heart Dis.* 2010;5(4):343-353.

ABOUT THE AUTHORS

Dr. Golden (goldena2@ccf.org; 216.445.7116) is a pediatric cardiologist in the Center for Pediatric and Congenital Heart Disease and a member of the Vascular Anomalies Committee.

Dr. Tamburro (tamburj@ccf.org; 216.444.5772) is a pediatric dermatologist in the Department of Dermatology.

Dr. Vidimos (vidimoa@ccf.org; 216.444.3345) is Chair of the Department of Dermatology. She treats children and adolescents as well as adults.

A Front-Line Report from Diabetes TrialNet

Profiling Cleveland Clinic Children's participation in the NIH-sponsored study of screening, monitoring and immunomodulating treatment of type 1 diabetes

By Douglas G. Rogers, MD

Although understanding of the early metabolic abnormalities in type 1 diabetes (T1D) is steadily increasing, many unknowns remain regarding the natural history of T1D. In response, the National Institute of Diabetes and Digestive and Kidney Diseases has sponsored the Natural History Study of the Development of Type 1 Diabetes, which was launched a decade ago as part of the Diabetes TrialNet international network for the study, prevention and early treatment of T1D. The aim is to improve characterization of the demographic, immunologic and metabolic characteristics of individuals at risk of developing T1D.

Cleveland Clinic Children's Center for Pediatric and Adolescent Endocrinology is proud to have been an active affiliate site for the NIH-sponsored multicenter Diabetes TrialNet network since October 2004, and we report here our experience to date in the natural history substudy and related Diabetes TrialNet investigations.

Diabetes TrialNet at a Glance

In view of T1D's status as a T cell-mediated autoimmune disease, Diabetes TrialNet monitors the natural history of subjects who have tested positive for antibodies associated with T1D, indicating that they are at a high risk for developing T1D. A positive test is an early indication that damage to insulin-secreting beta cells in the pancreas may have begun. Relatives of individuals with T1D have an approximately 3 to 4 percent chance of testing positive for T1D-associated antibodies.

Diabetes TrialNet also enrolls selected subjects into substudies to determine whether any immunomodulating treatment may prevent or delay the onset of T1D — or may maintain some endogenous insulin secretion so that patients with T1D can remain in a state of partial remission of T1D, often referred to as the "honeymoon" period.

Cleveland Clinic Children's Experience and Contributions

In Cleveland Clinic Children's first 10 years as a Diabetes TrialNet affiliate site, we have screened 588 first- and second-degree relatives of individuals with T1D for antibodies associated with T1D. Although most of these subjects are relatives of children with T1D followed at Cleveland Clinic Children's, we are happy to screen any relative of a patient with T1D.

Thirty-six subjects from our site have tested positive for antibodies associated with the development of T1D. Fourteen of those subjects have enrolled in the natural history monitoring substudy. These subjects have their antibody levels checked and undergo an oral glucose tolerance test twice a year in Cleveland Clinic's general clinical research center.

One of our antibody-positive subjects had a very high level of insulin autoantibodies. This subject has enrolled in the Diabetes TrialNet oral insulin substudy (Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus) here at Cleveland Clinic Children's to determine if this antigen-specific therapy can induce anergy or depletion of T cells attacking the beta cells.

Other antibody-positive subjects can enroll in a Diabetes TrialNet-sponsored anti-CD3 antibody study. This substudy targets activated T cells wherever they are in the body, with the aim of reducing the attack on the beta cells. There is also a study evaluating CTLA4-Ig therapy, which is known to regulate T-cell activation.

Broadening Benefits Beyond Today's Patients

Cleveland Clinic Children's is honored to offer Diabetes TrialNet study participation to relatives of patients with T1D throughout Northeast Ohio. Subjects can benefit by finding out if they are at elevated risk for developing T1D and, if so, initiating treatment before they become seriously ill from untreated T1D. Some subjects may have the opportunity to enter immunomodulating studies to determine if the development of T1D can be prevented, delayed or kept in a state of partial remission.

ABOUT THE AUTHOR

Dr. Rogers (rogersd@ccf.org; 216.445.8048) is Head of the Center for Pediatric and Adolescent Endocrinology.

BY THE NUMBERS:

Cleveland Clinic Children's Involvement in Diabetes TrialNet

10
Years as a Diabetes TrialNet affiliate site

588
First- and second-degree relatives of T1D patients screened for antibodies

36
Screened relatives testing positive for antibodies

14
Screened relatives currently enrolled in the natural history monitoring substudy

1
Subject currently enrolled in the oral insulin substudy

PERSPECTIVE

In Brief:

More Developments in T1D at Cleveland Clinic Children's

Diabetic Ketoacidosis: Tackling Frequent Admissions with an Intensive Clinic

After identifying a small percentage of patients with poorly controlled type 1 diabetes (T1D) who accounted for most hospital admissions for diabetic ketoacidosis, specialists from our Center for Pediatric and Adolescent Endocrinology recently acted to make a difference. We devised an intensive, multidisciplinary, three-hour patient visit in the hope of reducing the frequency of admissions for diabetic ketoacidosis and improving overall control of patients' T1D. During a visit to this new diabetic ketoacidosis clinic, the patient and family spend 45 minutes with each of the following provider types:

- Pediatric endocrinologist and nurse
- Pediatric dietitian
- Child psychologist
- Social worker

We look forward to reporting results as our experience with this intensive multidisciplinary clinic mounts.

Using Shared Appointments to Ease the Transition to Adult Care

Within the past few years, Cleveland Clinic Children's has been among the nation's very first centers to introduce shared medical appointments (SMAs) to improve medical management and ease the transition to adult care for emerging adults (17- to 23-year-olds) with T1D.

Our SMA program for this population, dubbed "Transition ESCALAIT," is based on the formula of our successful Enrichment Services and Care for Adolescents Living with Autoimmune Insulin-Dependent Type 1 Diabetes (ESCALAIT) program for preadolescents and adolescents, which was launched in early 2011.

In the Transition ESCALAIT program for emerging adults, patients participate in an age group-specific SMA every three months over a two-year period. The program involves close collaboration between Center for Pediatric and Adolescent Endocrinology staff and Cleveland Clinic adult-care endocrinologists, who together devote special attention to issues specific to this age group, such as safety concerns associated with driving and maintaining good T1D management while living away from family for the first time.

Taking Diabetes Clinics into the Community

In 2014, Cleveland Clinic Children's began offering dedicated twice-monthly clinics for patients with T1D or type 2 diabetes at a Cleveland Clinic family health center in the community in addition to the traditional offerings on Cleveland Clinic's main campus. This new dedicated clinic allows patients to see a pediatric endocrinologist specializing in diabetes and to benefit from technology — such as hemoglobin A1C testing equipment for real-time results and software for downloading data from glucometers and insulin pumps — often not available in other community settings. The result is greater convenience for families of children with diabetes, who no longer have to come to the main campus for comprehensive care.

Reshaping Early-Phase Endoscopy Training with a Virtual-Reality Endoscopy Simulator

Cleveland Clinic Children's helps pioneer its use in pediatric training

By Lori Mahajan, MD, and Marsha Kay, MD

Gastrointestinal endoscopy represents a valuable tool for the diagnosis and treatment of gastrointestinal mucosal disorders. The procedures involved, however, are technically challenging and require considerable training to ensure safe and skilled performance. Fellowship trainees have traditionally learned to perform endoscopic procedures only in a clinical setting under direct supervision of a trained endoscopist. However, these procedures are uniquely challenging to teach in such an apprenticeship model, for several reasons:

- Patient comfort during the procedure cannot be compromised.
- Patient time under conscious sedation or anesthesia cannot be significantly prolonged for educational purposes. Therefore, if the patient experiences discomfort or the procedure cannot be completed in a timely fashion, the instructor must take control of the endoscope and complete the study. This leaves the endoscopy trainee to potentially learn in fragmented steps.
- Because pathologic findings in pediatric gastroenterology are intermittent, a trainee must complete hundreds of procedures in order to acquire the knowledge necessary to identify, interpret and correctly manage endoscopic findings.

Enter the Endoscopy Simulator

To help ease these training challenges, Cleveland Clinic Children's has utilized a virtual-reality endoscopy simulator since 2012 to help fellows in its Pediatric Gastroenterology Fellowship Program acquire and practice endoscopy skills in a risk-free environment. This computer-assisted endoscopy simulator (GI Mentor™, Simbionix USA) is a shared resource with Cleveland Clinic's Digestive Disease Institute, which is ranked among the top 2 adult gastroenterology programs in the nation by *U.S. News & World Report*. As this type of cutting-edge endoscopy simulator is available to only a few pediatric gastroenterology training centers in the country, it represents a clear benefit of Cleveland Clinic Children's status as a "hospital within a hospital," with all the resulting resource support.

A Risk-Free Setting for Building Skills

The endoscopy simulator is introduced to fellows during the early stages of training. Its simulated environment permits learners to acquire knowledge and build a framework of basic skills through repetitive practice of relevant tasks with the aim of better preparing novices for patient-based training. Trainees are able to rehearse psychomotor and perceptual skills in a risk-free environment so that they attain some degree of proficiency before performing endoscopy in the clinical setting.

The simulator provides trainees who have just begun the hands-on phase of learning with five interactive modules. Two upper endoscopy modules and two colonoscopy modules take fellows through 40 cases arranged hierarchically from a simple diagnostic procedure to advanced therapeutic procedures. Fellows master how to complete a survey of the upper and lower gastrointestinal tract using a forward-viewing videoendoscope. They perform diagnostic and therapeutic procedures in simulated patients and learn to recognize pathology commonly encountered in clinical practice. The final module is an advanced endoscopy module designed to provide skilled endoscopists, fellows and nurses with a training model for emergency gastrointestinal bleeding situations that require urgent therapy. Therapeutic procedures using a variety of appropriate endoscopy tools intended for bleeding pathologies are practiced.

Individualized Performance Reporting

The simulator logs the trainee's performance by saving data under a unique code. The trainer can then examine each trainee's progress at any time. The simulator provides objective measures of performance, including:

- Ability to complete procedures independently
- Time taken to complete a task
- Depth of endoscope insertion
- Overall rating of performance
- Number of errors
- Percentage of mucosa visualized
- Degree of estimated patient pain during the procedure
- Composite score of competency

Drs. Kay and Mahajan provide guidance and feedback as pediatric gastroenterology fellows Brian Maksimak, DO, and Elizabeth Collyer, MD, receive hands-on experience with simulator training. The fellows learn to appropriately identify the source of gastrointestinal bleeding and are shown here injecting a bleeding vessel at the base of a simulated gastric ulcer.

Such measures can be used to help analyze trainees' actions, identify errors and potentially improve patient safety.

A Model for Others to Consider

To date, the endoscopy simulator has been used as a training tool for more than 15 pediatric gastroenterology fellows at Cleveland Clinic Children's. It provides a singular opportunity to repetitively practice and improve skills and confidence in a relaxed, nonthreatening, nonclinical environment. It will remain a valued, standard part of the first phase of training in our program, and we expect this tool will progressively gain more widespread use in pediatric training programs across the nation.

ABOUT THE AUTHORS

Dr. Mahajan (mahajal@ccf.org; 216.445.1572) is Director of the Pediatric Gastroenterology Fellowship Program and a staff physician in the Department of Pediatric Gastroenterology.

Dr. Kay (kaym@ccf.org ; 216.444.3564) is Director of Pediatric Endoscopy and Chair of the Department of Pediatric Gastroenterology.

PERSPECTIVE

Taking Hands-On Training Beyond Cleveland Clinic

In addition to training its own fellows in endoscopy, Cleveland Clinic Children's Department of Pediatric Gastroenterology has developed and directed hands-on endoscopy training for more than 200 pediatric gastroenterology trainees and clinicians annually at national conferences over each of the past seven years.

Department leaders expect this educational outreach in endoscopy to continue. For future offerings, check naspghan.org, the website of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Personalized Targeted Therapy for Pediatric Malignancies: Progress Lies in Networked Data Collection and Analysis

By Johannes E. Wolff, MD

We practice in an era that can easily create ambivalence for the pediatric oncologist. Never before have so many novel therapeutic agents for cancer been available, yet their safety in children is largely unknown, since most toxicity studies have been conducted only in adults. Moreover, these agents' efficacy has been demonstrated only for common cancers for which it was possible to assemble large populations for phase 3 clinical trials. This leaves pediatric oncologists with a handful of tried-and-true agents used in highly standardized protocols developed from multi-institutional consortia — but with precious little guidance for treating rarer cancers or treatment-refractory cases.

The Case for Targeted Therapy

Today, pediatric oncologists at Cleveland Clinic Children's are taking a novel approach by offering targeted therapy to children with cancers unresponsive to standard treatment options. In contrast to strategies based on traditional histological diagnosis, this promising form of individualized therapy involves analyzing each tumor with genetic and morphoproteomic methods using a panel of markers to reveal treatment targets. Based on this analysis, a drug is selected from a list of novel agents known to be effective against these markers.

The Challenge — and Opportunity — of Too Much Information

Analysis of individual tumor composition requires examination of a plethora of factors, including genetic analyses, protein expression, pathway activation in tumor cells, spatial tumor heterogeneity and tumor development over time. Digesting this enormity of information and turning it into actionable clinical decisions is highly time-consuming and often overwhelming. Moreover, reports from different laboratories typically do not agree, and some seem to suggest no actionable items at all.

Yet on the flip side of this challenge is an opportunity. The opportunity lies in channeling the individual pediatric oncologist's experience and knowledge into a multidisciplinary discussion to identify — with support from innovative technology and in the setting of a targeted therapy tumor board — the medication(s) most likely to benefit an individual pediatric patient. At Cleveland Clinic Children's, we are taking this opportunity by partnering with adult-care oncologists and pharmacists in Cleveland Clinic's Taussig Cancer Institute in an elaborate, standardized process that supports selection of the most appropriate agents.

Ensuring Patient Safety in a Changed Landscape

The agents most commonly considered for tumor targeting are FDA-approved for other diagnoses, thus requiring off-label use in pediatric cancers. Whereas in the past we could readily form nationwide committees to develop age- and weight-appropriate dosing and ensure safety for off-label pediatric uses, this solution is not consistently applicable today, with 10 times as many agents available, less-common malignancies to be treated and a need to make individual therapy decisions more quickly.

To ensure patient safety in this changed landscape, Cleveland Clinic Children's is employing the latest information technology to monitor for known drug interactions and other safety red flags. Doses are escalated cautiously. Clinical monitoring is extremely vigilant, with laboratory, imaging and functional tests conducted far more frequently than for patients undergoing traditional standardized treatments with one protocol for all.

Patient by patient, we have built our targeted therapy experience into a broadly standardized approach. Patients on targeted therapy are initially examined twice weekly and closely monitored with electrocardiograms and blood, liver and kidney function tests even in the absence of clinical signs. Under this surveillance, doses are gradually increased and synergistic combinations developed until we are confident their anti-cancer effect is not matched by additive toxicity. Once the patient's therapy schedule and dosing are stable and have proved tolerable, monitoring can be eased.

Harnessing Statistics to Predict Success

Determining whether a new therapy choice works requires treating the patient, collecting data and analyzing the outcomes. It takes many attempts to learn how to do it right.

Our treatment decisions as clinicians are generally based on what has worked before — or what should work, given the biology of a particular tumor. However, tumors of the same type often differ.

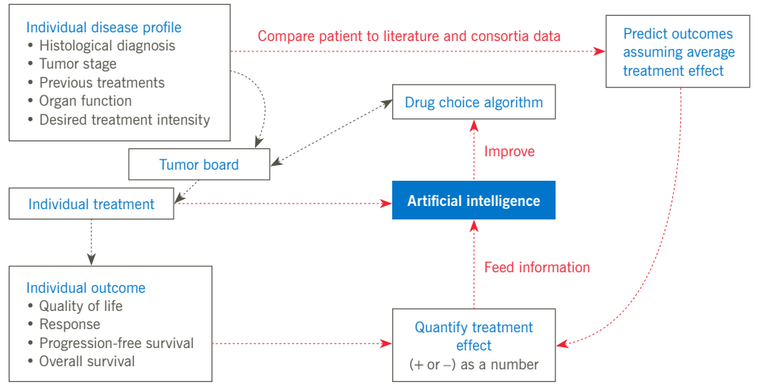


Figure. Schematic showing the central role of data-driven artificial intelligence in the process to continuously improve targeted therapy treatment selection for pediatric malignancies.

The dead cancer cells seen under a microscope might differ from growing cancer cells. Two patients with the same diagnosis may differ from each other. Even the cancer cells within one individual might differ in different body locations — or may change over time. For these and other reasons, a treatment protocol might succeed in one patient and fail in another.

This argues for an individualized approach in which the standard for determining efficacy — the phase 3 trial requiring a large sample size — is simply not possible. This reality, together with the volume of tumor information available and the clinical challenges of giving novel drug combinations, demands enhanced use of biostatistics to predict and determine treatment efficacy.

Several new statistical tools have been proposed. Our targeted therapy program uses an approach developed at MD Anderson Cancer Center, where I practiced before coming to Cleveland Clinic Children's. At the model's core is the comparison of an individual outcome prediction with the observed outcome following targeted therapy. The approach requires a research project description, IRB approval, patient consent and other trappings of traditional clinical studies, but it combines them with a number of more novel features:

- Use of large amounts of data to predict individual outcome
- Mathematical models to maximize predictive accuracy
- Quantification of differences between predicted and observed outcomes
- Hypothesis-driven analysis of the quantifiers used

These features, which are reflected in the above schematic (Figure), amount to an artificial intelligence-like approach to therapy selection using a biostatistical algorithm that harnesses big-data computing capabilities to improve medication choice.

Next Step: Networked Data Analysis

While we are excited by this new data- and biostatistics-driven targeted therapy paradigm at Cleveland Clinic Children's, its utility is limited while it remains at the scale of a single institution. We do not plan on doing this work alone, and the program is now ready for the next step: networking.

Past successes in pediatric oncology have stemmed from combining the efforts of multiple institutions. Targeted therapy will follow the same path. After all, the main challenge for targeted therapy in pediatrics is no longer tumor analysis but rather how to analyze treatment outcomes so that cumulative experience from the past will lead us all to better treatment decisions in the future.

Standardized, ongoing data collection is the key to proving the efficacy of targeted therapy and eventually making it practical, affordable, and capable of continuous refinement and improvement. For this effort, all hands will be needed on deck, and we welcome the opportunity to move forward in collaboration with pediatric oncology colleagues around the nation.

ABOUT THE AUTHOR

Dr. Wolff (wolffj@ccf.org; 216.445.3588) is Chair of the Department of Pediatric Hematology, Oncology and Blood & Marrow Transplantation.

Optimized Weight-Based Antibiotic Dosing: Designing a Strategy to Make It Happen and to Assess Effects on Surgical Site Infections

By Charles B. Foster, MD, and Ritika Coelho, MD

Surgical site infections (SSIs) represent an important cause of healthcare-associated morbidity and mortality and are increasingly the focus of regulatory agencies and patient safety organizations. While national quality improvement initiatives like the Surgical Care Improvement Project have developed measures to reduce SSIs, these measures, including on-time delivery of preventive antibiotics, have not typically applied to patients younger than 18, resulting in inconsistent adoption by pediatric hospitals.[1,2]

Ohio's Lead Role in Preventing Healthcare-Associated Complications

Two measures important to the prevention of pediatric SSIs occurred in Ohio in the past few years. The first was a state mandate for public reporting of pediatric procedure-specific SSI rates. The second was the establishment of Ohio Children's Hospitals' Solutions for Patient Safety (OCHSPS), an innovative collaborative of eight children's hospitals throughout Ohio to reduce healthcare-associated complications, including SSIs. Its success spawned formation of the Children's Hospitals' Solutions for Patient Safety National Children's Network, a group of 80+ children's hospitals with a similar mission at the national level.[3]

As part of the OCHSPS and in preparation for public reporting, Cleveland Clinic Children's adopted a simple "SSI prevention bundle" that included the following primary components:

- Not using razors to remove hair
- On-time delivery of an appropriate preoperative antibiotic
- Use of an appropriate surgical prep

The bundle was later expanded to include a preoperative bath and receipt of an appropriately timed antibiotic redose. For the OCHSPS, hospitals were urged to perform mini root-cause analyses on all SSIs and to add components to their own SSI prevention bundles.

SSI Cluster Prompts Refinement of Prevention Bundle

Around this time, our hospital experienced a cluster of SSIs in scoliosis surgery patients, mainly due to *Propionibacterium acnes*. Without performing a formal case-control study, we developed a standardized root-cause analysis form to identify possible risk factors. While our analysis indicated compliance with the core SSI prevention bundle recommended by the OCHSPS, additional risk factors were suggested, including failure to use cefazolin, low weight-based antibiotic dose, prolonged surgical procedure time with increased blood loss, and inconsistent redosing.

In response, we implemented pediatric perioperative antibiotic dosing guidelines that increased weight-based doses and shortened intraoperative redosing intervals. We combined these with an enhanced surveillance and quality improvement program aimed at ensuring compliance. We initiated quality improvement projects to optimize the dose and timing of intraoperative antibiotics, with the goal of 100 percent compliance. The following changes were implemented:

- The need for surgical antibiotic prophylaxis was added to the points to be considered during the surgical time-out.
- Optimal pediatric doses were recommended (e.g., 50 mg/kg of cefazolin up to an adult dose of 2 g instead of 25 mg/kg up to 1 g).
- Antibiotic redosing intervals for long surgical procedures were shortened (e.g., 3 instead of 4 hours for cefazolin).
- Standard pediatric antibiotic doses were added to the operating room's automated medication dispensing cabinet.
- An operating room reminder light was programmed to signal intraoperative redose time.
- The surgical and anesthesia teams were provided with antibiotic dosing cards and performance feedback.

Database Takes Efforts to the Next Level

To facilitate data collection for key process measures, we created the Pediatric Healthcare-Associated Infection (Peds HAI) Database to automate data extraction from the electronic medical record. This database, a collaboration with Cleveland Clinic's Department of Quantitative Health Sciences, contains data from 2006 to the present and is refreshed nightly.

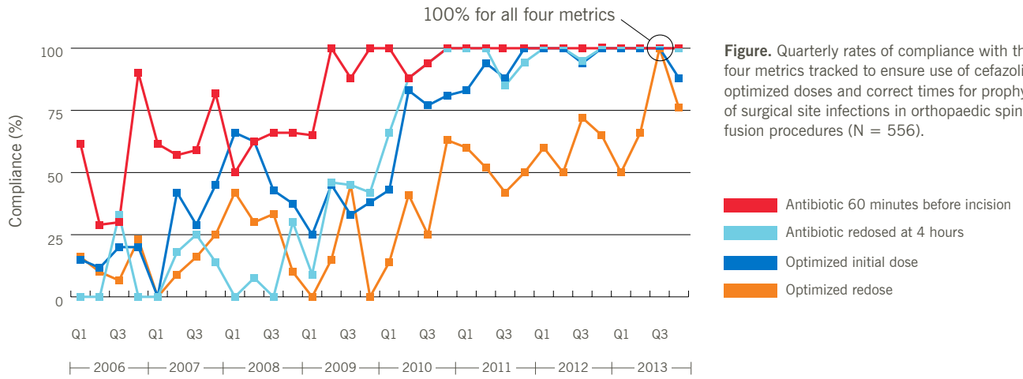


Figure. Quarterly rates of compliance with the four metrics tracked to ensure use of cefazolin at optimized doses and correct times for prophylaxis of surgical site infections in orthopaedic spine fusion procedures (N = 556).

The database captures data on pediatric surgical procedures corresponding to over 750 CPT codes. For each procedure, data are retrieved from the Anesthesia Automated Record Keeping System (ARKS) database, operating room nursing databases (OpTime and ORIS) and Epic's Clarity database (Epic's data warehouse). Data are stored in a searchable Oracle Discoverer database.

Our Peds HAI Database is optimized to retrieve data on antibiotic timing and dosing for patients with CPT-encoded procedures related to cardiac, spine and neurological shunt surgeries. Report features facilitate automated counts of cases and generation of process data such as correct antibiotic timing, dosing and redosing. Further information (surgeon, anesthesiologist, type of implant, operating room number, blood loss, etc.) for a given procedure is retrievable on a case-by-case basis, enabling automated data collection for apparent or root-cause analyses.

Snapshot of the Database's Power

We used the Peds HAI Database to track compliance with antibiotic timing and dosing in the pediatric orthopaedic spine population from 2006 to the present. For the antibiotic cefazolin, we track four key process measures:

- Time of preoperative dose (within 60 minutes before incision)
- Time of intraoperative redosing (before 4 hours, if required)
- Use of optimized initial dose (50 mg/kg up to 2 g)
- Use of optimized subsequent dose (50 mg/kg up to 2 g)

As a testament to the power of quality improvement initiatives coupled with real-time data collection, in the third quarter of 2013 we achieved 100 percent compliance with all four metrics (Figure).

The infection rate after orthopaedic spine procedures decreased from 9.9 percent in 2009 to 4.9 percent in 2010 to 2.1 percent in 2011 and to 2.7 percent in 2012 ($P < .01$ for 2009 vs. 2011-2012). Despite improved compliance with the weight-based dosing and redosing metrics, the infection rate in 2013 increased to 4.2 percent, suggesting that factors beyond optimized weight-based dosing may contribute to SSI risk.

Case-Control Study in the Works

We are now using the Peds HAI Database to perform a formal case-control study to test the hypothesis that a cefazolin-based perioperative dosing schedule with optimized weight-based doses and shortened redosing intervals reduces the risk of wound infections following pediatric spine surgery. It should soon be possible to track risk factors for SSIs in real time by linking our Peds HAI Database to outcomes data collected by the infection prevention team or inferred from surrogate markers for infection.

REFERENCES

1. Ingraham AM, Cohen ME, Bilimoria KY, et al. Association of Surgical Care Improvement Project infection-related process measure compliance with risk-adjusted outcomes: implications for quality measurement. *J Am Coll Surg.* 2010;211(6):705-714.
2. Foster CB, Sabella C. Health care-associated infections in children. *JAMA.* 2011;305(14):1480-1481.
3. Children's Hospitals' Solutions for Patient Safety. Available at: www.solutionsforpatientsafety.org. Accessed Jan. 2, 2015.

ABOUT THE AUTHORS

Dr. Foster (fosterc3@ccf.org; 216.445.4574) is a staff physician in the Center for Pediatric Infectious Diseases.

Dr. Coelho (coelhor@ccf.org) is a pediatric infectious diseases fellow in the Center for Pediatric Infectious Diseases.

Case Study: Integrating Complementary Therapies with Traditional Medicine to Enhance Rehabilitation in Medically Complex Patients

By David Gurd, MD; Benjamin Katholi, MD; and Chelsea Behling, PT

Presentation and Diagnosis

On July 30, 2013, a 16-year-old male presented to Cleveland Clinic Children's Center for Pediatric Orthopaedics and Spine Deformity with significant, rapidly progressing kyphoscoliosis. Radiographs revealed a 90-degree thoracic curve, 67-degree lumbar curve and 100-degree kyphosis. After assessment by neurology, genetics, orthopaedics, pulmonary medicine and cardiology, the patient was found to have multiple medical problems and severely compromised pulmonary function. His condition was consistent with the kyphoscoliotic form of Ehlers-Danlos syndrome.

Management: Presurgical Spine Elongation

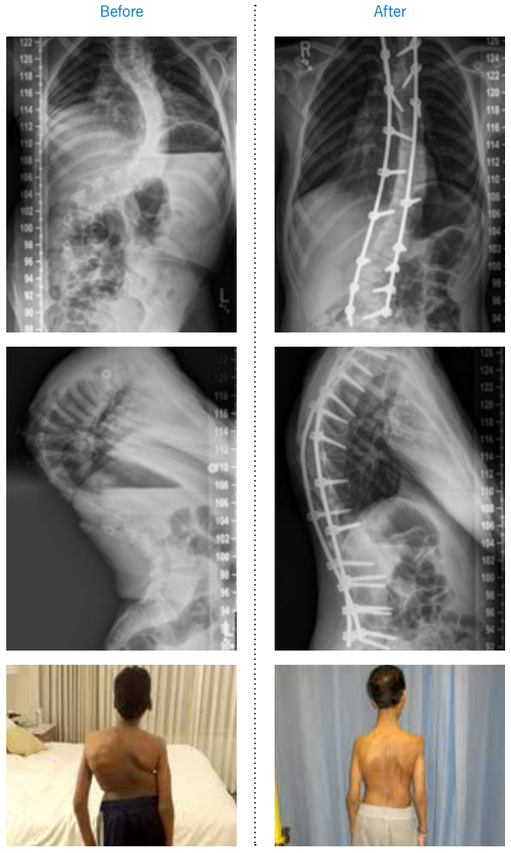
Spinal fusion was recommended. It was felt that the risk of neurological damage could be reduced by elongating the spine before surgery. After a lengthy discussion with the patient and family about risks, benefits and possible complications, the decision was made to proceed with treatment.

In September 2013, the patient was taken to surgery at Cleveland Clinic's main campus and fitted with a halo brace. He was then transferred to Cleveland Clinic Children's Hospital for Rehabilitation to begin intensive "prehabilitation."

At Cleveland Clinic Children's, orthopaedic surgeons typically employ halo traction for three months prior to scoliosis surgery in severe scoliosis cases, particularly with kyphosis, where the deformity is significant. Use of gradual traction allows for safe stretching of soft tissues, including major blood vessels, the esophagus and nerves. Gaining elongation in the stiff, large curves makes definitive fusion safer and easier. Halo traction is not typically used for standard curves.

Beds, chairs, walkers and wheelchairs equipped with pulley systems enable patients to remain in traction 23 hours a day. For this patient, traction was started at 10 lbs. in the chair and walker and 5 lbs. in bed. His initial therapy focused on spinal stretching and muscle strengthening. Traction was increased by 2 lbs. a day up to 40 lbs. in the chair and walker and 10 lbs. in bed.

As the patient's body adapted, he began to experience pain in his back and sides. The physical therapists noted areas of fascial thickening and initiated a program of myofascial release using deep dural pulls. The patient's pain rapidly decreased, and his alignment rapidly improved. The therapists were granted permission to keep the patient off traction for longer periods to work on his fascia and provide postural retraining.



Radiographs and photographs of the patient at presentation (left) and after spinal fusion and rehabilitation (right).

Management: Spinal Fusion and Rehabilitation

After only two months of intensive therapy, the patient underwent successful posterior spinal fusion from T2 to L4. The following day, he resumed myofascial release therapy, gait training, stretching and taping, and yoga. In 10 days, he was discharged to rehabilitation at the day hospital, with biofeedback for postural retraining added to his therapeutic regimen. After 12 days, he was discharged to outpatient physical and occupational therapy.

When the patient was last seen (February 2014), he had a 32-degree thoracic curve, 27-degree lumbar curve and 51-degree kyphosis. His pulmonary function had increased by 33 percent from his July 2013 presentation. He was ambulating with a nonantalgic gait and had gained several inches in height. His parents felt he was dramatically better not just physically but also psychologically and socially.

Personalizing Rehabilitation

Cleveland Clinic Children's Hospital for Rehabilitation is accustomed to patients with complex care needs. These children can also receive multidisciplinary assessment by a team at the Center for Pediatric Integrative Medicine with individual expertise in complementary therapies. The goal is to identify impairments that may aggravate symptoms and to incorporate specific services into the child's care plan to improve global functioning.

For this patient, myofascial release complemented the innovative use of traction to counteract the extreme kyphosis and to lengthen nerve fibers gradually. Breaking down the thickened fascia that would have complicated spine-straightening efforts lessened the patient's pain and shortened his length of stay by one month.

Other complementary therapies incorporated into this patient's rehabilitation plan included (1) pre- and postoperative yoga for essential strengthening and to improve breathing, balance and flexibility; and (2) biofeedback therapy (surface electromyography) to improve gait training.

We have found that prehabilitation prior to spinal fusion results in fewer postsurgical complications. While this young man has other medical problems that will need to be addressed, no additional surgery or therapy for his spinal issues should be required.

PERSPECTIVE

The Center for Pediatric Integrative Medicine:

Pioneering Integrative Practice

As evidence for integrative medicine grows, Cleveland Clinic Children's Center for Pediatric Integrative Medicine is committed to offering patients the latest therapies and services to address physical, emotional and lifestyle needs.

The team includes specialists in physical and occupational therapy, pain management, physical medicine and rehabilitation, pulmonary medicine, recreational therapy, speech-language therapy, behavioral health and general pediatrics. They work closely with colleagues in traditional medical specialties to improve care for children with a diversity of chronic diseases and conditions, including:

- Allergies
- Anxiety
- Arthritis
- Asthma
- Brain injury
- Chronic pain
- Headache
- Pulmonary issues
- Sports injuries

Our certified physicians and therapists use an array of therapies and services that currently includes acupuncture, biofeedback, craniosacral therapy, guided imagery, hypnosis, integrated dry needling, frequency-specific microcurrent therapy, myofascial release, osteopathic manipulation, reiki, relaxation therapy, therapeutic touch, hypnosis and yoga.

The goal is to accelerate and enhance rehab by relieving pain and anxiety, reducing the severity or frequency of disease episodes, speeding the healing process, and improving the child's global health and well-being.

ABOUT THE AUTHORS

Dr. Gurd (gurdd@ccf.org; 216.445.8001) is Head of Pediatric Spinal Deformity Surgery in the Center for Pediatric Orthopaedics and Spine Deformity.

Dr. Katholi (katholb@ccf.org; 216.448.6254) is a pediatric physiatrist in the Department of Developmental and Rehabilitation Pediatrics and the Center for Pediatric Integrative Medicine.

Ms. Behling (behlinc@ccf.org; 216.448.6657) is a physical therapist in the Center for Pediatric Integrative Medicine and Cleveland Clinic Children's Hospital for Rehabilitation.

The Quest for Zero: Improving Quality of Care and Patient Safety for Newborns

By Marita D'Netto, MD; Ajith Mathew, MD; and Ricardo Rodriguez, MD

More than 365 days. That's how long Cleveland Clinic Children's was free of central line-associated bloodstream infections (CLABSIs) across all the neonatal intensive care units (NICUs) in the Cleveland Clinic health system for a period extending from late 2013 to late 2014.

This sustained eradication of NICU CLABSIs followed and improved on Cleveland Clinic Children's achievement in 2013 of an enterprisewide NICU rate of 0.8 CLABSIs per 1,000 central line days, which compared favorably to the 2012 National Healthcare Safety Network (NHSN) benchmark of 1.3 CLABSIs, as detailed in Figure 1.

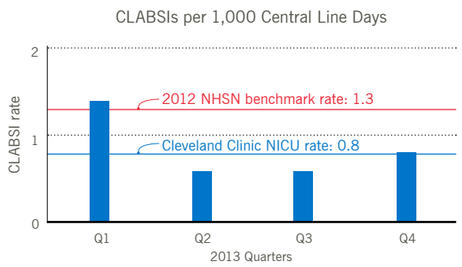


Figure 1. Rates of CLABSIs per 1,000 central line days for NICU patients of all gestational ages across all three Cleveland Clinic Children's NICUs in 2013. NHSN = National Healthcare Safety Network.

CLABSI Successes Stem from Broad Quality Efforts

These achievements stem in part from Cleveland Clinic Children's long-standing participation in the Ohio Perinatal Quality Collaborative, a statewide effort to reduce the incidence of CLABSIs and necrotizing enterocolitis and to develop best practices to standardize and optimize management of neonatal abstinence syndrome.

The application of line insertion and maintenance bundles derived from this effort has had a significant impact on patient care, as demonstrated by the CLABSI data shared above, which represent a dramatic reduction in CLABSI rates in recent years.

These efforts are now augmented by early introduction of maternal breast milk for newborns, with the aim of minimizing use of formula and further reducing the incidence of late-onset infections and necrotizing enterocolitis.

Another Quality Payoff: Exemplary VLBW Mortality

As a member of the Vermont Oxford Network, Cleveland Clinic Children's reports its NICU outcomes on a yearly basis, which are then compared with those of similar centers around the world. These outcomes place our Department of Neonatology's NICUs among the best units in the nation, as illustrated by our 2013 risk-adjusted mortality data for babies with very low birth weight (VLBW) (Figure 2).

Quality's Role in Perpetuating Excellence

Commitment to quality improvement and patient safety is a foundational principle of Cleveland Clinic Children's Department of Neonatology, which is the largest provider of neonatal intensive care in Northeast Ohio (see "By the Numbers" sidebar).

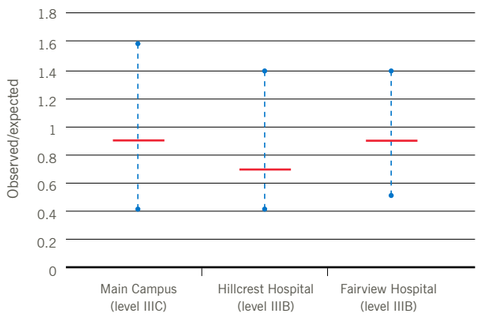


Figure 2. Plots from the Vermont Oxford Network showing 2013 shrunken risk-adjusted mortality rates for very-low-birth-weight infants (501 to 1,500 g) at each of Cleveland Clinic Children's NICUs. The red lines show each NICU's risk-adjusted mortality rate, and the dashed blue lines show the 95 percent upper and lower bounds as determined by the Vermont Oxford Network.

Source: Vermont Oxford Network, 2013

In addition to the deep experience resulting from the considerable patient volumes presented in the sidebar, the department offers state-of-the-art therapies including novel modalities of respiratory support, nitric oxide therapy and extracorporeal membrane oxygenation (ECMO). Other points of distinction include the following subspecialized offerings:

- A dedicated neonatal neurointensive care team
- A neurometabolic team
- An intestinal rehabilitation program
- Dedicated intensive care for infants with neonatal short gut syndrome

These programs, developed and managed by our neonatologists in collaboration with other subspecialists, have benefited patients from surrounding communities as well as from across the nation and around the world. The Department of Neonatology works closely with Cleveland Clinic Children's Critical Care Transport fleet, allowing us to reach remote areas by ground or air. A team of caregivers trained in both critical care and neonatal transport is available to retrieve critically ill newborns, including those on ECMO or other advanced modes of respiratory support.

Additionally, with the support of Cleveland Clinic's large maternal-fetal medicine staff, our neonatal team also staffs Cleveland Clinic's Special Delivery Unit (SDU), where babies with prenatally diagnosed medical and surgical problems can be delivered and promptly treated. The SDU also accommodates mothers with complex medical or surgical problems, making it the nation's first such unit designed expressly to provide specialized care for both mothers and newborns with serious medical issues.

The evolving quality improvement initiatives described above are designed to build on these distinctive aspects of Cleveland Clinic Children's family-centered neonatology care. By fostering a culture of safety and ongoing quality improvement, we are committed to continuing and enhancing our center's impressive outcomes on clinically relevant NICU measures.

ACKNOWLEDGMENT

The authors thank infection control practitioner Gregory Gagliano, Department of Infection Prevention, Quality & Patient Safety Institute, for his contributions to the CLABSI data reported here.

ABOUT THE AUTHORS

Dr. D'Netto (dnettom@ccf.org; 216.444.2568) is Quality Control Officer for the Department of Neonatology.

Dr. Rodriguez (rodrigr4@ccf.org; 216.444.0297) is Chair of the Department of Neonatology.

Dr. Mathew (mathewa2@ccf.org; 216.444.2568) is a staff physician in the Department of Neonatology.

BY THE NUMBERS:

Cleveland Clinic Children's Department of Neonatology

3
Level III NICUs
(2 level IIIB and 1 level IIIC)

87
NICU beds
(70 level IIIB and 17 level IIIC)

18
Board-certified/eligible neonatologists providing 24/7 in-house coverage at the above NICUs plus an additional regional hospital

20
Neonatal nurse practitioners

> 11,000
Babies delivered annually in Cleveland Clinic health system

> 1,200
Newborns admitted to our NICUs annually

Making Headway in Nephrotic Syndrome

Multicenter trials hold the key to better understanding, new treatments

By Katherine Dell, MD

Nephrotic syndrome (NS) remains one of the most challenging diseases in pediatric nephrology. This rare kidney condition is classically defined by edema, heavy proteinuria, hypoalbuminemia and hyperlipidemia. Treatments are limited, have varying effectiveness and are potentially toxic.

Two Trials, Shared Objectives

In an effort to answer critical questions about this disease that may lead to better treatments, Cleveland Clinic Children's is participating in two important NIH-sponsored studies.

The Nephrotic Syndrome Study Network (NEPTUNE) is an ongoing, prospective, observational study that seeks answers to questions about etiologies, diagnostics, effective treatments, quality of life and complications in children and adults with primary NS. Started in 2010, the study has been collecting blood and urine samples from participants several times per year, in addition to tissue samples and DNA. The second phase of this study will soon be opening and will enroll children with new-onset NS in hopes of capturing the full spectrum of pediatric NS.

The second study, Cure Glomerulonephropathy (CureGN), is a multicenter, longitudinal, prospective study of glomerular diseases, including primary NS. The study recently opened and will eventually enroll approximately 2,400 children and adults with one of the following conditions:

- Minimal change NS (MCNS)
- Focal segmental glomerulosclerosis (FSGS)
- Membranous nephropathy
- IgA nephropathy

CureGN will collect both genetic and biological samples.

Novel Treatments Emerge from Multicenter Collaborations

A major advantage of multicenter studies such as NEPTUNE and CureGN is the ability to connect a larger number of patients than would be available at an individual site with investigators who are interested in studying the disease. This often produces ancillary studies.

One example is the DUET study, a joint venture between NEPTUNE and a pharmaceutical company. Cleveland Clinic Children's is one of 10 pediatric nephrology centers participating in this study of an investigational medication — the dual endothelin receptor and angiotensin receptor blocker RE-021 — to reduce proteinuria in pediatric and adult patients with FSGS.

In another example, we and other pediatric NEPTUNE investigators are working to develop a prospective study of a gluten-free diet as an adjunct to standard treatment for NS. The idea sprang from observations made in NEPTUNE that suggest a strict gluten-free diet may improve proteinuria in a subset of patients with steroid-resistant NS or frequently relapsing or steroid-dependent steroid-sensitive NS.

One Syndrome, Three Pathologies, Myriad Causes

The most common causes of primary NS are MCNS, FSGS and (less commonly in children) membranous nephropathy.

Younger children (typically ages 2 to 6) who present with the classic features of NS have a very high likelihood of having MCNS. They do not typically undergo renal biopsy but are empirically treated with prednisone. Those who respond and enter remission are deemed to have steroid-sensitive NS. Their long-term prognosis is excellent, with resolution of the disease occurring in the majority by adolescence. However, relapses may occur throughout childhood.

A subset will have steroid-dependent NS or frequently relapsing NS, which may require additional immunosuppressive therapies such as cyclophosphamide or mycophenolate mofetil to avoid the significant side effects of long-term steroid use.

More worrisome are those who do not respond to the initial course of steroids and are deemed to have steroid-resistant NS. These children, as well as those with clinical features at presentation that increase their likelihood of having steroid-resistant NS (including

LEFT — Dr. Dell with a patient enrolled in the NEPTUNE study. See profile, p. 29.

Patients with steroid-resistant nephrotic syndrome constitute about 20 percent of the pediatric end-stage renal disease population.

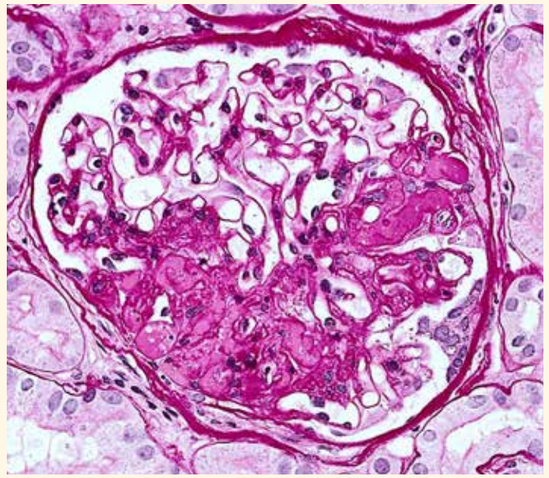


Figure. Pathology image of a glomerulus from a patient with nephrotic syndrome showing a lesion of segmental scarring typical of focal segmental glomerulosclerosis (FSGS). Image courtesy of Leal Herlitz, MD, Cleveland Clinic.

acute kidney injury, hypertension, older age and African-American race), undergo diagnostic kidney biopsies. FSGS is the most likely finding, but MCNS or its variants (such as mesangial proliferative glomerulonephritis) are not uncommon.

Why New Treatments Are Needed

Calcineurin inhibitors such as cyclosporine or tacrolimus are considered first-line therapy for steroid-resistant NS and produce a full or partial response in about 50 percent of patients. It is impossible to predict who will respond to these treatments or how long they will remain responsive. Newer therapies, such as rituximab, have also been utilized, but with variable results.

Steroid-resistant NS may require intermittent, prolonged courses of corticosteroids in addition to maintenance immunosuppression. The overall prognosis for these patients remains poor, with the majority eventually progressing to end-stage renal disease (ESRD). In fact, patients with steroid-resistant NS constitute about 20 percent of the pediatric ESRD population. FSGS also is associated with a high risk of relapse after kidney transplantation, with no reliable predictors of which patients will relapse.

Clues from Recent Genetic Studies

Although the three major underlying causes of primary NS have been well-characterized histologically (see figure for example), their underlying etiologies remain elusive. Increasingly, genetic defects have been identified as a cause of steroid-resistant NS, especially FSGS. Attention has been focused on genes encoding proteins that compose or support the slit diaphragm, the structure that connects individual podocytes and maintains integrity of the glomerular filtration mechanism. Mutations in several of these genes have been identified in patients with familial and sporadic FSGS. These genetic studies have also highlighted the phenotypic variability of diseases that appear similar under the microscope.

At Cleveland Clinic Children's Center for Pediatric Nephrology, we recognize the challenges inherent in NS and are encouraged by recent findings. We remain committed to offering the latest treatments by making innovative studies available to our patients and their families.

ABOUT THE AUTHOR

Dr. Dell (dellk@ccf.org; 216.444.6123) is Associate Professor of Pediatrics, Cleveland Clinic Lerner College of Medicine, as well as a staff physician in the Center for Pediatric Nephrology and Cleveland Clinic Children's Director of Clinical and Translational Research.

PERSPECTIVE

A Personal Glimpse into the NEPTUNE Study

Montanna Hirsch puts a face on the promise of the NEPTUNE study. The 6-year-old kindergartner from Willowick, Ohio, has been in the care of pediatric nephrologist Katherine Dell, MD, since developing edema in late 2011, shortly before her third birthday.

Blood work and urine studies suggested nephrotic syndrome, and Montanna and her family were connected with Dr. Dell, who placed her on steroid therapy. But the 3-year-old did not respond to treatment, suffering edema, lethargy and difficulty breathing, which landed her in the hospital. In light of the lack of response to steroid therapy, a kidney biopsy was done, which showed that Montanna had minimal change nephrotic syndrome (MCNS).

Dr. Dell reduced Montanna's steroid dose and started immunosuppressant therapy with cyclosporine. She also invited Montanna's parents to enroll their daughter in the NEPTUNE study (see main article) — an invitation they accepted. "Dr. Dell explained that Montanna would be a good candidate because her case was in the middle of the severity range — not the most severe, but with the potential for a downturn at any time," says her mother, Coletta Hirsch. "That presents a lot of opportunities to learn more about the condition."

Montanna entered remission on cyclosporine. She has since been hospitalized several times with symptoms similar to those at her initial hospitalization. At these times, Dr. Dell typically adjusts her medication dosages, which puts her into remission again, generally allowing discharge within a week. "We check Montanna's urine every day," says her mother. "When we get abnormal readings for two or three days, we call Dr. Dell, since that's how the relapses usually start."

The hospitalizations have grown less frequent over time, with the last one being in spring 2014. Montanna's parents say she has fared better since Dr. Dell switched her immunosuppressive therapy from cyclosporine to tacrolimus in late 2013. They add that she "plays like a normal kid" and participates in the normal school day like her classmates. Her biggest limitations include sensitivity to especially hot or cold weather due to her immunosuppressive therapy.

Participation in NEPTUNE involves a periodic series of blood draws and 24-hour urine collections, taking of nail clippings, and measurement of blood pressure, weight and height. Montanna will continue to be followed in the study for at least five years. Her long-term prognosis is difficult to predict. "They just don't know enough about the condition yet," says her mother.

And that's precisely why the Hirsch family is happy to contribute to NEPTUNE. "This study might ultimately help explain why Montanna has this condition while our other three daughters don't," says Ed Hirsch, Montanna's father. "Or it might help clarify why some cases are worse than others. Montanna understands that the study is about helping other kids with nephrotic syndrome."

Montanna Hirsch (bottom center) with her father, her mother and one of her three sisters, all of whom are unaffected by nephrotic syndrome.

New Center of Excellence Enhances Management — and Understanding — of *CDKL5*-Related Disease Through Multidisciplinary Expertise

By Sumit Parikh, MD, and Elia Pestana Knight, MD

Mutations in the cyclin-dependent kinase-like 5 *(CDKL5)* gene lead to a characteristic infant-onset epileptic encephalopathy and neurodevelopmental disorder known as *CDKL5*-related disease. Because this serious condition has been recognized as a clinical entity for little more than a decade, understanding of its clinical phenotype remains incomplete.

To expand understanding and promote a standard of care, the nonprofit International Foundation for CDKL5 Research (IFCR) was formed in 2009 and has begun designating CDKL5 Centers of Excellence. In 2014, Cleveland Clinic Children's was designated one of only three CDKL5 Centers of Excellence to date. In making the designation, the IFCR cited long-standing clinical interest and research initiatives in *CDKL5*-related disease among staff in Cleveland Clinic Children's Center for Pediatric Neurology and Neurosurgery.

This article profiles *CDKL5*-related disease and the work our center is doing with the IFCR and partner institutions to advance understanding of the condition and its treatment.

Profile of the Presentation of *CDKL5*-Related Disease

The initial presentation of *CDKL5*-related disease includes:

- Early-onset seizures (within the first three months of life)
- Seizures that often but not always become refractory to many antiepileptic drugs
- Multiple seizure types that can change as the patient gets older
- Delayed neurocognitive development without a history of regression
- Other manifestations, such as poor social interaction, stereotypic hand movement, severe hypotonia, visual disturbances, feeding difficulties, dysphagia and autonomic changes
- No specific facial dysmorphic features

The sidebar summarizes clinical findings in patients with *CDKL5*-related disease.

PERSPECTIVE

Clinical Findings in *CDKL5*-Related Disease

- Early-onset epileptic encephalopathy with a seizure mix including infantile spasms, myoclonic seizures and prolonged generalized tonic-clonic seizures
- Severe early developmental delay
- Absence of facial dysmorphic features
- Normal head circumference
- Absent speech/language
- Poor eye contact
- Reduced social interactions
- Visual disturbances
- Severe hypotonia
- Absent or impaired walking
- Hand stereotypies
- Bruxism
- Autonomic dysfunction
- Feeding difficulties and dysphagia
- Poor sleep pattern

Seizure Types and EEG Patterns

Seizures in patients with *CDKL5*-related disease present as early as the neonatal period. Seizure types may change across the life span. In nearly half of patients, the initial presentation includes early-onset infantile spasms with or without other associated seizures. Other associated seizure types include focal motor, tonic, myoclonic, apneic and complex motor with oral automatisms.

As these children grow older, a variety of mixed seizures can be seen, including myoclonic, tonic, absence and complex partial. Generalized tonic-clonic seizures are frequent and common. Epileptic spasms persist in some patients. Often seizures are long, lasting more than five minutes. Seizures are often highly refractory to antiepileptic treatment, but honeymoon periods after initiation of a new antiepileptic drug have been described.

No specific EEG pattern has been associated with *CDKL5*-related disease. EEG abnormalities seem to change with age and seizure

Figure 1.

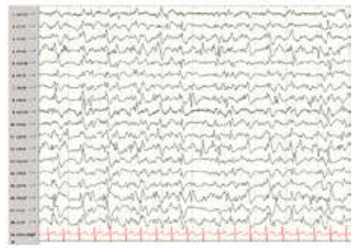


Figure 1. Sample of a video EEG recording showing hypsarrhythmia. The patient is a 4-year-old boy with seizures since age 2½ months, severe neurodevelopment delay, visual impairment, swallowing dysfunction, gastroesophageal reflux and gastric tube requirements for feeding. Since seizure onset, he has had persistent daily clusters of infantile spasms and tonic seizures despite treatment with phenobarbital, rufinamide, topiramate, levetiracetam, valproic acid and the ketogenic diet. He has a confirmed pathogenic mutation in the *CDKL5* gene.

Figure 2.

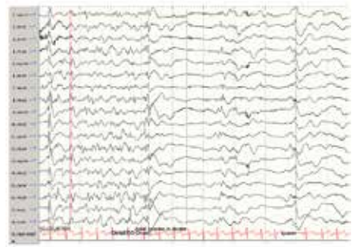


Figure 2. Sample of a video EEG recording showing ictal pattern during epileptic spasms in the same patient.

types. The initial EEG can be interpreted as normal, but a hypsarrhythmia pattern (Figure 1) often becomes a prominent finding once infantile spasms begin. Focal, multifocal, diffuse or generalized sharp waves can also be seen on initial EEGs. Ictal findings (Figure 2) are dependent on the seizure type. Abnormalities of the background rhythm are a common finding in these patients and are present in all patients as they grow older.

Basics of Screening and Etiology

CDKL5-related disease is a dominant X-linked condition that should be considered for any child with an early-onset epileptic encephalopathy, especially when infantile spasms begin before 3 months of age. Although the condition is considered rare, it is likely underidentified, and its true incidence is not yet known.

The yield of *CDKL5* testing in children with an early-onset epileptic encephalopathy is about 5 percent for males and 14 percent for females. A *CDKL5* gene mutation can be found in up to 31 percent of females with Rett syndrome-like features and negative testing for *MECP2* (the gene implicated in Rett syndrome).

CDKL5-related disease results from mutations in the *CDKL5* gene on the X chromosome. Patients with the condition were first identified in the early 2000s, following introduction of the first clinical tests in late 2000. Scientific knowledge of the disease's pathophysiology is still rudimentary, although the gene primarily is expressed in the brain and expression overlaps that of *MECP2* during neuronal maturation. *CDKL5* and *MECP2* may belong to the same neurodevelopmental pathway.

Understanding of the clinical phenotype is improving but remains general and incomplete. Symptoms include varying degrees of refractory epilepsy and developmental disability, with notable variability in severity from patient to patient. At least one patient without epilepsy has been identified to date. The condition's natural history is not yet known.

Bringing Multidisciplinary Management to Bear

A key goal of the IFCR's Centers of Excellence initiative is to recognize and promote multidisciplinary clinics to improve clinician familiarity with *CDKL5*-related disease across the country and provide a standard of care to patients and families. Such centers can better ascertain how the condition unfolds, allowing their researchers to study its natural history.

At Cleveland Clinic Children's, we hold a multidisciplinary "clinic without walls" where patients with *CDKL5*-related disease can see as many as 12 different specialists over the course of one to two days. These include dedicated specialists in epilepsy, neurogenetics, genetic counseling, gastroenterology, rehabilitation medicine, orthopaedics, pulmonology, cardiology, ophthalmology, gynecology and physiotherapy. A social worker also is available.

In conjunction with these comprehensive clinical offerings, we are participating in a funded collaborative study to collect a fixed set of data points from each specialist at each patient visit. These data are fed into a national database for long-term tracking of aggregated parameters with the aim of illuminating the natural history of *CDKL5*-related disease and yielding implications for therapy. Stay tuned as we collectively gain a better handle on this emerging clinical entity.

ABOUT THE AUTHORS

Dr. Parikh (parikhs@ccf.org; 216.444.1944) is a pediatric neurologist in the Center for Pediatric Neurology and Neurosurgery, where he directs the Multidisciplinary CDKL5 Syndrome Clinic and the Neurogenetics, Metabolic and Mitochondrial Disease Program.

Dr. Pestana Knight (pestane@ccf.org; 216.445.6739) is a pediatric neurologist specializing in epilepsy in the Center for Pediatric Neurology and Neurosurgery.

Novel Approach to Classifying Elbow Osteochondritis Dissecans Gives Lesion Location Its Due

By Joel Kolmodin, MD, and Paul Saluan, MD

Osteochondritis dissecans (OCD) of the elbow is increasingly prevalent in the U.S. pediatric population, particularly in young throwing athletes such as baseball players. The condition is thought to be secondary to repetitive compressive and shearing forces exerted by the radial head on the humeral capitellum during the throwing motion. These forces have been shown to cause microtrauma of the articular cartilage, leading to avascularity, fracturing and ultimately overt detachment from subchondral bone. Traumatic cartilage changes invariably lead to the insidious onset of pain and functional limitation, often with mechanical symptoms and significant loss of motion in advanced lesions.

The Takahara Classification

Treatment options for capitellar OCD lesions are numerous, ranging from simple rest to arthroscopic debridement and drilling, fragment fixation, and autograft or allograft transfer. All management options can be successful when used in the appropriate clinical scenario.

Since its publication in 2007, the Takahara classification for pediatric OCD lesions of the capitellum[1] has proved to be a valuable tool for guiding management of OCD lesions. The classification establishes two groups of patients:

- Those with stable lesions, which can heal completely with rest
- Those with unstable lesions, which require surgery to obtain satisfactory results

Stable lesions were defined as those that occur in a capitellum with an open physis, display low-grade radiographic changes and have maintained elbow range of motion (ROM). Conversely, unstable lesions were defined as those that are found in a capitellum with a closed physis, display higher-grade radiographic changes and have restriction of elbow motion greater than 20 degrees.

Where the Takahara Scheme Comes Up Short

It is generally accepted that stable lesions can be effectively treated nonsurgically, but surgical decision-making regarding unstable lesions has not been fully elucidated. While the Takahara classification system has proved very useful in guiding the decision to pursue nonoperative over operative management, it does not include discrete guidelines to direct surgical management based on lesion characteristics.

One key element not accounted for in the classification scheme is lesion location on the capitellum, which is increasingly recognized as having significant implications in surgical management.

Past cadaveric biomechanical studies have shown that capitellar valgus laxity and contact pressures increase in the presence of capitellar OCD lesions and that these contact pressures are greater in lateral defects than in central defects. Similarly, many clinical studies have demonstrated that lateral lesions tend to be associated with more severe symptoms and loss of function. Much better outcomes are seen when lateral lesions are treated with aggressive surgical interventions such as autograft reconstruction (Figure 1).

Table. Proposed Update to the Takahara Classification

	Capitellar physis	Radiographic grade	Range of motion	Location	Management
Type I	Open	I	Normal	Not applicable	Rest
Type II	Closed	II/III	Restricted > 20°	Medial to the radial head centerline	Debridement
Type IIIa	Closed	II/III	Restricted > 20°	Extending lateral to the radial head centerline	Repair or reconstruction
Type IIIb	Closed	II/III	Restricted > 20°	Extending lateral to the radial head centerline, including the lateral cartilage margin	Reconstruction

Reprinted from Kolmodin and Saluan.[2]

Our Proposal for a Modified Classification

In view of this evidence, we have proposed and published a refinement of the Takahara classification for OCD lesions of the elbow (Table).[2] This modification is based on the location of the lesion on the capitellum, as determined on a 45-degree flexed, supinated view of the elbow (Figures 2 and 3). The capitellum is divided into two halves, defining medial (type II) and lateral (type III) lesions. Radiographic grade is assessed using the Minami classification.

Type I lesions ("stable") have an open capitellar physis, grade I radiographic findings and nearly full ROM at the time of diagnosis. Most of these lesions heal completely if treated with thorough rest.

Type II lesions ("unstable") are those with a closed capitellar physis, a grade II/III radiographic profile *or* presentation with restricted elbow ROM, and a location *medial* to the radial head centerline. These lesions tend to respond well to simple debridement or repair.

Type IIIa lesions ("unstable") have a closed capitellar physis, grade II/III radiographic findings *or* presentation with restricted elbow ROM, and a location *lateral* to the radial head centerline. They tend to do better with more aggressive therapies, such as repair or reconstruction.

Type IIIb lesions ("unstable") are those with a closed capitellar physis, a grade II/III radiographic profile *or* presentation with restricted elbow ROM, and a location *lateral* to the radial head centerline, *including the lateral cartilage margin*. These lesions require reconstruction, which enhances stability and reduces shear forces experienced by the lateral capitellum.

Better Real-World Guidance in Store

We believe our update to the Takahara classification, by accounting for lesion location, better reflects the clinical scenarios physicians are encountering and the current questions being addressed in the literature. We anticipate that our updated classification scheme will improve the way capitellar OCD lesions are characterized and systematically treated and will help guide surgical management more effectively and shape further research efforts.

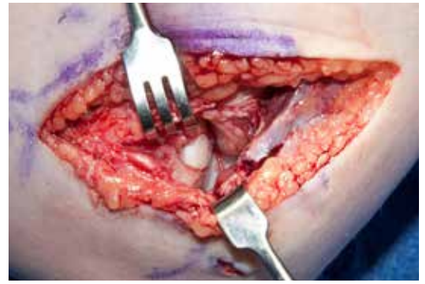
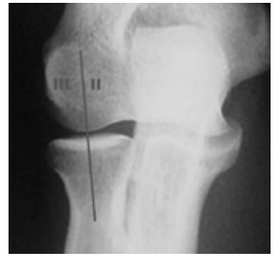


Figure 1. Intraoperative photo of osteochondral autograft transfer at the elbow.



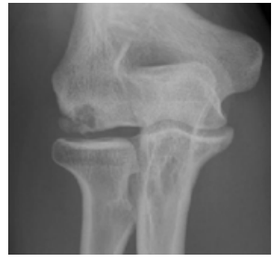


Figure 2 (above left). A 45-degree flexed, supinated anteroposterior X-ray view of an elbow with type II (medial) and type III (lateral) OCD lesions. Reprinted from Kolmodin and Saluan.[2]

Figure 3 (above right). X-ray of an elbow with a type IIIb OCD lesion. Reprinted from Kolmodin and Saluan.[2]

REFERENCES

1. Takahara M, Mura N, Sasaki J, et al. Classification, treatment, and outcome of osteochondritis dissecans of the humeral capitellum. *J Bone Joint Surg Am.* 2007;89:1205-1214.
2. Kolmodin J, Saluan P. Osteochondritis dissecans of the humeral capitellum. The significance of lesion location. *Orthop J Sports Med.* 2014;2(4):2325967114530840.

ABOUT THE AUTHORS

Dr. Kolmodin (kolmodj@ccf.org) is a fellow in the Department of Orthopaedic Surgery.

Dr. Saluan (saluanp@ccf.org; 216.518.3473) is a surgeon in the Center for Pediatric Orthopaedics and Spine Deformity.

Botulinum Toxin — the Cosmetic 'Toxin Turned Treatment' — Earns a Place in Pediatric Otolaryngology

By Brandon Hopkins, MD

Botulinum toxin (BTX) injections may have gained fame as a tool to slow the wheels of time, but their use has expanded to include the treatment of many head and neck disorders outside the cosmetic arena. We at Cleveland Clinic Children's are pleased to offer this minimally invasive treatment to our pediatric patients with various head and neck disorders.

Proliferating Clinical Applications

The safety profile of this medication has opened doors for its use in pediatrics beyond strabismus, which was its first medical use. Spasmodic dysphonia and essential voice tremor are well-known laryngeal indications, but in pediatric head and neck patients, BTX has been used to treat airway obstruction due to bilateral vocal cord paralysis and laryngeal dystonia.

Beyond laryngeal indications, there is strong evidence for BTX use in chronic daily headaches, cervical dystonia, masticatory myalgia, sialorrhea, temporomandibular joint disorders, bruxism, blepharospasm, hemifacial spasm and nasal rhinitis. Its use has also been reported for facial paresis, palatal and stapedial myoclonus, trigeminal neuralgia, first-bite syndrome and Frey syndrome. Four brands of BTX have been approved by the FDA: Botox®, Dysport®, Myobloc® and Xeomin®.

At Cleveland Clinic Children's, we have found BTX to be effective for three indications in particular: congenital muscular torticollis, sialorrhea and facial nerve dysfunction.

Torticollis: Avoiding a Surgery

Torticollis is a relatively common condition in newborns, with an incidence as high as 1 in 250. The most common type is congenital muscular torticollis (CMT). CMT is caused by a unilateral shortening of the sternocleidomastoid muscle (SCM), which leads to an ipsilateral head tilt and contralateral head rotation. This twisted position often leads to positional plagiocephaly. CMT can present as:

- A palpable SCM tumor
- Tightness or fibrosis of the SCM with no mass
- Torticollis without SCM tightness

At Cleveland Clinic Children's, pediatric otolaryngologists work with our physical medicine and rehabilitation team, physical therapists, primary care teams and others to care for children with CMT. Our approach is to identify patients early, rule out other causes of torticollis and implement therapy early in life.

Standard treatment for CMT involves physiotherapy, stretching exercises, molding helmets and neck braces. These conservative treatments are most successful when started at a young age. However, some children — especially those with an SCM tumor or fibrosis and those resistant to physical therapy and conservative interventions — are recommended for surgery. Since surgery can leave patients with functional and cosmetic limitations, families welcome the nonsurgical alternative offered by BTX injections. Studies have shown that BTX injections have a high rate of success when they are used early, often before 12 months of age.

With the child under light anesthesia, we turn the head to the contralateral side to isolate and grasp the SCM. Under sterile conditions, the syringe is placed and then pulled back to ensure it is not being placed within a blood vessel. (Ultrasound guidance for needle placement can be helpful but is not usually necessary.) BTX is then injected under direct vision. It is common to find that trapezius tightness also limits head rotation; if so, this muscle can also be treated. Typically 25 to 50 units of BTX (10 units/0.1 mL) are injected into each muscle, depending on its size and bulk. We take care to avoid injection and diffusion into surrounding muscles to avoid the possibility of dysphagia.

These outpatient injections are typically well-tolerated by infants and children, which allows them to quickly return to physical therapy. Repeat injections are occasionally helpful.

Excessive Drooling: Stemming the Flow

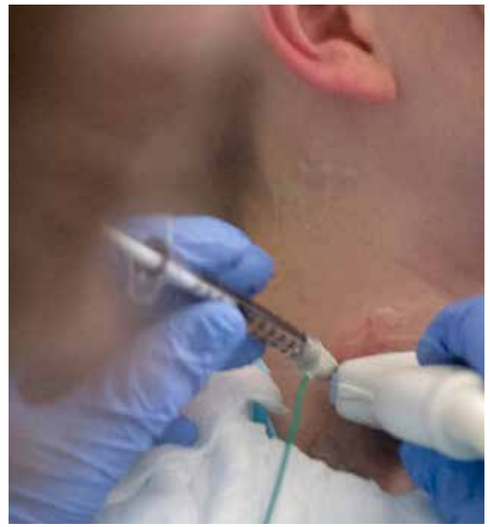
Sialorrhea, which occurs in as many as one-third of children with cerebral palsy, is a common indication for BTX at Cleveland Clinic Children's. The clinical consequences of excessive drooling include skin breakdown and an increased risk of aspiration. Its quality-of-life implications can include constant bib changes, social isolation and compromised school performance.

In addition to BTX, medical therapy options include optimizing body position to lessen salivary egress from the oral cavity, intraoral appliances and anticholinergic medications to reduce salivary flow. Traditional surgical options have included transtympanic neurectomy to decrease the neural input triggering salivation, submandibular gland excision, duct ligation, duct rerouting and other procedures.

BTX has been shown both subjectively and objectively to decrease salivation for up to four or five months. We inject bilateral parotid and submandibular glands with 70 to 100 units spread between the glands. Minimizing the volume of injection is important to prevent diffusion of BTX into the facial musculature, which can lead to facial weakness.

For selected compliant patients, the minimally invasive nature of these injections allows us to perform them with ultrasound guidance, minimal sedation and topical anesthesia in an outpatient setting. Other patients are treated in the OR.

Our experience has been consistent with studies showing improved quality of life with these injections, and families often wish to repeat the treatments. BTX injections can also serve as a trial to gauge improvement and help patients feel comfortable proceeding to a more permanent surgical approach.



Ultrasound- and electromyography-guided botulinum toxin injection in a pediatric patient.

Facial Paralysis: Restoring the Smile

Marginal mandibular nerve paralysis is a relatively common condition that results in an asymmetric smile and even asymmetry at rest, which can be socially and emotionally distressing. Its causes include congenital anomalies, viral insults, trauma, iatrogenic surgery and many other etiologies.

Interventions can be directed to either the paralyzed or the normal side. Procedures on the former include partial lip resection, hypoglossal nerve transfer, local muscle transfers and free tissue transfers. These approaches have drawbacks, however, including scarring, the need for secondary incisions and often a lack of functional restoration. Procedures on the nonparalyzed side attempt to create facial symmetry, ideally at rest and with movement. Surgical options include severing the remaining marginal mandibular nerve and myectomy of the lower lip depressor muscles.

BTX injections are a form of chemical myectomy. Many children can be treated in the outpatient setting with topical anesthesia. The injection can be repeated as needed every four or five months, with dosage adjustments to achieve desired effects. Again, BTX can be used as a trial before proceeding to a more permanent surgical approach, such as myectomy. This offers families the opportunity to "try before they buy" a procedure that has lifelong cosmetic implications.

Further Exploration Ahead

In a multidisciplinary effort, we work with adult-care colleagues in Cleveland Clinic's Head & Neck Institute to select appropriate pediatric candidates for treatment with BTX. We look forward to further exploring the varied uses of this "toxin turned treatment."

A bibliography/suggested reading list is available from the author at hopkinb@ccf.org.

ABOUT THE AUTHOR

Dr. Hopkins (hopkinb@ccf.org; 216.444.0322) is a pediatric otolaryngologist in the Section of Pediatric Otolaryngology.

Introducing a Novel Computerized Clinical Decision-Support System for Pediatric Rheumatology: Patient Risks, Outcomes and Barriers Evaluation (PROBE)

By Vibha Anand, PhD; Steven J. Spalding, MD; and Andrew S. Zeft, MD, MPH

Pain is the most distressing aspect of disease in children and can play a predominant role in their daily lives. A landmark report from the Institute of Medicine (IOM), *Relieving Pain in America*,[1] addresses deficiencies in pain assessment and management in the U.S. healthcare system and calls for progress in providing complete and consistent assessment of pain while identifying the need for more pain research.

Children and families who live with one or more chronic conditions, such as juvenile idiopathic arthritis (JIA), can ardently confirm the findings of this IOM report. Children with JIA who experience pain regularly perceive themselves to be more disabled and are more likely to restrict their activity. Their disease-related pain commonly persists into adulthood and can significantly impact their productivity and quality of life. Past research has shown that disease activity and pain often do not correlate in children and adolescents suffering from one or more chronic conditions. However, certain behavioral risk factors may influence the pain experience in children with JIA.[2-4]

PROBE-ing a Pathway to Better Pain Assessment

To promote complete and consistent assessment of pain in our pediatric rheumatology practices, Cleveland Clinic Children's Center for Pediatric Rheumatology has developed a computerized clinical decision-support system referred to as Patient Risks, Outcomes and Barriers Evaluation (PROBE).

PROBE screens patients and their families in the waiting room using standardized instruments administered via iPads®. The instruments were developed using evidence-based guidelines for pain and associated behavioral risk factors, such as sleep deprivation, anxiety, depression or painful conditions affecting a caregiver living in the child's home.

Results from this screening are integrated into the busy clinical workflow of our pediatric rheumatology practices. Patients are screened in the waiting room at every visit, the screening instruments are auto-scored, and pertinent risk factors and above-threshold scores are flagged for the clinician. Additionally, clinicians document patients' disease activity-related measures (e.g., active joint counts) in PROBE, which allows monitoring of patient outcomes and process measures. This may ultimately enable treatment decisions guided by predictive modeling as more data are collected.

A Distinctive Approach to Pain in Pediatric Rheumatology

We believe our approach to pain assessment in pediatric rheumatology is unique and innovative. By using PROBE, we have embedded into a pediatric clinical decision-support system the process of identifying children and adolescents who are at increased risk for developing chronic pain. Furthermore, PROBE is based on principles of shared decision-making,[5] a theoretical model that involves active participation of both the provider and the patient/caregiver in exchange for information related to care or treatment decisions.

Because the system can be deployed in both the waiting room and the exam room and used by patients/caregivers and clinicians alike, PROBE represents an attractive and viable IT platform for both clinical research and practice.

A Predictive Tool in the Works Too

As we continue to collect PROBE-based screening data, we are developing a predictive tool, the Pain Comorbidity Assessment Tool (P-CAT). P-CAT will be used to prospectively identify children and adolescents at higher risk of pain. This tool will also support more tailored and dynamic interventions, such as facilitating self-management of pain-related conditions using educational materials, provider notifications or patient surveys.

Promising Results from an Early Assessment

To the best of our knowledge, our center is the first site to prospectively evaluate behavioral risk factors for chronic pain in routine pediatric rheumatology care.

In a pilot study using PROBE screening data from 136 patients presenting to our pediatric rheumatology clinic, we found that 44 percent of patients (n = 60) report chronic pain (self-report of pain greater than three days a week for more than three months). Compared with their counterparts from the sample who did not report chronic pain, patients reporting chronic pain:

- Tended to be older (median age, 15 years)
- Had higher weekly pain scores (3 points higher, on average)
- Reported significantly poorer overall well-being (median score of 7 on a 0-10 scale, with 10 being worst)

Additional study findings are summarized in the sidebar above.

Our findings have implications for long-term treatment and care planning. For example, assessment of sleep impairment requires referral to a sleep specialist and appropriate follow-up. Similarly, assessment of inadequate coping skills should prompt referral for cognitive behavioral therapy (with follow-up), and anxiety-related symptoms call for a full psychosocial evaluation.

Thus, as we continue to develop the PROBE tool, we plan to generalize it for care settings outside our health system. We believe our approach has value for pain assessment in many chronic pediatric conditions — such as sickle cell disease, inflammatory bowel disease and cancer — and can be used in additional research and clinical settings as well.

PERSPECTIVE

More Characteristics of Patients Reporting Chronic Pain from the PROBE Pilot Study

Compared with pediatric rheumatology patients not reporting chronic pain, those patients who do report chronic pain:

- Are at least two times more likely to report sleep issues (e.g., problems falling asleep or feeling sleepy during the day, in school or while driving)
- Have significantly poorer pain coping skills and efficacy (e.g., less frequently feel they can do something to change their pain, change their moods/feelings when hurt in or in pain, or easily deal with the pain)
- Have significantly higher anxiety-related symptom scores (e.g., school avoidance and significant somatic symptoms)
- Are significantly more likely to have a parent with a history of jaw, spine, lower back, leg or arthritis-related pain

REFERENCES

1. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, D.C.: National Academies Press; 2011.
2. Bromberg MH, Gil KM, Schanberg LE. Daily sleep quality and mood as predictors of pain in children with juvenile polyarticular arthritis. *Health Psychol.* 2012;31(2):202-209.
3. Margetic B, Aukst-Margetic B, Bilic E, et al. Depression, anxiety and pain in children with juvenile idiopathic arthritis (JIA). *Eur Psychiatry.* 2005;20(3):274-276.
4. Schanberg LE, Anthony KK, Gil KM, et al. Family pain history predicts child health status in children with chronic rheumatic disease. *Pediatrics.* 2001;108(3):E47.
5. Ruland CM, Bakken S. Developing, implementing, and evaluating decision support systems for shared decision making in patient care: a conceptual model and case illustration. *J Biomed Inform.* 2002;35(5-6):313-321.

A complete bibliography is available from Dr. Anand at anandv@ccf.org.

ACKNOWLEDGMENT

The authors gratefully acknowledge two sources of partial funding for the pilot study of PROBE: the Research Program Committee of Cleveland Clinic's Lerner Research Institute, and donor funds made available through Cleveland Clinic's Pediatric Institute.

ABOUT THE AUTHORS

Dr. Anand (anandv@ccf.org; 216.442.5565) is a researcher in the Center for Pediatric Rheumatology and the Department of Quantitative Health Sciences.

Dr. Spalding (spaldis@ccf.org; 440.695.4000) is a pediatric rheumatologist in the Center for Pediatric Rheumatology.

Dr. Zeft (zefta@ccf.org; 216.444.9000) is Head of the Center for Pediatric Rheumatology.

Single-Port Cholecystectomy Is a Viable Alternative to the Four-Port Technique

An efficient, cost-effective, essentially scarless procedure is achievable in children using first-generation laparoscopes

By Federico G. Seifarth, MD

Minimally invasive cholecystectomy has become the gold standard for gallbladder removal in adults and children. In an effort to improve cosmesis and reduce postoperative pain, single-incision techniques have been developed in recent years. These operations require placement of an umbilical multichannel port or an umbilical incision big enough to accommodate multiple laparoscopic instruments. Although umbilical single-incision procedures have proved safe and effective in children, the use of multichannel ports is not optimal for small children due to the relatively large incisions they require for placement.

Reducing Instrumentation to Curb Pain and Scarring

In 2010, surgeons in Cleveland Clinic Children's Department of Pediatric General Surgery began to investigate how established single-port and single-incision techniques might be refined to reduce associated pain and scarring while maintaining the procedure's safety and efficacy. To this end, we employed a first-generation operating laparoscope that has demonstrated success in single-port appendectomy. By reducing instrumentation to its bare essentials, we were able to develop a cost-effective procedure that is not inferior to standard laparoscopic technique and results in a short hospital stay and excellent cosmetic results.

The Procedure at a Glance

This novel procedure utilizes a 10-mm Storz Hopkins® telescope with zero-degree fiber optics and an inbuilt 6-mm working channel. It is inserted into the abdominal cavity (Figure 1) through a 10-mm transumbilical port.

Under direct vision, two portless 2.3-mm Clutch Graspers are introduced into the peritoneal cavity through stab incisions in the right subcostal area (Figure 2). The graspers are used to retract and manipulate the gallbladder during the procedure. The cystic artery and ducts are dissected with blunt instruments and hook electrocautery. Low-cost, nonabsorbable Hem-o-lok® clips are used to seal the cystic artery and cystic duct. The gallbladder is separated with electrocautery and removed through the umbilical port site. The umbilical ring is closed with absorbable sutures, and the stab wounds are closed with cyanoacrylate skin glue.

The zero-degree optic provides sufficient visualization in combination with the use of two holding graspers for patients with standard anatomy.

Our Initial Published Experience

We recently published[1] our initial experience with this single-port technique on 20 pediatric patients with cholecystolithiasis (n = 13) or biliary dyskinesia (n = 7) over a 14-month period. Patient BMIs ranged from 11.6 to 42.3 kg/m^2.

Eighteen patients were treated without incident. Severe pericystic adhesions in two patients required conversion to conventional four-port laparoscopic cholecystectomy. Blood loss in all 20 patients was minimal. No intra- or postoperative complications were experienced.

The average postoperative stay was 24 hours. All patients reported complete resolution of postoperative pain after day 5 and were allowed to resume full physical activity after three weeks.

Subsequent Experience and Expanded Use

Since completion of this study, we have expanded the application of this single-port approach to include patients of all sizes and weights with benign gallbladder disease, including gallstones, biliary dysfunction, gallbladder inflammation and infection. Our experience to date includes 124 cholecystectomies with no intraoperative complications. The procedure is now considered the standard approach in our department.

Relative contraindications are few and include the presence of severe scar tissue, patient height of 6 feet or more, and anatomical variants or tissue findings that require better visualization, manipulation with more rigid instruments or conversion to an open approach. The procedure applies standard laparoscopic principles and was quickly adopted by surgeons in training.

A Host of Benefits, Including Likely Cost Savings

In general, we have found that this single-port cholecystectomy technique provides equivalent results to conventional, four-port laparoscopic cholecystectomy. Operative times are comparable to, if not shorter than, those with standard cholecystectomy. The use of smaller and fewer skin incisions results in less postoperative discomfort and offers improved cosmetic results. Preliminary cost analysis suggests that even while this technique maintains the highest standards of safety and outcome, it appears to offer cost savings through reduction of costly operative devices and shortening of operative time and hospital stay.

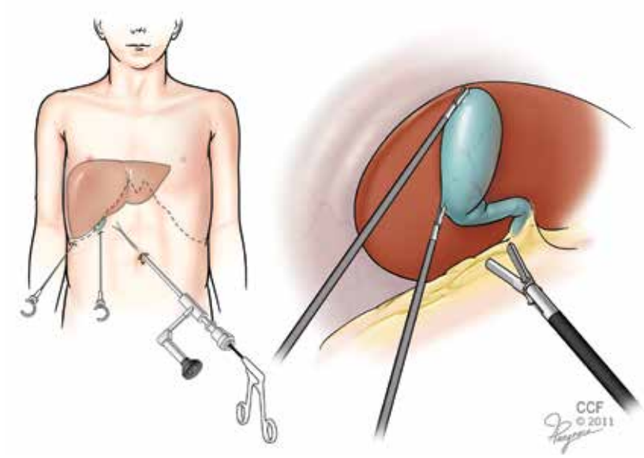


Figure 1. Instrument and trocar placement in the single-port cholecystectomy technique.

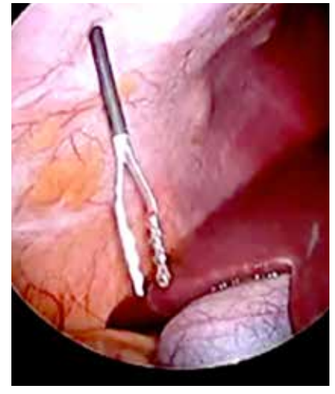


Figure 2. Intraoperative photo showing introduction of the Clutch Graspers into the peritoneal cavity through a stab incision in the right subcostal area.

REFERENCE

1. Seifarth FG, Ramirez JR, Magnuson DK. Hybrid single-port cholecystectomy in children. *JSLS.* 2012;16:401-405.

ABOUT THE AUTHOR

Dr. Seifarth (seifarf@ccf.org; 216.444.8042) is a staff surgeon in the Department of Pediatric General Surgery.

PERSPECTIVE

Quick Takes on the Single-Port Cholecystectomy Technique

2010 Year developed and first used at Cleveland Clinic Children's

124 Number of times technique used (as of December 2014)

Indications:
- Gallstones
- Gallbladder dysfunction
- Gallbladder inflammation and infection

Relative contraindications:
- Presence of severe scar tissue
- Patient height > 6 feet
- Anatomical variations that demand better visualization or tissue manipulation

Transitional Urology: Bringing Continuity of Care to Balance Complex Needs of Adolescents with Congenital Genitourinary Defects

By Hadley Wood, MD

Defects in the genitourinary tract are among the most common congenital problems. Affected children can have problems such as abnormal size, shape or location of their genitals or lack of proper function. They may be missing reproductive organs or have duplicates of an organ. Patients with neurological conditions such as cerebral palsy or spina bifida often have substantial urological comorbidity.

During youth and adolescence, these patients typically are treated by pediatric specialists, including pediatric urologists, who primarily focus on renal deterioration, incontinence and genital appearance.

Improvements in pediatric care have enabled more patients with genitourinary defects to survive into adulthood and enjoy a higher quality of life. As they grow older, many patients are better served by being transitioned into adult-centered care (Figure). Such a transition can allow physicians to focus on the medical, psychosocial and educational aspects of these patients' unique maturation issues, such as sexuality, fertility or postpubertal genital function and appearance.

Timing the Transition

Pediatric specialists have an integral role in deciding when to begin transitioning patients and helping them make the change. In some cases, they remain an important part of the patient's healthcare team even after transition has occurred.

I am often asked when transition should begin. My typical answer: "When everyone is ready." Transition requires agreement from all parties — the patient, his or her personal caregivers and the providers. The process can take several years, so starting as early as age 12 allows ample time for full readiness by age 18 to 20. Many pediatric facilities do not permit patient admission beyond age 24 or 26, so this often represents the upper age limit for transition.

Transition typically involves a stepwise process in which pediatric providers regularly assess the patient's readiness. Factors to consider include the patient's cognitive level and ability to assist in his or her care, as well as whether the patient's urological issues are of an adult nature, such as those related to sexual activity or pregnancy.

Pediatric providers should document the findings of their readiness assessment and initiate conversations with all involved about the optimal timing for transition. They should help the youth identify an appropriate adult-care provider and, after obtaining consent, communicate with that provider about the pending transfer of care and share medical records.

After the patient has begun seeing the adult-care provider, pediatric providers should follow up to confirm that the transfer of care has occurred, answer any questions and offer ongoing consultation as needed.

Forgoing Transition Can Be a Mistake

Simply transferring these patients into any adult urology practice can be a mistake, as adult-care providers often lack specialty expertise in congenital anomalies and the clinical resources to treat these very complex patients. Transitional urology and urological congenitalism often require an approach more akin to geriatrics or palliative medicine, since the patient has many competing medical issues that must be considered to achieve optimal outcomes.

Diagnoses that fit into this category include:

- Myelomeningocele (spina bifida)
- Exstrophy
- Hypospadias
- Disorders of sexual differentiation (intersex)
- Posterior urethral valves
- Pediatric cancer
- Problems (such as muscular dystrophies) that affect the urological system with progression of age

These patients are not typical new consults. Initial examinations can be difficult and may need to be conducted under anesthesia to define the anatomy thoroughly. These patients often have been heavily dependent on family members for daily care, so taking a history may require two interviews: one with the caregivers present and one with them outside the exam room. As these patients begin to assume a decision-making role after a lifetime of others being in charge of their care, recognize that the change may cause some tension for patients and their caregivers.

Transitional urology and urological congenitalism often require an approach more akin to geriatrics or palliative medicine, since the patient has many competing medical issues that must be considered to achieve optimal outcomes.

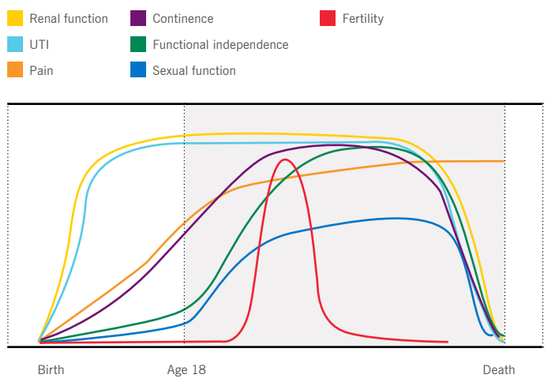


Figure. Schematic showing the relative importance of urological and other health issues throughout the life span of a patient with myelomeningocele. As in most conditions involving congenital genitourinary defects, the patient's needs change in character after puberty and into adulthood, underscoring the need for continued full-spectrum urological expertise throughout postpubertal life.

Balancing Patients' Needs and Goals

Patients often present with a single focus of interest, such as erection quality, whereas I may be more concerned with other urological issues that seem more critical, such as worsening hydronephrosis. Addressing both takes time and, sometimes, careful negotiation.

After gathering a full medical history, I perform a thorough baseline assessment of patients' urological health and ask about their goals and how their urological issues affect their quality of life. From there, we jointly begin to map out treatment plans.

These are just a few highlights of what transitional urology offers and how it can be a valuable resource for pediatricians and pediatric urologists with young adult patients whose needs have expanded beyond those of childhood. Pediatric providers are central to making the transition a success, as they help lay the groundwork for transition, perceive the patient's readiness for it and ultimately connect the patient with the right provider for the next phase of his or her life.

PERSPECTIVE

Sampling of Conditions That Transitional Urologists Manage

- Urinary incontinence
- Catheterization problems, including stomal stenosis or urethral strictures
- Penile curvature with erections
- Abnormalities of penile appearance
- Problems resulting from abnormal vaginal development
- Renal insufficiency due to kidney scarring
- Kidney stones
- Increased bladder cancer risk
- Male and female infertility
- Hernias from prior surgeries
- Chronic constipation from neurogenic bowel

ABOUT THE AUTHOR

Dr. Wood (woodh@ccf.org; 216.444.2146), a urologic surgeon with a specialty interest in adolescents, practices in the Center for Genitourinary Reconstruction.

New 'Be Well Kids Clinic' Provides a Platform for Research into the Features and Treatment of Childhood Obesity

By Naim Alkhouri, MD, and Sara Lappé, MD, MS

The prevalence of childhood obesity has reached epidemic levels in the United States in recent years. To better address the resulting challenges, Cleveland Clinic Children's established the Be Well Kids Clinic in April 2013 to provide long-term management of overweight and obese children. At this comprehensive, multidisciplinary clinic, children undergo an extensive baseline evaluation to determine obesity-related medical problems and then participate in a weight management program that involves dietary and behavioral modifications, exercise and, when indicated, medications.

In addition to this core clinical mission, the Be Well Kids Clinic is facilitating enhanced research into childhood obesity by Cleveland Clinic Children's researchers. We profile here two research studies that have emerged from the clinic so far: (1) an examination of the comorbidity profile of initial clinic enrollees and (2) experience from one of the earliest reported uses of a protein-sparing modified fast diet in an adolescent population in the outpatient setting.

Snapshot of Obesity-Related Comorbidities: Common, Often Underdiagnosed

Obese children may have obesity-related comorbidities such as hypertension, dyslipidemia, diabetes, nonalcoholic fatty liver disease (NAFLD), asthma, obstructive sleep apnea, insulin resistance and others.

To determine the prevalence of such comorbidities in the Be Well Kids Clinic population, we conducted a cross-sectional study involving all children (N = 290) seen at the clinic from its April 2013 opening to May 2014. Data collected included anthropometric measures, family and medical history, examination findings and laboratory results.

The population's demographic profile was as follows:

- Mean age, 11.4 ± 7.4 years
- Mean BMI, 98th percentile (range, 87.2-99.9)
- 60 percent female
- 55 percent Caucasian

We found the following prevalences for common comorbidities:

- Hypertension, 12 percent
- Prediabetes, 22 percent; diabetes, 2.3 percent
- Dyslipidemia, 60 percent (either HDL < 40 mg/dL, LDL > 110 mg/dL, triglycerides > 150 mg/dL or total cholesterol > 200 mg/dL)
- NAFLD, 54 percent among patients undergoing abdominal ultrasound
- History of obstructive sleep apnea, 13 percent
- History of asthma, 23 percent

Among children older than 10, 25 percent met International Diabetes Federation criteria for metabolic syndrome. Additionally, 43 percent of patients had elevated ultrasensitive CRP (> 3 mg/L), indicating chronic inflammation and potentially increased cardiovascular risk. Females had a significantly higher prevalence of insulin resistance (50 percent vs. 33 percent in males; $P = .014$).

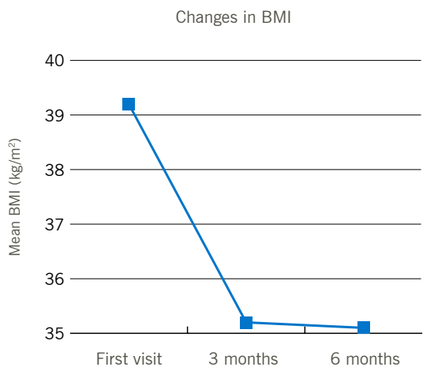
Analysis of the total number of known comorbidities mentioned above revealed that three-quarters of patients had at least one comorbidity and nearly half had two or more (Table). Our patients had higher rates of dyslipidemia as well as prediabetes and diabetes than nationally representative data.[1] This may

Table. Prevalence of Multiple Comorbidities Among Enrollees in the Be Well Kids Clinic

Number of Comorbidities	Share of Enrollees
0	25.3%
1	29.8%
2	26.6%
3	12.8%
4	3.1%
5	1.4%
6	1.0%

Cleveland Clinic Children's is one of the few tertiary care centers that offer the protein-sparing modified fast (PSMF) diet for rapid weight loss in severely obese adolescents.

Figure. Graph showing changes in BMI among severely obese adolescents (N = 12) on the protein-sparing modified fast (PSMF) diet.



be due to the fact that 55 percent of our patients were severely obese and would thus be expected to have a higher prevalence of comorbidities. Notably, many of these comorbidities were not diagnosed until patients were evaluated in the Be Well Kids Clinic, which suggests that in addition to being exceedingly common, comorbidities in obese children may often be underdiagnosed by pediatricians.

A Pioneering Study of the PSMF Diet in Severely Obese Adolescents

The protein-sparing modified fast (PSMF) diet is a rigorous way of rapidly losing a large amount of body weight. It involves eliminating all carbohydrates and added fats while obtaining nutrition from lean meat, poultry and seafood (hence "modified fast"). The PSMF diet requires close monitoring and a multidisciplinary approach. Data on the use of this diet in adolescents are limited, and some centers require hospital admission for the diet.[2]

Candidates for the diet are severely obese adolescents who have reached skeletal maturity. A dietary assessment is taken at the initial visit to provide patients with a strict dietary regimen and instructions, including a food plan outlining daily nutrient intake. Patients are monitored with frequent laboratory testing to avoid electrolyte imbalances. Patients attend medical visits biweekly during the first month and then on a monthly basis until weight loss goals are achieved. Typically, the PSMF diet is used for three to six months followed by a refeeding phase.

At the Be Well Kids Clinic, we placed 12 adolescents (mean age, 16 ± 2.8 years) with severe obesity on the PSMF diet and followed them for six months. At the three-month follow-up visit, mean weight loss was 9.5 kg (range, 4.1-15.5), and there was a remarkable decrease in mean BMI by six months, from 39.2 to 35.1 kg/m² (Figure). Improvements were also noted in total and HDL cholesterol levels. Side effects reported were nausea (n = 2), decreased energy (n = 1) and transient labile mood (n = 1). Mild weight gain was noted during the refeeding phase over six to eight weeks as patients returned to a more balanced diet with guidance from our medical team.

After patients complete the PSMF diet, we continue to see them in the Be Well Kids Clinic to work on maintaining a healthy diet and weight. Cleveland Clinic Children's is one of the few tertiary care centers that offer the PSMF diet for rapid weight loss in severely obese adolescents. We plan to continue to study use of the diet in this population to gain further knowledge on its safety and to compare long-term patient outcomes with this severely restrictive diet relative to outcomes following other specialized diets and bariatric surgery.

REFERENCES

1. May AL, Kuklina EV, Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999-2008. *Pediatrics.* 2012;126(6):1035-1041.
2. Koeck E, Davenport K, Barefoot LC, et al. Inpatient weight loss as a precursor to bariatric surgery for adolescents with extreme obesity: optimizing bariatric surgery. *Clin Pediatr (Phila).* 2013;52(7):608-611.

ABOUT THE AUTHORS

Dr. Alkhouri (alkhoun@ccf.org; 216.445.7126) is a staff physician in the Department of Pediatric Gastroenterology and Co-Director of the Be Well Kids Clinic.

Dr. Lappé (lappes@ccf.org; 216.445.1710) is a staff physician in the Department of General Pediatrics and Co-Director of the Be Well Kids Clinic.

STAFF

Our Referring Physician Hotline, 855.REFER.123 (855.733.3712), provides 24/7 access to information on Cleveland Clinic Children's more than 300 pediatricians and pediatric subspecialists.

LEADERSHIP TEAM

Giovanni Piedimonte, MD
Chairman and Physician-in-Chief, Cleveland Clinic Children's
President, Cleveland Clinic Children's Hospital for Rehabilitation

Michael McHugh, MD
Executive Vice Chair, Cleveland Clinic Children's

Camille Sabella, MD
Vice Chair, Education

Elaine Schulte, MD
Vice Chair, Mentoring and Development

Deborah Lonzer, MD
Vice Chair, Outpatient Operations

Vera Hupertz, MD
Vice Chair, Quality and Safety

Katherine Dell, MD
Director, Clinical and Translational Research

Blanca Gonzalez, MD
Co-Director, Pediatric Clerkship

Skyler Kalady, MD
Co-Director, Pediatric Clerkship

Wendy Van Ittersum, MD
Director, Pediatric Fellowship Programs

Charles Kwon, MD
Director, Pediatric Residency Program

Amrit Gill, MD
Patient Safety Officer

Alec Kulik
Administrator

ADOLESCENT MEDICINE

Ellen Rome, MD, MPH
Head

ALLERGY AND IMMUNOLOGY

Al Melton Jr., MD
Head
Sheila Armogida, MD
Sandra Hong, MD
Lisanne Newton, MD
Velma Paschall, MD
Christine Radojicic, MD
Brian Schroer, MD
Roxanne Siles, MD
Ahila Subramanian, MD
Rachel Szekely, MD

ANESTHESIOLOGY

Stephen Kimatian, MD
Chair
Alina Bodas, MD
Pilar Castro, MD
Tara Hata, MD
Sara Lozano, MD
Dorothea Markakis, MD
Marco Maurtua, MD
Julie Niezgoda, MD
Nelson Riveros, MD
Shelly-Anne Rodriguez, MD
Kenneth Saliba, DO
John Seif, MD
Wai Sung, MD
E. Christian Tucker, MD

AUTISM

Thomas Frazier, PhD
Director
Leslie Markowitz, PsyD
Leslie Speer, PhD

BEHAVIORAL HEALTH

Michael Manos, PhD
Head
Gerard Banez, PhD
Ethan Benore, PhD, BCB, ABPP
Cara Cuddy, PhD
Wendy Cunningham, PsyD
Kristen Eastman, PsyD
Kate Eshleman, PsyD
Thomas Frazier, PhD
Catherine Gaw, PsyD
Vanessa Jensen, PsyD
Eileen Kennedy, PhD
Kathleen Laing, PhD
Katherine Lamparyk, PsyD
Amy Lee, PhD
Alana Lopez, PhD
Leslie Markowitz, PsyD
Beth Anne Martin, PhD
Alison Moses, PhD
Pamela Senders, PhD
Sandra Sommers, PhD
Leslie Speer, PhD

BRAIN TUMOR AND NEURO-ONCOLOGY

Erin Murphy, MD
Violette Recinos, MD

CARDIOLOGY

Peter Aziz, MD
Gerard Boyle, MD
Thomas Edwards, MD
Francine Erenberg, MD
Alex Golden, MD
Rukmini Komarlu, MD
S. Ken Mehta, MD
Adriana Prada-Ruiz, MD
Tamar Preminger, MD
Lourdes Prieto, MD
Marcy Schwartz, MD
Ernest Siwik, MD
Patcharapong Suntharos, MD
Kenneth Zahka, MD

CARDIOTHORACIC SURGERY

Gösta Pettersson, MD, PhD
Chair
Robert Stewart, MD, MPH

CRITICAL CARE MEDICINE

Letitia Castillo, MD
Chair
Kshama Daphtary, MD
Steve Davis, MD
Chidebere Ezetendu, MD
Michael McHugh, MD
Keshava M.N. Narayana Gowda, MD
Patricia Raimer, MD
Sue Sreedhar, MD

DERMATOLOGY

Allison Vidimos, MD
Chair
Douglas Kress, MD
Joan Tamburro, DO

DEVELOPMENTAL PEDIATRICS / PHYSICAL MEDICINE AND REHABILITATION

Douglas Henry, MD
Director
Carol Delahunty, MD
Benjamin Katholi, MD
Virmarie Quinones-Pagan, MD

ENDOCRINOLOGY

Douglas Rogers, MD
Director
Anzar Haider, MD
Nouhad Raissouni, MD
B. Michelle Schweiger, DO
Laurie Tsilianidis, MD

EPILEPSY

Ajay Gupta, MD
Head
William Bingaman, MD
Tatiana Falcone, MD
Jorgé Gonzalez-Martinez, MD, PhD
Jennifer Haut, PhD, ABPP-CN
Patricia Klaas, PhD
Prakash Kotagal, MD
Ahsan Moosa Naduvil Valappil, MD
Elia Pestana Knight, MD
Elaine Wyllie, MD

GASTROENTEROLOGY

Marsha Kay, MD
Chair
Naim Alkhouri, MD
Lisa Feinberg, MD
Rishi Gupta, MD
Vera Hupertz, MD
Barbara Kaplan, MD
Lori Mahajan, MD
Kadakkal Radhakrishnan, MD
Rita Steffen, MD
Robert Wyllie, MD

GENETICS

Charis Eng, MD, PhD
Chair
Rocio Moran, MD
Director
Angelika Erwin, MD, PhD
Timothy Moss, MD, PhD
Marvin Natowicz, MD, PhD
Vickie Zurcher, MD

GYNECOLOGY (PEDIATRIC AND ADOLESCENT)

Marjan Attaran, MD
Head

HEMATOLOGY, ONCOLOGY AND BLOOD & MARROW TRANSPLANTATION

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

HOSPITAL MEDICINE

Michelle Marks, DO
Chair
Moises Auron, MD
Nella Blyumin, MD
Julie Cernanec, MD
Rolly Chawla, MD
Julia Frantsuzov, MD
Amrit Gill, MD
Sangeeta Krishna, MD
Jennifer Marcy, MD
Rita Pappas, MD
Katie Pestak, DO
Shannon Phillips, MD, MPH
Rajyalakshmi Rambhatla, MD
Colleen Schelzig, MD
Christine Traul, MD
Wendy Van Ittersum, MD
Elena Wahmhoff, MD
Marin Waynar, MD
Kathryn Weise, MD
Maohe Yan, MD
Arnaldo Zayas-Santiago, MD

INFECTIOUS DISEASES

Camille Sabella, MD
Head
Charles Foster, MD
Johanna Goldfarb, MD
Blanca Gonzalez, MD

NEONATOLOGY

Ricardo Rodriguez, MD
Chair
Jalal Abu-Shaweesh, MD
Hany Aziz, MD
Vladimir Burdjalov, MD
Marita D'Netto, MD
Michelle Elias Ruiz, MD
Sabine Iben, MD
Sreenivas Karnati, MD
Wasim Khasawneh, MD
Yoav Littner, MD
Ajith Mathew, MD
Marina Perez-Fournier, MD
Jennifer Peterson, MD
Subhash Puthuraya, MD
Firas Saker, MD
Jeffrey Schwersenski, MBChB
Natalie Yeaney, MD
William Zaia, MBChB, DCH

NEPHROLOGY

Charles Kwon, MD
Head
Raed Bou Matar, MD
Charles Davis, MD
Katherine Dell, MD
Halima Janjua, MD

NEUROLOGY

Neil Friedman, MBChB
Director
Mohammed Aldosari, MD
Gary Hsich, MD
Sudeshna Mitra, MD
Manikum Moodley, MBChB, FCP, FRCP
Sumit Parikh, MD
A. David Rothner, MD

NEUROSURGERY

William Bingaman, MD
Jorgé Gonzalez-Martinez, MD, PhD
Kambiz Kamian, MD
Mark Luciano, MD, PhD
Violette Recinos, MD

OPHTHALMOLOGY

Elias Traboulsi, MD
Head
Fatema Ghasia, MD
Andreas Marcotty, MD
Jonathan Sears, MD
Arun Singh, MD

ORTHOPAEDIC SURGERY

Ryan Goodwin, MD
Director
R. Tracy Ballock, MD
David Gurd, MD
Thomas Kuivila, MD
Paul Saluan, MD

OTOLARYNGOLOGY

Paul Krakovitz, MD
Head
Samantha Anne, MD
Brandon Hopkins, MD

PALLIATIVE MEDICINE

Christine Traul, MD
Director
Julia Frantsuzov, MD
Gary Hsich, MD
Michelle Marks, DO
Sue Sreedhar, MD

PLASTIC SURGERY

Francis Papay, MD
Chair
Bahar Bassiri Gharb, MD, PhD
Mark Hendrickson, MD
Antonio Rampazzo, MD, PhD

PRIMARY CARE PEDIATRICS

Deborah Lonzer, MD
Chair, Community Pediatrics
Elaine Schulte, MD
Chair, General Pediatrics

PSYCHIATRY/PSYCHOLOGY

Joseph Austerman, DO
Head
Manish Aggarwal, MD
Venna Tripathi Ahuja, MD
Tatiana Falcone, MD
Jennifer Haut, PhD, ABPP-CN
Patricia Klaas, PhD
Barry Simon, DO
Mackenzie Varkula, DO
Molly Wimbiscus, MD

PULMONARY MEDICINE

John Carl, MD
Head
Silvia Cardenas Zegarra, MD
Nathan Kraynack, MD
Giovanni Piedimonte, MD
Frederick Royce Jr., MD

RADIATION ONCOLOGY

John Suh, MD
Chair
Samuel Chao, MD
Erin Murphy, MD

RADIOLOGY & NEURORADIOLOGY

Paul Ruggieri, MD
Director
Stephen Jones, MD, PhD
Brooke Lampl, DO
Ihsan Mamoun, MD
Doksu Moon, MD
Ellen Park, MD
Unni Udayasankar, MD
Neil Vachhani, MD
Esben Vogelius, MD

RHEUMATOLOGY

Andrew Zeft, MD
Head
Vibha Anand, PhD
Robert Rennebohm, MD
Steven Spalding, MD

SLEEP DISORDERS

Sally Ibrahim, MD
Frederick Royce Jr., MD

SPORTS MEDICINE

Mark Schickendantz, MD
Director
Jack Andrish, MD
John Bergfeld, MD
Alan Davis, MD
Carly Day, MD
Lutul Farrow, MD
Richard Figler, MD
Jason Genin, DO
Kim Gladden, MD
Morgan Jones, MD
Susan Joy, MD
Anthony Miniaci, MD
Richard Parker, MD
Vernon Patterson, DO
Anne Rex, DO
Kelly Richter, MD
James Rosneck, MD
Paul Saluan, MD
Kurt Spindler, MD
Kim Stearns, MD
James Williams, MD

SURGERY

David Magnuson, MD
Chair
Anthony DeRoss, MD
Federico Seifarth, MD

TRANSPLANT

Nathan Kraynack, MD
Director, Pediatric Transplant Center
Medical Director, Lung & Heart-Lung
Gerard Boyle, MD
Medical Director, Heart & Heart-Lung
Rabi Hanna, MD
Medical Director, Blood and Marrow
Vera Hupertz, MD
Medical Director, Liver
Charles Kwon, MD
Medical Director, Kidney
Kadakkal Radhakrishnan, MD
Medical Director, Intestinal/ Multivisceral & Pancreas

UROLOGY

Jeffrey Donohoe, MD
Audrey Rhee, MD
Hadley Wood, MD

Referring Physician Hotline

24/7 access to information on Cleveland Clinic Children's specialists and services

855.REFER.123 (855.733.3712)

PEDIATRIC PERSPECTIVES | 2014-2015

Katherine Dell, MD, *Medical Editor*
Glenn R. Campbell, *Managing Editor*
Chip Valleriano, *Art Director*
Tom Merce, Steve Travarca, *Principal Photographers*

Please direct correspondence to Katherine Dell, MD, at dellk@ccf.org.

Resources for Pediatricians

Stay Connected with Cleveland Clinic Children's

Consult QD – Pediatrics
A blog featuring insights and perspectives from Cleveland Clinic Children's experts. Visit today and join the conversation.
consultqd.clevelandclinic.org/pediatrics

Facebook for Medical Professionals
Facebook.com/CMEClevelandClinic

Follow us on Twitter
@CleClinicMD

Connect with us on LinkedIn
clevelandclinic.org/MDlinkedin

On the Web at
clevelandclinicchildrens.org

24/7 Referrals

24/7 Hospital Transfers/Admissions
Children's hospital, main campus
216.448.7000 or 866.547.1467

Cleveland Clinic Children's Hospital for Rehabilitation
216.448.6400 or 800.635.2417

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

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

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.

The Cleveland Clinic Way
By Toby Cosgrove, MD, CEO and President, Cleveland Clinic

Great things happen when a medical center puts patients first. Visit clevelandclinic.org/ClevelandClinicWay for details or to order a copy.

About Cleveland Clinic

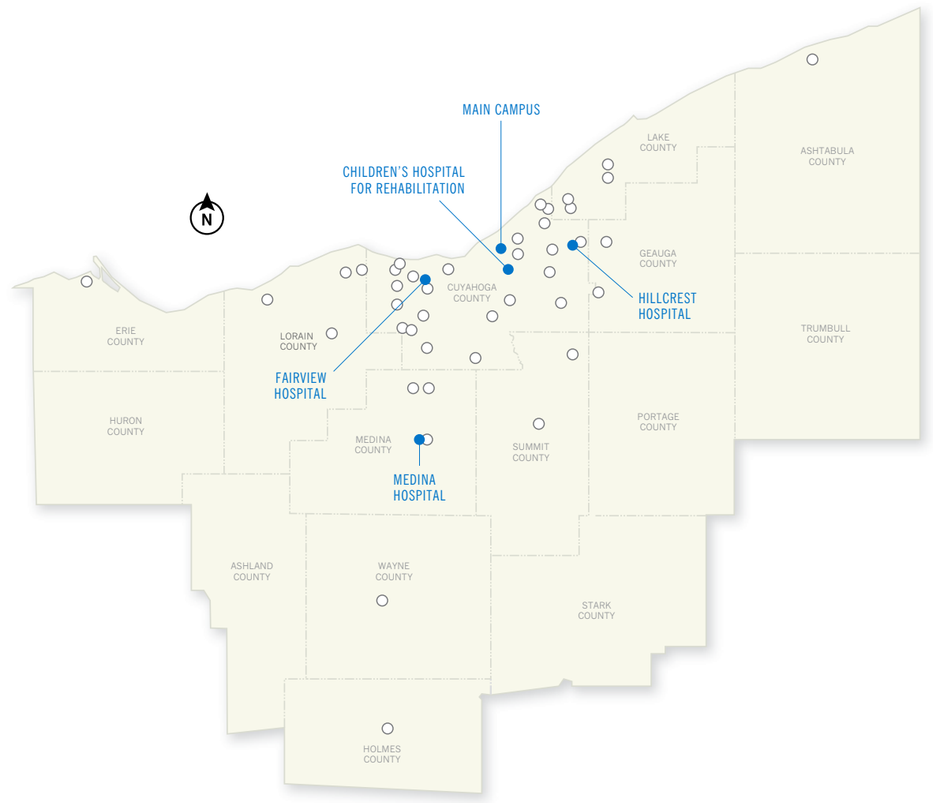
Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2014, Cleveland Clinic was ranked one of America's top four 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 20th consecutive year) and urologic care.

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

Cleveland Clinic Children's Locations

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



Highlights of our facilities and broad-ranging services include:

- 429 pediatric beds (overall)
- 87 level III NICU beds at our main campus and Fairview and Hillcrest hospitals
- 52 beds at Cleveland Clinic Children's Hospital for Rehabilitation
- 24/7 pediatric EDs at Fairview and Hillcrest hospitals
- Special Delivery Unit on our main campus
- Pediatric dialysis unit at our 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 Northeast Ohio thanks to Cleveland Clinic Children's Critical Care Transport fleet. To arrange a pediatric transfer from anywhere in the world, call 216.448.7000 or 866.547.1467.

Cleveland Clinic Children's

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

BEST CHILDREN'S HOSPITALS
U.S.News & WORLD REPORT
RANKED IN 10 SPECIALTIES
2014-15

Coming in June: Pediatric Innovation Summit

Cleveland Clinic Children's Pediatric Innovation Summit
June 11-13, 2015

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

Join us for Cleveland Clinic Children's second annual evidence-based review of pediatric care topics recently impacted by new data, screening tools or therapies. Sessions across the three-day CME-certified program focus on in-depth analysis of the crucial data and their practice implications.

Faculty are drawn from Cleveland Clinic Children's expert staff and other leading institutions and societies.

PROGRAM HIGHLIGHTS

Two full-day symposium options on Thursday, June 11:

- The 8th Annual Helen and Ronald Ross Symposium on pediatric congenital heart disease
- A nursing symposium exploring the latest advances in managing common pediatric conditions

A core summit program featuring:

- An immunization update focused on recommendations and controversies
- A spirited review of the year's top 10 pediatric papers
- Updates on topics from early and late puberty to enterovirus D68 and many more
- In-depth workshops on sports-related health, celiac disease, periodic fever syndromes and more
- A panel discussion — "The Future of Pediatric Healthcare" — featuring nationally prominent guest faculty

A half-day autism/ADHD symposium the afternoon of Saturday, June 13

- Reviews of the latest screening and management options for autism
- Strategies for combining pharmacotherapy and behavioral therapy for optimal ADHD outcomes

Attendees may register for the entire three-day summit or just for the one or two days of greatest interest.

Visit **ccfcme.org/pediatrics** for full program and registration/accommodation information.

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

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

CLEVELAND CLINIC CHILDREN'S | PEDIATRIC PERSPECTIVES | 2014-2015

Spine art ...
Width TBD!