University Hospitals
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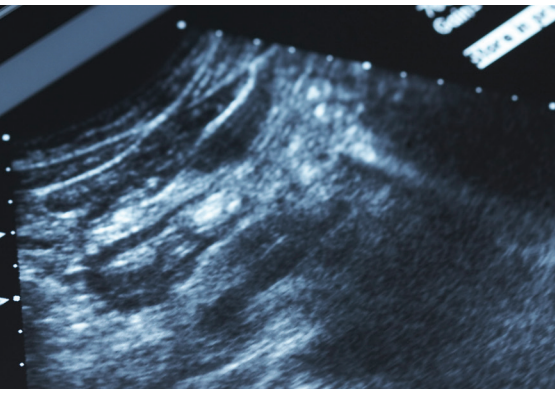
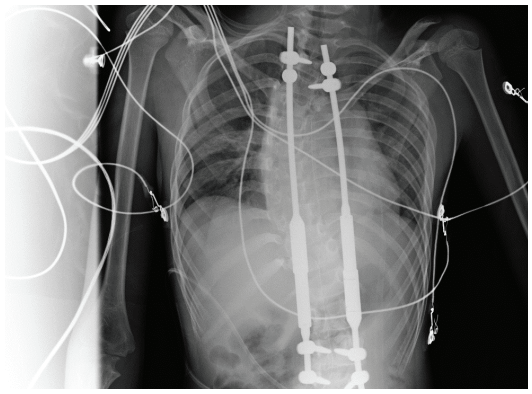
Rainbow Babies & Children's Hospital

School of Medicine
Case Western Reserve University

INNOVATIONS IN PEDIATRICS





BEST CHILDREN'S HOSPITALS
U.S.News & World Report
NEONATOLOGY 2015-16
Ranked #3 in Neonatology

THE LEAPFROG GROUP
TOP CHILDREN'S HOSPITAL 2015
Recognized for Top Quality

WINTER 2016

Sparing the Scalpel

Newly approved devices decrease repeated surgeries for children with early-onset scoliosis

Surgical treatment for early-onset scoliosis (EOS) has typically been limited to attaching growing rods to the spine, with repeat surgeries every six months to manually move the rods and allow for growth.

"Kids who develop scoliosis early in life have lots of growth left," says Christina Hardesty, MD, a pediatric orthopaedic surgeon at University Hospitals Rainbow Babies & Children's Hospital. "We can't treat them in the typical way by fusing the spine. The chest still needs to grow."

Two newly approved devices, however, are decreasing the need for repeat surgeries among kids with EOS. The Shilla™ growth guidance system, marketed by Medtronic, uses a special nonlocking screw at the top and bottom of the growing rod, allowing correction of the child's curvature by screws that slide along the rod as the child's spine grows.

Another new device, MAGEC®, marketed by Ellipse Technologies, Inc., uses a magnetic device inside the central housing on the growing rod. The orthopaedic surgeon expands the rod painlessly in the clinic via external remote control.

Shilla and MAGEC both received approval from the U.S. Food and Drug Administration (FDA) in September 2014. At UH Rainbow Babies & Children's Hospital, Dr. Hardesty is using both new devices for select patients with EOS.

"These new devices are best for kids whose curves are flexible enough that they can be relatively straight when you start the process," she says. "MAGEC is probably getting more attention at the moment, but Shilla is right behind it."

By reducing the number of surgeries a child needs, these devices reduce hospitalization time, infection risk and anesthesia exposure, likely leading to better outcomes and lower costs.

"With every surgery, risk of infection goes up by 17 percent," Dr. Hardesty says. "That's huge. If you're eliminating these repeat surgeries, you're lowering the risk of infection and you're lowering the risk of the spine healing. Every time we open them up, we risk early fusion of the spine because we're exposing bone. Children are also at a slightly increased risk of decrease in cognitive function when they're exposed to repeat anesthetics."

Dr. Hardesty and her colleague, George Thompson, MD, Division Chief of Pediatric Orthopaedic Surgery at UH Rainbow Babies & Children's Hospital, are documenting outcomes for their Shilla and MAGEC patients as part of the Growing Spine Study Group, the prestigious research consortium addressing EOS. However, Dr. Hardesty says she's already encouraged about the potential of the new devices.

"Fewer surgeries are always better," she says. "These devices represent a lower-risk way of treating EOS that means a slightly more normal life for these kids."

For more information on treatment for EOS or other pediatric orthopaedic services at UH Rainbow Babies & Children's Hospital, email Peds.Innovations@UHhospitals.org.

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The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

A New Tool in the Arsenal

Young cancer patients to benefit from Ohio's first Proton Therapy Center

Patients at University Hospitals Rainbow Babies & Children's Hospital will soon have access to the distinct dosimetric advantages of proton therapy, thanks to a new Proton Therapy Center scheduled to open in summer 2016. Expected to be the first in Ohio and regionally, the Proton Therapy Center between UH Rainbow Babies & Children's Hospital and UH Seidman Cancer Center will accommodate patients from a multistate region. While the Proton Therapy Center will treat adult patients also, pediatric, adolescent and young adult cancer patients at the Angie Fowler Adolescent & Young Adult Cancer Institute at UH Rainbow Babies & Children's Hospital stand to benefit most from this advanced treatment.

"UH Seidman Cancer Center's Proton Therapy Center will be located on the same campus as a nationally ranked children's hospital – one of the only places in the country to achieve that distinction," says David Mansur, MD, Director of Pediatric and Hematologic Radiation Oncology at UH Seidman Cancer Center, who is overseeing the launch of the Proton Therapy Center. "Proton therapy is uniquely suited for treating the pediatric and young adult population.

"While the targeted dose is the same with proton therapy as traditional radiation treatment, proton therapy eliminates potentially significant doses to uninvolved tissues. It eliminates a lot of unnecessary low and intermediate doses, which is especially significant for pediatric patients, many of whom have curable malignancies."

An advanced form of radiation therapy, proton therapy targets tumors more directly and spares much of the surrounding tissue from the side effects of radiation. This targeted therapy can provide advantages for treatment of certain tumors, such as those in the brain, base of skull and in the head and neck. Proton therapy also is effective in treating sarcomas, or cancer of the soft tissue, connective tissue or bone, such as Ewing's sarcoma and rhabdomyosarcoma.

With greater power and precision, however, comes an enhanced focus on patient selection and risk management. "Proton therapy is a more unforgiving treatment," says Dr. Mansur. "With proton therapy, changes in density and tumor motion have a greater potential to introduce uncertainty in the radiation dose than in photon beam cases. We will be exercising caution in proper selection of patients who will benefit the most."

For patients, the differences between traditional radiation therapy and proton therapy are largely invisible. Proton therapy may minimize typical radiation therapy side effects, but patients typically undergo the same number of treatments. While patients may still experience hair loss, fatigue and skin irritation, there is potential to spare patients some adverse side effects. For example, nausea may be reduced in treating a spine tumor because the beam penetrates and stops, rather than exiting out the front of the body and through the stomach, causing nausea.

Participation in clinical trials is expected to be an important component of care for patients treated with proton therapy at UH Seidman Cancer Center. A registry will track outcomes, and the vast majority of patients will be enrolled in a clinical trial.

Dr. Mansur says he's looking forward to the enhanced treatment that proton therapy will offer his pediatric patients, as well as the convenient way they'll be able to access this innovative care. While traditional proton therapy systems cost hundreds of millions of dollars to build and can be as large as a football field, the compact, gantry-mounted design of the Mevion S250™ superconducting synchrocyclotron accelerator being built at UH Seidman Cancer Center requires less space, fewer staff and significantly less energy to operate.

"When you cure a 10-year-old, the hope is that you will have 70 to 80 years of life expectancy," says Dr. Mansur. "It's not magic, but if you can limit the number of patient years of late effects of treatment, it is worth it."

For more information about UH Seidman Cancer Center's new Proton Therapy Center, contact David.Mansur@UHhospitals.org.

DAVID MANSUR, MD

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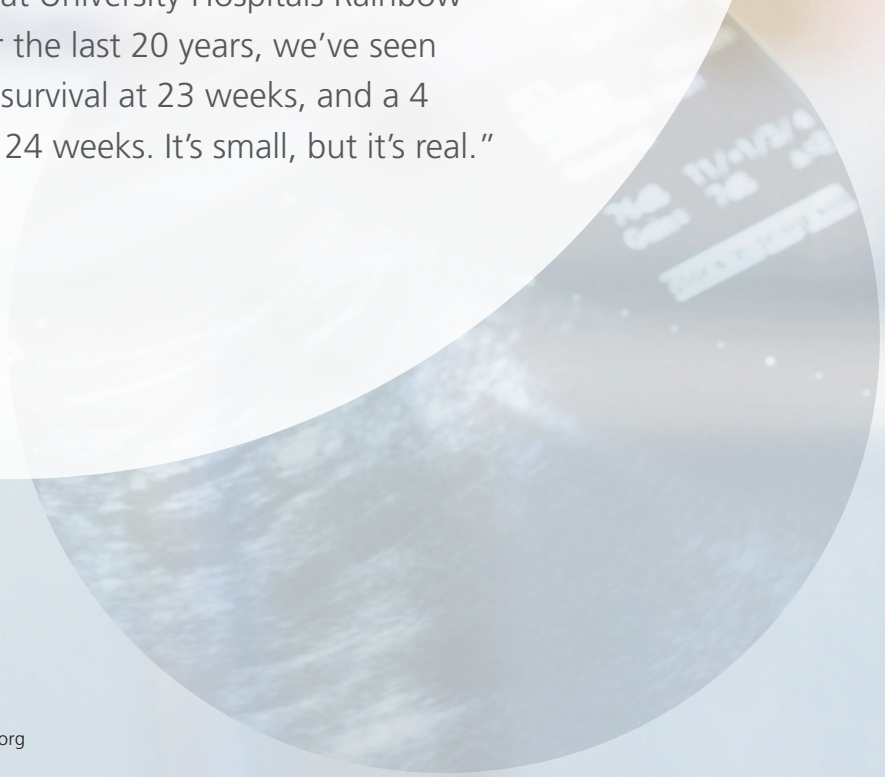
Research shows improving outcomes for some of the tiniest newborns

Preterm *Progress*

Neonatologists have spent the past two decades refining and improving the quality of care for infants born extremely premature. Now, new research suggests these efforts are making a small yet measurable difference, especially for infants born at 23 and 24 weeks.

"It's been a slow and steady increase," says Michele Walsh, MD, MS Epi, Division Chief of Neonatology at University Hospitals Rainbow Babies & Children's Hospital. "Over the last 20 years, we've seen about a 9 percent improvement in survival at 23 weeks, and a 4 percent improvement in survival at 24 weeks. It's small, but it's real."



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Dr. Walsh and fellow members of the National Institutes of Health's (NIH) Neonatal Research Network recently released outcomes data for infants born between 22 and 28 weeks gestation between 1993 and 2012, publishing their findings in the Journal of the American Medical Association. UH Rainbow Babies & Children's Hospital was a founding member of the Neonatal Research Network, under the leadership of former neonatology Division Chief and Principal Investigator Avroy Fanaroff, MD. The hospital has maintained continuous membership in the consortium since 1986, one of only two centers to do so. Dr. Walsh has participated in the network since 1992.

For Dr. Walsh, the new data highlight the synergistic effect of multiple neonatal interventions.

"It's not any one intervention," she says. "It's the increasing sophistication of the high-risk OBs and neonatologists in taking care of them. It's making sure that the moms get antenatal steroids before delivery. It's avoiding injuring their lungs as much as possible and improving their nutritional status by using human milk. The more human milk we are able to get them, the more protected they are from severe infections, both in the bloodstream and in the intestines."

Although the improvements in survival are real, Dr. Walsh says, challenges remain in other areas. "The developmental outcomes for the tiniest ones – the 23- and 24-weekers – are still not what we would want," she says. "Half of them have a significant learning disability or mental retardation."

Dr. Walsh says she hopes the new findings will be used to inform the conversations neonatologists have with parents, especially for those who have infants born in the "gray zone" of 23 or 24 weeks.

"At 25 and 26 weeks, interventions have high rates of survival, with very little disability," she says. "At 22 weeks, most centers offer full resuscitation only in exceptional circumstances. The 23- and 24-weekers are more 'gray.' In that gray zone, we feel it's really important to respect the family's wishes, how the family is involved in what is an agonizing process."

For her part, Dr. Walsh is continuing research into other neonatal interventions. She is co-principal investigator on the Neonatal Research Network's clinical trial of hydrocortisone for the prevention of bronchopulmonary dysplasia. But she's also working the other side of the equation: prevention.

"With existing technologies, we think we're at the lowest limit for how a baby can survive outside the womb," she says. "The next big area of research is new and better methods of preventing preterm birth. Once a treatment has been shown to be beneficial, how can we make sure that everyone who needs that treatment gets it at the right time, in the right place?"

Through the Ohio Perinatal Quality Collaborative, Dr. Walsh and colleagues are working to get one such proven treatment – progesterone – to pregnant women at risk of preterm birth.

"Progesterone is effective in decreasing premature birth if we can get it to the moms early enough, between 16 and 20 weeks," she says. "If you've had a previous preemie and you get progesterone, we believe that we can decrease the chances of having a second preemie. The data shows that very strongly."

She and her UH Rainbow Babies & Children's Hospital colleagues are also exploring ways to reduce the thorny problem of infant mortality in Greater Cleveland.

"It's very complicated, but it has a lot to do with racial disparities," Dr. Walsh says. "African-American babies still have 2.5 times the mortality of white infants. Prematurity is the biggest contributor to that, but sleep practices, poor health on the mother's part, diabetes, obesity and hypertension also contribute. There's also increasing attention being paid to the social determinants of health. Institutional racism, chronic stress, poverty and all of the environmental factors that go along with that are thought to account for about two-thirds of the disparities in infant mortality."

Although the problem is daunting, Dr. Walsh says she and her neonatology team are committed to meeting the challenge.

"Ultimately, we need to find ways to have healthy moms who've made a choice to get pregnant, seek prenatal care and achieve the best health outcomes for themselves and their babies," she says.

For more information on UH Rainbow Babies & Children's Hospital's role in the Neonatal Research Network or Ohio Perinatal Quality Collaborative, email PedsInnovations@UHhospitals.org.

Another Bite at the APPLE

New studies suggest link between vitamin D deficiency and atherosclerosis in pediatric lupus patients

When it launched in 2003, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial aimed to determine whether atorvastatin could slow the progression of atherosclerosis in children, teens and young adults with systemic lupus erythematosus (SLE).

"Kids with lupus grow up to be adults who have early heart attacks, especially women, who are the majority of lupus patients," says Angela Byun Robinson, MD, a pediatric rheumatologist at University Hospitals Rainbow Babies & Children's Hospital. "For a woman with lupus, her risk of having a heart attack is 50 times that of a healthy woman. We don't know when that starts. The APPLE trial was designed to see whether atorvastatin could help decrease that risk."

The APPLE trial showed no significant difference in carotid intima medial thickness (CIMT) between SLE patients taking the statin and those taking a placebo. But the wealth of data gathered in the trial got Dr. Robinson and her colleagues thinking – especially about the role of vitamin D.

"We were interested in looking at vitamin D and how it correlates to disease activity and atherosclerosis in these patients," Dr. Robinson says. "Since lupus patients tend to have low vitamin D and tend to have atherosclerosis, wouldn't it be interesting if there were a link between the two?" The project was funded through a pilot grant from the UH Rainbow Babies & Children's Hospital Department of Pediatrics and a grant from the National Institutes of Health (NIH) to Case Western Reserve University School of Medicine.

In re-analyzing the APPLE trial data, Dr. Robinson and her colleagues have confirmed that vitamin D deficiency and insufficiency are indeed common in pediatric SLE patients, despite many of these patients taking daily vitamin D supplements. Plus, they've shown that patients' vitamin D status is correlated with the inflammatory marker high-sensitivity C-reactive protein (hsCRP) – the first time this has been shown in pediatric lupus patients. These results were published in the journal Lupus Science and Medicine.

"The association between vitamin D deficiency and hsCRP is novel in pediatric lupus and suggests that vitamin D deficiency may contribute to heightened inflammation and cardiovascular risk in this high-risk population," Dr. Robinson says.

In another subgroup analysis, also published in Lupus Science and Medicine, Dr. Robinson and colleagues have shown that pediatric lupus patients with higher vitamin D levels are more likely to benefit from atorvastatin therapy.

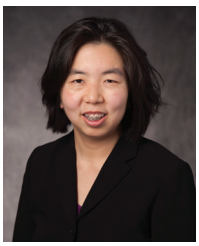
"For the first time in SLE, we find that vitamin D status may affect response to atorvastatin in cardiovascular disease risk and CIMT progression over time," Dr. Robinson says. "These findings suggest that underlying vitamin D deficiency may negatively impact the efficacy of atorvastatin in atherosclerosis prevention."

For Dr. Robinson, these findings point to the need for increased monitoring of vitamin D levels in pediatric lupus patients.

"We should be checking," she says. "There is some suggestion that if you get their vitamin D levels more toward normal, it could be beneficial to them. It's not necessarily part of the standard of care, but more and more of us are checking it frequently. We don't have a great idea of what the optimal vitamin D level should be for these kids, but we do know now that if you are severely deficient, it's not good for your bones, not good for your cardiovascular health and not good in terms of inflammation."

Contact Dr. Robinson at Peds.Innovations@UHhospitals.org.

The research referenced in this article was funded by a pilot grant from UH Rainbow Babies & Children's Hospital and a grant from the National Institutes of Health to Case Western Reserve University School of Medicine.



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Building the **Knowledge Base**

New Children's Oncology Group study provides important insights on adolescent boys with malignant testicular germ cell tumors

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As rare as malignant germ cell tumors are, data on how adolescent boys fare with these cancers is rarer still.

"If you look at testicular tumors in children, there are really two separate groups," says Jonathan Ross, MD, Division Chief of Pediatric Urology at University Hospitals Rainbow Babies & Children's Hospital. "There are little kids, maybe 2 or 3 years old, and the others are teenagers. The problem is that there are very few studies of adolescent testicular cancer. Most pediatric studies exclude them, and most adult studies start including patients at age 18."

However, Dr. Ross and his fellow members of the Children's Oncology Group's (COG) committee on germ cell tumors are working to change that. They've recently published study results including a wider population of testicular cancer patients, ranging in age from infancy to age 15.

Their findings, published recently in the Journal of Pediatric Surgery, show markedly different outcomes between children and teenagers after orchiectomy for stage I testicular cancer.

"What we found is that these patients generally do well, but the older kids don't do nearly as well as the younger kids," Dr. Ross says. For patients under age 11, event-free survival (lack of recurrence) at four years after surgery was 80 percent. For patients age 11 and older, the same metric was only 48 percent.

"Although the overall survival was still 100 percent, the older kids' cancer was more likely to recur," Dr. Ross says.

Histological differences between the tumor types can explain much of this disparity, Dr. Ross says. "Pediatric tumors are almost all pure yolk-sac tumors, whereas adolescents are more likely to have mixed histology with different types of cells in it, which is also more typical of adult tumors."

One potential prognostic factor to emerge from the recent study is lymphovascular invasion – a measure of how aggressive the tumor is locally. For patients without lymphovascular invasion, the recurrence four years after surgery was 16 percent. For those with lymphovascular invasion, the recurrence rate was 38 percent.

"Lymphovascular invasion has been shown in adults to have some predictive value," Dr. Ross says. "In this study, it seemed to correlate, but there were so few patients to analyze, we need to investigate further."

Dr. Ross has served as pediatric urologist on the COG's Germ Cell Tumor Committee for the past 15 years. Going forward, he and other committee members are planning new studies to further develop the knowledge base on these tumors.

"We're working to include all adolescents in future studies, without that age 15 cut-off," he says. "There's so little data about adolescents. My guess is that they'll behave like adult patients, but we don't have a lot of evidence to know for sure. This work dovetails nicely with Rainbow's emphasis on tumors in adolescents and young adults through the Angie Fowler Adolescent & Young Adult Cancer Institute."

The hope is to provide more definitive information about the prognostic factors that matter most for boys and teens with these tumors.

"Going forward, we're going to be able to answer more questions by including more patients," Dr. Ross says. "Our current study wasn't designed to ask the question of whether lymphovascular invasion mattered or not. But now that we have data suggesting that it might be a factor, we can look at it intentionally."

For more information about this study or other COG projects under way at the Angie Fowler Adolescent & Young Adult Cancer Institute at UH Rainbow Babies & Children's Hospital, email Peds.Innovations@UHhospitals.org.

The research referenced in this article was funded by a grant from the National Cancer Institute to Case Western Reserve University School of Medicine.

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WIDENING THE NET

New Primary Ciliary Dyskinesia Center at Rainbow first in U.S. to be site-visited and fully accredited by the PCD Foundation

Pulmonologists estimate that as many as 20,000 patients in North America have the autosomal recessive condition primary ciliary dyskinesia (PCD), but that fewer than 1,000 of these people have received a definitive diagnosis.

"Diagnosis remains a challenge," says pediatric pulmonologist Benjamin Gaston, MD, Director of the new Primary Ciliary Dyskinesia Center at University Hospitals Rainbow Babies & Children's Hospital. "About 70 percent of PCD patients have a positive genetic test, and that number is getting higher every year. But to make a valid diagnosis requires considering several different factors. We consider the specific clinical phenotype, genetics, nasal nitric oxide measurements, and sometimes ciliary structure and function."

Confounding the diagnostic process are the high false-positive and false-negative rates of ciliary biopsy and the clinical precision required to accurately measure nasal nitric oxide.

"Ciliary biopsy is falsely positive about one-third of the time and falsely negative almost as frequently," Dr. Gaston says. "In addition, the nasal nitric oxide test must be done in the proper way. There are errors that can occur with the instrument, the flow rate, the calibration and the patient interface. And even when done properly, it can be easily misinterpreted."

To provide for increased and more reliable diagnosis of PCD, the PCD Foundation has launched a network of approved clinical and research centers across the U.S. The PCD Center at UH Rainbow Babies & Children's Hospital is the first clinical center to earn the PCD Foundation endorsement. Of note, the new center is also the only accredited center in Ohio.

"You need to have an entire team of people dedicated to PCD, including a dedicated nurse," Dr. Gaston says. "You need the technology to do nasal nitric oxide testing properly and be within a children's medical center with an integrated, multidisciplinary team. We're very pleased our center meets these criteria and has been approved by the PCD Foundation."

Dr. Gaston says he hopes the new UH Rainbow Babies & Children's Hospital center will improve diagnosis and treatment for people with PCD. He encourages pediatricians to refer patients to the new center who have at least two of the following four characteristics:

- Heterotaxy/organ(s) backward or partly backward
- Newborn respiratory distress requiring oxygen in a term infant with no other underlying disease
- Chronic nasal congestion beginning in the first year of life
- Chronic cough beginning in the first year of life

Also, patients who've received a diagnosis of bronchiectasis should be evaluated using the PCD Center's nasal nitric oxide test if no definite cause for the bronchiectasis has been identified, Dr. Gaston says.

For more information, contact Peds.Innovations@UHhospitals.org.

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In 2015, UH Rainbow Babies & Children's Hospital again ranked as one of America's Best Children's Hospitals in eight pediatric specialties, including #3 in neonatology, #7 in orthopaedics, #11 in pulmonology and #19 in oncology.

Learn more at Rainbow.org/USNews.

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