INNOVATIONS IN PEDIATRICS

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SPRING 2016
A Wider Lens
Antimicrobial stewardship program at UH defies convention

Antimicrobial stewardship programs have started to gain traction in children’s hospitals in recent years. A 2015 study in the journal Pediatrics reported that between 2004 and 2012, children’s hospitals that implemented formal programs to monitor antibiotic use reduced prescriptions for certain medications by about 8 percent.

Such a program is in place at University Hospitals Rainbow Babies & Children’s Hospital, led by pediatric infectious disease specialist Ankita Desai, MD.

“In the hospital, any prescription for a broad-spectrum antibiotic gets a review,” she says. “Our process ensures the drug is appropriate. We give recommendations to the prescriber to narrow therapy once cultures confirm the micro-organism. We have a pharmacist dedicated to that task.”

However, the program at UH also includes an unexpected element – a focus on increasing the amount of antibiotic-free meat in the hospital’s supply chain.

“Our approach considers antimicrobial stewardship through a wider lens,” says UH Rainbow Babies & Children’s Hospital’s pediatrician Aparna Bole, MD, who also advises the health system’s Office of Sustainability. “We typically think about the clinical environment – our prescription practices and our patient education. But with more than 80 percent of antibiotics in the U.S. being used in agriculture and most of those for nontherapeutic purposes, we believe it only makes sense to make antibiotic-free meat purchasing part of our antimicrobial stewardship mission. There is a growing body of evidence that links the overuse of antibiotics in agriculture to antibiotic resistance in human pathogens.”

Drs. Desai and Bole made this case to UH clinical leaders. As a result, the hospital system now purchases antibiotic-free ground beef, burger patties and chicken for retail cafeterias, patient meals and catering applications. This represents about 20 percent of the total pounds of meat purchased annually, and UH continues to seek more opportunities to expand antibiotic-free meat purchasing. In January, they presented this novel approach in a national webinar to the Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS) collaborative, which focuses on establishing best practices for the use of antimicrobials among hospitalized children.

“Judicious use of antibiotics is a really important public health issue to prevent the incredible burden of antibiotic-resistant infections,” Dr. Bole says. “In order to do that, it really takes collective action, not only in the prescribing setting, in the hospital and in primary care, but also in the agricultural and food purchasing settings. I’m proud to say that Rainbow and UH are real leaders in this arena.”

For more information on how to advocate for more antibiotic-free meat in your hospital system, contact Dr. Desai or Dr. Bole at 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.
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“A respiratory stimulant could be lifesaving,” says Dr. Gaston, who serves as pulmonology Division Chief at UH Rainbow Babies & Children’s Hospital. “It stimulates respiratory drive and overcomes narcotic-induced respiratory depression. Remarkably, it does not blunt analgesia,” he says. “We anticipate that we should be able to get to quite low therapeutic doses in humans with parenteral, transdermal and/or oral preparations. We anticipate reduced hospital costs with this agent and significantly decreased mortality. We therefore believe that our novel respiratory stimulant will be a major breakthrough when it is translated into clinical practice.”

Dr. Gaston’s research is funded by the Harrington Discovery Institute at University Hospitals in Cleveland, Ohio – part of The Harrington Project for Discovery & Development – an international initiative designed to support and encourage innovative physician-researchers who want to help expand and improve the range of medications available to patients.

Initial results with the target compound, performed in close collaboration with pharmacologist Stephen J. Lewis, PhD, Professor of Pharmacology and Pediatrics at the School of Medicine, are encouraging, Dr. Gaston says.

For about a third of children with brain tumors involving visual pathways, their vision deteriorates despite intense treatment. However, new research suggests that survivors of childhood astroglial tumors who experience vision impairment can fare quite well as adults – psychologically, cognitively and economically.

UH Rainbow Babies & Children’s pediatric neuro-oncologist Peter de Blank, MD, MSCE, led a team of researchers that studied 1,233 survivors of childhood brain tumors, about 23 percent of whom had a visual impairment. They found that adult survivors with childhood blindness showed no significant differences in measures of psychological distress, income loss or neurocognitive impairment. Survivors with some remaining vision had no negative effects in any measured outcome. The group published its findings in the journal Cancer. Dr. de Blank is also Assistant Professor of Pediatrics at Case Western Reserve University School of Medicine.

“Taken as a whole, this suggests that adult survivors of astroglial tumors adapt well to early impairment of vision, although survivors with bilateral vision loss may experience worse socioeconomic outcomes,” Dr. de Blank says. “This is promising news for children with optic pathway gliomas who may have permanent vision loss despite our best current therapies. We hope that this study provides some evidence that for many survivors, childhood vision impairment does not have to impact their long-term psychological or socioeconomic outcomes.”

Visual Impairment Doesn’t Deter Survivors of Childhood Brain Tumors, Study Finds

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Dr. de Blank’s and Dr. Wiznitzer’s research was supported by grant funding from the National Institutes of Health to Case Western Reserve University School of Medicine.
When you say the words “proton therapy,” what comes to mind for many physicians is a large, football-field-sized facility that may occupy a city block. The space is necessary to accommodate three or four vaults, but it makes integrating the technology into an existing medical center impractical.

“Typical proton facilities are too large to be well integrated into most existing urban cancer centers, where space is at a premium,” says David Mansur, MD, Director of Pediatric and Hematologic Radiation Oncology at University Hospitals Seidman Cancer Center.

However, proton therapy technology has advanced to the point that creating a smaller superconducting synchrocyclotron is now possible. This novel proton accelerator is gantry-mounted and allows for constructing a single-room, compact facility, deep in the heart of a thriving medical center.

Such a facility is opening this summer at University Hospitals in Cleveland. The new Proton Therapy Center is housed in the space that once held the UH Case Medical Center emergency room, located between UH Seidman Cancer Center and UH Rainbow Babies & Children’s Hospital.

This is not by accident.

“Most proton centers are isolated from the nearest children’s hospital, to some extent,” says Dr. Mansur, who is leading the new Proton Therapy Center. “The goal was to have it physically connected to Rainbow, through a corridor, rather than several miles away or even across the street. Even facilities across the street must rely on ambulance transfer if a child requires emergency transport back to the PICU. Our 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.”

As the first in Ohio and regionally, the Proton Therapy Center will accommodate patients from a multistate region. Adult patients can and will benefit. But the children, teens and young adults treated at the Angie Fowler Adolescent & Young Adult Cancer Institute stand to benefit most.

“Proton therapy is uniquely suited for treating pediatric and young adult population,” Dr. Mansur says. “These patients are at greatest risk for long-term effects from radiation treatment, such as cognitive problems and second cancers.”
The science of proton therapy

To truly understand the benefits of proton therapy requires a quick review of medical physics. Traditional radiation therapy uses X-ray beams. They pass into the patient, to the tumor, then out again through the patient's body. The photons' lack of charge and mass means most of their energy is deposited in normal tissues near the body's surface, as well as areas of the body beyond the site of the cancer. With proton therapy, heavy, charged particles penetrate the tumor. But then they stop. Because protons are energized to specific velocities, the radiation oncologist can determine how deeply in the body they will deposit their maximum energy. Their depth-dose relationship is characterized by the Bragg peak, beyond which no dose is deposited.

The elimination of the exit dose for passively scattered proton beams results in greatly reduced low and intermediate doses to distant, uninvolved normal tissues, but little or no difference in conformality of higher prescription doses immediately surrounding the targeted tissue.

"With the X-ray beam, you get very conformal high dose, but the cost of that is all the lower dose from the exit of all the beams," Dr. Mansur explains. “You can greatly reduce that by using proton therapy. It hugs the targeted area as well as X-rays. It's actually no more precise in the high-dose region. But you can lessen the lower doses, which is significant.”

Indications and outcomes

Proton therapy can provide advantages for treatment of certain tumors, Dr. Mansur says, such as those in the brain, spine, base of skull, and in the head and neck. Proton therapy also is effective in treating sarcomas, such as Ewing's sarcoma and rhabdomyosarcoma. For adults, proton therapy can be a good option for patients with lung cancer and breast cancer. It helps protect delicate lung tissue from damage and helps reduce the radiation dose to the heart among left-sided breast cancer patients.

Numerous studies have compared the dosimetric advantages of proton beam therapy compared with other advanced X-ray treatments. “These studies have demonstrated significantly reduced doses to uninvolved tissues in children with pediatric tumors and adult patients with cancers of the breast, lung and head and neck,” Dr. Mansur says.

Outcomes for pediatric brain tumor patients treated with proton beam therapy have recently been reported with encouraging results. “Long-term follow-up is needed to determine if adverse effects are reduced compared with photon treatments,” Dr. Mansur says. “Subtle differences don’t immediately translate into a clinical endpoint you can measure. Second cancer risk, for example, takes decades to manifest. However, a recent modeling report estimates the risk of a radiation-induced second cancer can be reduced with proton beam therapy, compared with conventional photon radiation therapy.”

Getting ready for patients

Dr. Mansur estimates that the new Proton Therapy Center at UH will treat about 20 to 25 patients a day, when fully operational in July. Patient selection and risk management will be paramount. “Proton therapy is a more unforgiving treatment," he says. "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.”

The center has been undergoing a rigorous installation and quality assurance process for the past year or so. The journey began back in June 2011, when the decision to build the facility was announced. Builders broke ground in September 2013, the vault was completed in June 2014 and the proton accelerator arrived on the scene in June 2015.

It's been a long road, but 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. “Proton therapy is not intended to replace traditional radiation therapy, and it's not right for every cancer patient. But it provides us with another tool in the arsenal,” Dr. Mansur says. “The benefits of proton therapy are most significant in younger patients who have curable cancers and decades of life expectancy ahead of them. It’s not magic, but if you can limit the late effects of treatment, it’s worth it.”

You can learn more about the Proton Therapy Center at UH from Dr. Mansur’s article, “Incorporating a Compact Proton Therapy Unit Into an Existing National Cancer Institute-Designated Comprehensive Cancer Center.” It appeared in the journal Expert Reviews in Anti-Cancer Therapies in September 2014. Visit http://www.ncbi.nlm.nih.gov/pubmed/25109233. For more information, contact Dr. Mansur at Peds.Innovations@UHhospitals.org.
Youth-onset type 2 diabetes is a growing clinical problem, spurred by America’s epidemic of childhood obesity. Unfortunately, there are currently few good approaches for managing these patients. The first and largest randomized clinical trial addressing the issue was the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, reported in The New England Journal of Medicine in April 2012. It found that almost half of participants in the study, all with type 2 diabetes, could not maintain adequate glycemic control while taking metformin alone.

"Within a year, almost 50 percent of them had failed treatment," says Rose Gubitosi-Klug, MD, PhD, Chief of Endocrinology & Metabolism at University Hospitals Rainbow Babies & Children’s Hospital. "This was surprising, because most adults do pretty well on oral medications for five to 10 years. These young ‘type 2s,’ however, were no longer responding to oral medications very early on." Dr. Gubitosi-Klug joined the TODAY study in November 2015, as principal investigator at UH Rainbow Babies & Children’s Hospital.

Now, however, a new analysis of data from the TODAY study is pointing to a more effective predictor for managing these patients. Researchers writing recently in the journal Diabetes Care report that children and adolescents with type 2 diabetes can be divided into two groups, based on their HbA1c levels after a few months on metformin therapy. These levels, in turn, predict the likelihood of treatment success.

Paul McGuigan, RN, a certified diabetes educator and nurse coordinator for the TODAY study, both at UH Rainbow Babies & Children’s Hospital and nationally, was a co-author of the Diabetes Care study.

“Our analysis shows that type 2 diabetes is heterogeneous, with some individuals who are more or less likely to have durable glycemic control on oral therapy,” McGuigan says. “It also shows that HbA1c, after a few months of metformin monotherapy, was the strongest predictor of response.”

For both McGuigan and Dr. Gubitosi-Klug, the new analysis reinforces the importance of early diagnosis of type 2 diabetes in children and teens – and early, aggressive treatment to get HbA1c levels down.

“We believe identifying these kids even earlier, treating them promptly and closely monitoring their A1c levels, may have long-lasting benefits on the progression to requiring additional therapies,” Dr. Gubitosi-Klug says.

It also suggests that current HbA1c targets may be too high for this unique group of young patients.

“In clinical practice, typically the goal is to achieve A1c levels less than 7 to 7.5 percent,” Dr. Gubitosi-Klug says. “But maybe we should be targeting lower. The current study suggests that perhaps we need to push the clock back and be more aggressive once patients are diagnosed or identified as ‘prediabetes.’”

“The bottom line is that teens with type 2 diabetes who don’t attain a nondiabetes A1c after a few months on metformin are at increased risk of losing glycemic control,” McGuigan adds. “The clinician caring for these youth should not be reassured with an A1c that is ‘in target.’”

Building on the TODAY study, Dr. Gubitosi-Klug, McGuigan and their colleagues at other children’s hospitals have begun planning for another study aimed at identifying optimal treatment for children and teens with type 2 diabetes. They’ll continue looking more closely at patients who respond well, while at the same time monitoring the impact of multiple oral medications on glycemic control.

“Many of these oral medications are approved for type 2 diabetes in adults, but none of them have been well studied in pediatrics,” Dr. Gubitosi-Klug says. “There’s a huge knowledge gap. But there’s also a hopeful message here. There are kids who respond really well. We need to know who they are, why they do well and how that can be achieved for all youth.”

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

For more information about UH Rainbow Babies & Children’s Hospital’s role in the ongoing TODAY study, contact Dr. Gubitosi-Klug or Paul McGuigan at Peds.Innovations@UHhospitals.org.

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Evidence Emerges on Neonatal Abstinence Syndrome

Stringent weaning protocol improves outcomes for infants born addicted to opioids, new study finds

Two years ago, neonatology researchers from Ohio’s children’s hospitals had a game-changing insight into neonatal abstinence syndrome (NAS) – the emerging epidemic of infants exposed to opioids in utero. In comparing NAS treatment protocols across six hospitals, they found significant differences in outcomes, publishing their findings in the journal Pediatrics.

“Although we all had protocols, the children’s hospitals that had a shorter length of stay had a very strict weaning protocol for weaning their babies off the drugs,” says Moira Crowley, MD, a neonatologist at University Hospitals Rainbow Babies & Children’s Hospital and one of the study’s authors. “It was really being adherent to the protocol and making people accountable for weaning every day, if the baby allows us to do that.”

In reaction to these findings, the researchers, part of Ohio Children’s Hospital Neonatal Abstinence Syndrome Consortium (OCHNAS), developed a potentially better protocol, designed to humanely and safely wean infants off opioids over a two- to three-week period. They implemented it across all six Ohio children’s hospitals, and now the results are in: Children’s hospitals that adopted the strict weaning protocol decreased duration of opioid treatment from 34 days to 23 days, and decreased inpatient hospital stay from about 32 days to about 24. These results, too, were recently published in the journal Pediatrics. Michele Walsh, MD, MS Epi, Interim Chair of Pediatrics and Division Chief of Neonatology at UH Rainbow Babies & Children’s Hospital, designed the study.

“Two years ago, there was no strong evidence-based treatment for NAS and thus no consensus regarding NAS management,” Dr. Crowley says. “There is still no national consensus on how to treat these babies. However, there is emerging evidence from our work in Ohio.”

Dr. Crowley and her colleagues statewide are working with the Ohio Perinatal Quality Collaborative to spread adoption of the Ohio protocol. It is based on scoring all infants with NAS according to a modified Finnegan scoring system.

“Once they hit a certain score, you start treatment,” Dr. Crowley says. “Once they’re on a steady dose for 48 hours and the infant’s symptoms are controlled, then you start weaning by 10 percent of that highest dose. It should be a 10-day wean. Then we watch the baby for two days off therapy and discharge the baby from the hospital. Any opioid exposure, whether in utero or ex utero, can cause abnormal neurologic development, so limiting the exposure is what we all want to do.”

They’re also promoting the importance of nonpharmacologic measures in the protocol as essential to success.

“Swaddling, low stimulation, encouraging breastfeeding if appropriate and potentially using low-lactose formula or higher-calorie formula can all be helpful,” Dr. Crowley says.

The problem of NAS remains enormous, cutting across all demographic groups and health care settings, from community hospitals to teaching hospitals to children’s hospitals. Plus, for some of these NAS infants, the treatment can be quite complex.

“Many of these babies have polysubstance exposure,” Dr. Crowley says. “For the substances other than opiates, the withdrawal symptoms may be very similar to opiate withdrawal. By using morphine or methadone, we may not be effectively treating withdrawal from these other substances.”

Despite these challenges, however, Dr. Crowley and her colleagues are continuing to ask the questions necessary to arrive at the most humane and effective NAS protocol.

“Can we decrease the length of treatment any more?” she asks. “Can we decrease the dose? There’s been a lot of work done with the methadone part of the protocol. As we learn more about the pharmacokinetics of that drug in neonates, we may be able to decrease the length of treatment even further. But there are still safety issues to address. The best scenario is that physicians become more aware of what medications women are being prescribed while pregnant.”

For more information on the Ohio NAS protocol, contact Dr. Crowley at Peds.Innovations@UHhospitals.org.
MANAGING ANXIETY IN CHILDREN AND TEENS
New toolkit helpful for both pediatricians and parents

Anxiety is fairly common in children and teens, with studies showing the incidence between 8 and 12 percent. Nevertheless, it can sometimes be challenging for pediatricians to diagnose.

"It’s easy to miss, especially in younger children," says Nancy Roizen, MD, Chief of the Division of Developmental-Behavioral Pediatrics and Psychology at University Hospitals Rainbow Babies & Children’s Hospital. “When they’re anxious, these kids become irritable, lose it and have a temper tantrum, which can mask their underlying anxiety.” Dr. Roizen is also Professor of Pediatrics at Case Western Reserve University School of Medicine.

To address this issue, the UH Rainbow Care Network of primary care pediatricians has worked with Dr. Roizen and her division to develop an anxiety "toolkit,” with resources for both pediatricians and parents. For physicians and other clinicians, the toolkit includes evidence-based steps for anxiety management and the Screen for Child Anxiety-Related Disorders (SCARED) questionnaire for children, teens and their parents.

“The SCARED questionnaire is very helpful,” Dr. Roizen says. “It helps the caregiver and clinician understand what’s driving a child’s anxiety, such as whether it’s very school-focused or social-focused.”

For parents, the toolkit includes a fact sheet covering the causes and signs of anxiety disorders, the different types of anxiety disorders and examples of when anxiety is not normal. It also includes a comprehensive treatment overview, emphasizing the role of stress reduction at home and school, physical exercise and cognitive behavioral therapy (CBT). It also includes information for parents on anti-anxiety medications.

“First-line treatment for anxiety is always cognitive behavioral therapy,” Dr. Roizen says. “However, depending on the situation, therapy and medication are much more efficacious together than either alone. The evidence for medication is positive; the evidence for CBT is more positive, but both together have a synergistic effect. It’s the most positive. But first line should be therapy.”

Also featured in the toolkit is an up-to-date list of local agencies that provide anxiety counseling for children and teens, including the insurance plans they accept.

With all of these elements, Dr. Roizen says, the goal is to promote earlier diagnosis and more effective management of anxiety in children and teens.

“What we want to do is intervene and give children, families and the pediatricians they work with the tools they need,” she says. “In the end, we want to give kids tools they can snatch out of their pocket all their lives.”

The UH Rainbow Care Network at UH Rainbow Babies & Children's Hospital has also produced toolkits for pediatricians and parents on mild traumatic brain injury, ADHD, headache and asthma. To request these toolkits, email Peds.Innovations@UHhospitals.org or Corinne.Friend@UHhospitals.org.

The anxiety toolkit was developed by developmental-behavioral pediatricians and psychologists from UH Rainbow Babies & Children's Hospital and the MetroHealth System, with funding from Ohio's Medicaid Technical Assistance and Policy Program (MEDTAPP).

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 orthopedics, #11 in pulmonology and #19 in oncology.

Learn more at Rainbow.org/USNews.