Pediatric Insights

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An Update from the Division of Pediatric Nephrology

In This Issue

UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

American Academy of Pediatrics Releases New Clinical Guidelines on IV Fluid Use in Children

New Guidelines Will Help Prevent Cases of Hyponatremia

In November 2018, the American Academy of Pediatrics (AAP) published the first-ever clinical practice guidelines in the United States for the use of intravenous maintenance fluids in children. The new, evidence-based guidelines are meant, in part, to reduce or prevent as many cases as possible of hyponatremia and its often severe morbidities and mortalities. The literature shows approximately a 15 to 30 percent rate of hyponatremia in children and adults who are hospitalized.

Michael L. Moritz, MD, FAAP, clinical director and director of dialysis in the Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh, was the senior author in the committee that established the guidelines, which in part reflect a clinical practice change Dr. Moritz has pioneered and studied for the past 15 years: namely, the use of isotonic fluids over those of a hypotonic concentration.

"Hypotonic fluids have, unfortunately, been the standard of care in pediatrics for more than 50 years, primarily based on tradition and not on science. I introduced the concept of avoiding hypotonic fluids and using isotonic fluids to prevent hyponatremia about 15 years ago. Since then, numerous studies in thousands of children have demonstrated that isotonic fluids decrease the incidence of hyponatremia from greater than 20 percent to less than 5 percent," says Dr. Moritz.

Action Recommended for Physicians

The "Key Action Statement" from the new guidelines, "Recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia."[1]

Perspectives and Additional Details

"There has never been a clinical practice guideline in the United States for the use of intravenous fluids in children; physician practice heretofore has primarily relied upon tradition. Tradition is not a good substitute for evidence-based science. These new guidelines from the AAP for

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Acute Kidney Injury and eResearch

Emily Joyce, MD, joined the Division of Pediatric Nephrology in July 2017 after completing her residency and fellowship training at UPMC Children's Hospital of Pittsburgh. Dr. Joyce's research is focused on understanding the associations between medications — those that are or may potentially be nephrotoxic — and acute kidney injuries (AKI) in critically ill children receiving treatment in the intensive care unit. AKI rates in children during treatment for critical illness are approximately 25 percent, making for a high prevalence among a susceptible patient population and leading to both short- and long-term adverse effects on patient health.

Dr. Joyce has developed, in collaboration with her mentor John Kellum, MD, from the University of Pittsburgh Department of Critical Care Medicine, a high-density intensive care patient database of critically ill children that includes data points on more than 12,000 patient encounters over a five-year period, from 2010 to 2014. Dr. Joyce is using the database to understand the associations between the administration of certain medications and AKI to better determine risk stratification and how the risk of AKI can be minimized in certain medication scenarios. Dr. Joyce's initial investigations are probing antibiotics and antibiotic combinations associated with AKI in critical illness, particularly the use of the broad-spectrum antibiotic vancomycin — alone, and in combination with other agents, including piperacillin and tazobactam.

Recently, she and Dr. Kellum and colleagues published a paper in the journal *Nephrology Dialysis Transplantation* which outlines some of the electronic health record research and applications they have been able to derive from their database. They also describe methodologies for how eResearch in AKI can be conducted based on their experiences and pilot projects using the data to transform clinical practice.

Leveraging eResearch to Study AKI — Experiences and Learnings

One of Dr. Joyce and colleagues' first published papers outlining their use of the critically ill patient database to study AKI recounts how the database for studying AKI was conceived and built, and lays out for the first time a methodology for eResearch for studying aspects of acute kidney injury.

"Our goal with this paper was to describe some ideal methods for large database research in AKI, using some of our preliminary work as illustrative examples. One of our projects that is discussed in the paper describes our work to identify and stage acute kidney injury and the exposures and outcomes related to it based on the consensus definition of AKI that was established by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline several years ago," says Dr. Joyce.

Collaborative Investigations in Progress

Since developing her AKI database in collaboration with Dr. Kellum, Dr. Joyce has worked with several other members of the Division of Pediatric Nephrology on projects that have been able to utilize the database.

Colleagues **Michael L. Moritz, MD, FAAP**, clinical director of the Division, and **Cassandra Formeck, MD**, a third-year fellow, presented a study in poster format at the 2018 American Society of Nephrology Kidney Week annual meeting. The study is investigating the role of hyponatremia as a risk factor for development of AKI, and hyponatremia as a risk factor for development of sepsis.

In another study with Dr. Formeck and Dr. Kellum, AKI is examined as a risk factor for infection in patients who are critically ill. This research is evaluating a number of infection types — pneumonia, urinary tract infection, sepsis, and others — for which AKI may be a risk factor.

"Recently, I've teamed up with Dana Fuhrman, DO, MS, a researcher in our Division who is also interested in aspects of acute kidney injury, and Elisa Heipertz, MD, a resident interested in critical care medicine, on a new epidemiological study. We have become interested in the development of AKI after solid organ transplants and stays in the ICU," says Dr. Joyce. "With Dr. Fuhrman, we are doing another small study looking at the incidence of short- and long-term kidney outcomes in patients with congenital heart disease. Because our database contains cardiac intensive care unit (CICU) patient data, it's a population we are able to study that by and large has not received a lot of attention. Finally, alongside one of our fellows, Christine Crana, MD, we've started a small project to validate a severity-of-illness score in our AKI database. All this work is very preliminary, but we're excited at the prospects of contributing new knowledge to the field, and I'm very excited to be able to collaborate with other members of the Division to use the AKI database we have created."

K23 Young Investigator Proposal

In 2018, Dr. Joyce submitted a proposal to the National Institutes of Health for a K23 Young Investigator grant. Part of Dr. Joyce's proposal entails tracking pediatric patients who are exposed to specific types of nephrotoxic medications during treatment for a critical illness in a long-term follow-up scheme.

"It is my conjecture that we are not identifying a percentage of children who are at a high risk for the development of chronic kidney disease (CKD) — those children who have been critically ill or have developed CKD after they experienced an episode of acute kidney injury. My K23 proposal entails a short-term goal of conducting a feasibility study where a small cohort of these patients are brought back at defined intervals over a three-year period to monitor their kidney function and blood pressure," says Dr. Joyce.

Longer-term, Dr. Joyce's proposal would follow formerly critically ill children who are at high risk for developing CKD in an attempt at devising an early identification methodology that could lead to the ability to mitigate the long-term effects of exposure to critical illness and related AKI.

"It is my hope that this kind of research and intervention can augment and improve patient and family awareness relative to their increase in risk for chronic kidney disease after an episode of AKI. I think educating the parents and the patients, and monitoring them, could be incredibly beneficial for their long-term renal health," says Dr. Joyce.

Dr. Joyce will likely have her proposal scored sometime during 2019 by the NIH. Until then, she is continuing with her other collaborative studies and eResearch on aspects of chronic kidney disease, AKI, and their intimately entwined relationship.

References and Further Reading

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Considering Tests? Choose Wisely.

The American Academy of Pediatrics (AAP) Section on Nephrology and the Clinical Affairs Committee of the American Society of Pediatric Nephrology (ASPN) have developed a list of five important, evidence-based recommendations for physicians when it comes to ordering or recommending specific tests and procedures for nephrology patients. The recommendations are designed to cut down on the frequency of unnecessary diagnostics and procedures that can be of little value or utility for individual patients.

Michael L. Moritz, MD, FAAP, clinical director of the Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh, was part of the multidisciplinary committee that developed the recommendations for physicians.

Part of the AAP's broader Choosing Wisely® program, the recommendations for pediatric nephrologists include the following five areas:

1. Do not order routine screening urine analyses in healthy, asymptomatic pediatric patients as part of routine well-child care.
2. Do not initiate a work-up for hematuria or proteinuria before repeating an abnormal urine dipstick analysis.
3. Avoid ordering follow-up urine cultures after treatment for an uncomplicated urinary tract infection in patients who show evidence of clinical resolution of infection.
4. Do not initiate an outpatient hypertension work-up in asymptomatic pediatric patients prior to repeating the blood pressure measurement.
5. Do not place central lines or peripherally inserted central lines in pediatric patients with advanced (Stage 3-5) chronic kidney disease/end-stage renal disease without consultation with pediatric nephrology due to goals to avoid adverse events, preserve long-term vascular access, and avoid unnecessary and costly procedures.

To view Dr. Moritz's video rounds presentation on the Choosing Wisely® program, visit **UPMCPhysicianResources.com/VideoRounds**.

Meet the Fellows

UPMC Children's is one of the leading pediatric nephrology clinical and research programs in the United States. The Division has an extensive fellowship training program with a long track record of attracting and educating some of the best and brightest young physicians and scientists who are dedicated to transforming and evolving the practice of pediatric nephrology. In this new section of *Pediatric Insights Nephrology,* we profile our current fellows and highlight important clinical and research projects that have been a part of their training.

Elisabeth Cole, MD

First Year Fellow

Dr. Cole is a first-year fellow in the Division of Pediatric Nephrology. Dr. Cole earned her medical degree from the Tulane University School of Medicine in New Orleans, followed by residency and now fellowship training at UPMC Children's Hospital.

What experiences in your training prompted you to pursue pediatric nephrology as a subspecialty?

I decided to pursue pediatric nephrology largely because of my interactions with faculty members of the Division at UPMC Children's with whom I worked during my pediatric residency. Their dedication to their patients and their passion for teaching motivated me to enter the field.

Why did you select UPMC Children's for your fellowship?

Choosing UPMC Children's for my fellowship was an easy decision. Having matched in Pittsburgh for residency, I had three years of experience working at UPMC Children's, learning the system at the hospital and getting to know the incredible patients we care for on a daily basis. Having the opportunity to stay in Pittsburgh for fellowship meant that I could continue to work with the faculty and staff that helped me decide to become a pediatric nephrologist.

What are your research interests?

I am considering pursuing research into the influence of the gut microbiome in kidney disease, and I hope to be involved in a multi-subspecialty project regarding contraceptive education and options for patients with chronic medical problems in the future.

Aidan W. Porter, MD

First Year Fellow

Dr. Porter, who hails from Connecticut, earned his medical degree at The Warren Alpert Medical School of Brown University. He then completed his residency at UPMC Children's Hospital of Pittsburgh. While in residency, he worked with Kathyrn Torok, MD, in the Division of Pediatric Rheumatology to characterize antibody markers in pediatric scleroderma. In 2012, Dr. Porter was a recipient of an American Heart Association Student Scholarship in Cardiovascular Disease and Stroke, which allowed him to pursue research in the Harvard University Cardiovascular Research Laboratory at Spaulding Rehabilitation Hospital. During his fellowship, Dr. Porter studied the relationship between pulmonary function and exercise capacity in patients with spinal cord injuries as well as the effect of functional electrical stimulation of the lower extremities on aerobic capacity in these patients.

Why did you choose to concentrate your training in pediatric nephrology?

I am intrigued by hypertension, electrolyte disorders and renal transplant. I enjoy learning about the molecular and cellular mechanisms underlying renal diseases and then applying my understanding in clinical practice. I also appreciate the opportunity to provide ongoing care for children with chronic kidney disease, the challenge of preserving renal function and, when a transplant is necessary, the opportunity to share in my patients' joy at successful outcomes.

Why did you select UPMC Children's for your fellowship?

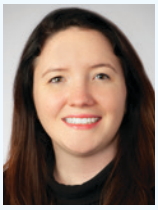
During my residency training at UPMC Children's, I had the opportunity to meet many of the attending nephrologists. The Division of Pediatric Nephrology — the office staff, nurses, fellows, and attending physicians have created a welcoming and collegial environment. I feel fortunate to have become part of their family. The long hours demanded of first-year fellows can at times seem overwhelming, but the pleasant and cooperative personalities of my colleagues help to make my workload seem just a little bit lighter. In addition, as a tertiary care center, UPMC Children's provides trainees experience caring for a diverse array of nephrology patients, including many transplant recipients.

What research have you been involved in or do you hope to pursue during your fellowship?

I will be joining the Brodski Lab at the University of Pittsburgh where I will be studying the regulation of epithelial sodium channels in a murine model of pseudohypoaldosteronism type 1.

Christine M. Crana, MD

Second Year Fellow



Dr. Crana is a second-year fellow in pediatric nephrology. She obtained her medical degree from SUNY Upstate Medical University in Syracuse, New York, in 2014, followed by her pediatric residency at UPMC Children's Hospital of Pittsburgh. She began her pediatric nephrology fellowship in 2017.

At present, Dr. Crana is an NIH T32 post-doctoral research fellow working on an investigation into acute kidney injury (see below). Past distinctions and awards include the Paul C. Gaffney Diagnostic Referral Service Award presented to one graduating pediatric resident by the hospitalist attending group at UPMC Children's. In 2016, Dr. Crana received an American Society of Pediatric Nephrology travel grant to attend the organization's annual meeting. During her first year of fellowship training, Dr. Crana participated in implementation of the Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) project at UPMC Children's. NINJA is designed to flag patients on two or more nephrotoxic medications and prompt clinicians to review or order creatinine and blood-urea-nitrogen levels.

Why did you choose to specialize in nephrology?

I chose the field of nephrology because it is complex and encompasses my love of learning. I can work in critical care settings, such as when we prescribe emergent dialysis in our intensive care units. I am also able to develop long-term relationships with patients in the outpatient setting, for example with those who have chronic kidney disease, helping to manage their condition which has such a profound impact on all aspects of their lives.

Why did you choose UPMC Children's for your nephrology fellowship?

I chose to continue training at UPMC Children's because I knew from my pediatric residency that it is an excellent place to learn and grow as a trainee. With UPMC Children's wide catchment area, the cases we see are varied. Most importantly, the attendings, nurses, and staff are supportive and invested in my education and success as a clinician and researcher.

What research are you conducting during your fellowship?

I am currently working in the laboratory of Neil Hukriede, PhD, in the Department of Developmental Biology at the University of Pittsburgh with the goal to develop treatments for acute kidney injury (AKI). Currently, there are no treatments available for patients who experience AKI. We are exploring whether small molecule compounds can inhibit a target protein that is postulated to have a role in whether the kidneys can experience recovery following injury. We also are exploring the use of kidney organoids as models for preclinical drug testing.

Cassandra Formeck, MD

Third Year Fellow

A native of Pittsburgh, Dr. Formeck completed her undergraduate studies in neuroscience at the University of Pittsburgh, followed by her medical degree from The Ohio State University College of Medicine and residency at Nationwide Children's Hospital. Dr. Formeck then moved on to UPMC Children's in 2016 to start her fellowship in pediatric nephrology. She is currently a postdoctoral scholar on the Division's NIH T32 training grant. Dr. Formeck gained an early interest in urinary tract pathology and physiology as an under-graduate, which led her to perform research on the neural regulation of urogenital tract function during postnatal development and following neural injury under the mentorship of William de Groat, PhD, at the University of Pittsburgh Department of Pharmacology and Chemical Biology. During medical school and residency, Dr. Formeck had the opportunity to investigate antimicrobial peptides and urinary tract immunity. In 2018, Dr. Formeck presented two abstracts at the American Society of Nephrology Kidney Week. Her research conducted at UPMC Children's involved studies of hyponatremia associated with the development of sepsis, and acute kidney injury epidemiology, risk factors, and prevention. In addition to her current pediatric nephrology fellowship, Dr. Formeck also is pursuing a Master of Science in Clinical Research through the University of Pittsburgh as part of her fellowship. After completing her fellowship, Dr. Formeck will continue on at UPMC Children's as a research attending and will be applying for acceptance as a UPMC Children's research scholar.

Why did you choose to concentrate in the field of pediatric nephrology?

Early in my medical training, I found myself drawn toward patients with complex renal issues. These patients tested my medical knowledge and engaged my critical thinking. Through residency and my exposure to the diversity of pediatric medicine, I found nephrology both compelling and fulfilling.

Why did you select UPMC Children's for your fellowship?

I chose UPMC Children's for my fellowship training because of its excellence in both clinical care and research. The hospital and the Division of Nephrology provide state-of-the-art patient care and perform cutting-edge research in a wide array of areas. Growing up in Pittsburgh and having received care as a young child at UPMC Children's, I felt privileged to have the opportunity to further my education and medical training at an institution that helped shaped my life and my desire to pursue medicine as a career.

What research projects have you undertaken during your fellowship?

With the impact of kidney disease on multiple aspects of pediatric health, as physicians we must utilize a broad scope of knowledge and make an effort to contribute to medical research in order to ensure the best possible outcomes in our patients. My research interests are in the association between acute kidney injury (AKI) and infection in the critical care setting. Under the mentorship of John Kellum, MD, who is the director for the Center for Critical Care Nephrology at UPMC, I am investigating various sources of infection as both a potential cause and consequence of AKI in critically ill children.

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New RO1 Grant Awarded to Dr. Swiatecka-Urban

Agnieszka Swiatecka-Urban, MD, is a basic science researcher in the Division who investigates aspects of nephrotic syndrome, protein-protein interactions, and the regulation of cell surface stability of transmembrane proteins, most notably in the mechanisms and pathways regulating the cystic fibrosis transmembrane conductance regulator (CFTR) and nephrin.

In January, Dr. Swiateck-Urban was awarded a new National Institutes of Health RO1 grant that will continue her studies on CFTR. CFTR controls the movement of salt and water in the lung to maintain normal function. Compromised CFTR function in cases of cystic fibrosis are typically the result of genetic mutations or deletions of the gene that regulates its expression. Inhibited CFTR function leads to accumulations of mucus and pathogens in the airway causing obstruction, chronic infection, and ultimately bronchiectasis. Ancillary molecules provide small compensation for the absent CFTR function in CF, but the protein known as TGF-beta inhibits these molecules and destroys their ability to restore the absent CFTR function. Learning how to block TGF-beta in this context may help to treat CF lung disease by allowing medications to effectively restore near normal CFTR function in the lung.

IV Fluid Use in Children *Continued from Page 1*

the administration of intravenous maintenance fluids now specifically recommend isotonic fluids and caution against using hypotonic fluids due to the risk they present for developing hyponatremia," says Dr. Moritz.

Excluded from the new guidelines are "patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, severe burns, and neonates who are younger than 28 days old or in the NICU."[1]

"The AAPs new clinical practice guidelines apply to most of the approximately two million children and adolescents ages 1-month to 18 years who are admitted to the hospital every year. The new guidelines apply to all pediatric patients who may need intravenous fluids in the emergency department, around the time of surgery, or after being admitted to the hospital," says Dr. Moritz.

References and Further Reading

The full text of the new guidelines can be found in the journal *Pediatrics*.

[1] Feld LG, Neuspiel DR, Foster BA, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. *Pediatrics*. 2018; 142(6): e20183083. Epub ahead of print.

Webinar Discussion on New Guidelines

The American Academy of Pediatrics Pediatric Care Online™ hosted a webinar discussion on the new guidelines on January 16. During the webinar Dr. Moritz, along with Leonard G. Feld, MD, PhD, MMM, FAAP from Nicklaus Children's Health System, and Matthew D. Garber, MD, FHM, FAAP from Wolfson Children's Hospital, discussed the objectives, methods, and implications of the new IV fluid guidelines.

Clinicians interested in viewing the one-hour webinar discussion can access an archived version by visiting **https://pediatriccare.solutions.aap.org/webinars.aspx.** To view the webinar directly please visit **https://pediatriccare.solutions.aap.org/MultimediaPlayer.aspx?multimediaid=17190570.**

UPMC Physician Resources

Visit **UPMCPhysicianResources.com/Pediatrics** for the latest news, videos, CME courses, and events in pediatric nephrology.

Video Rounds

Video Rounds is a series of short, informative, and educational videos created for physicians and covering a variety of medical and surgical disciplines.

Choosing Wisely® Program
Michael L. Moritz, MD, FAAP
Dr. Moritz discussed the new Choosing Wisely program from the American Academy of Pediatrics and its five recommendations for pediatric nephrologists.

Acute Kidney Injury
Sunder Sims-Lucas, PhD
Dr. Sims-Lucas discussed the types of acute kidney injury (AKI) and cell-based therapies for AKI under research, mediating the Sirtuin 5 gene as a potential therapy for AKI, and participation in the new NIH-funded Kidney Precision Medicine Project.

Advancing Research and Treatment for Nephrotic Syndrome
Agnes Swiatecka-Urban, MD
Dr. Swiatecka-Urban presents on the current treatments for nephrotic syndrome and new research being pursued at UPMC Children's Hospital of Pittsburgh to combat the condition.

CME Courses

Kidney Transplantation for the Pediatric Patient
Armando Ganoza, MD
Dr. Ganoza discussed the differences of renal transplantation in pediatric patients and the preoperative management of infant renal transplant recipients.

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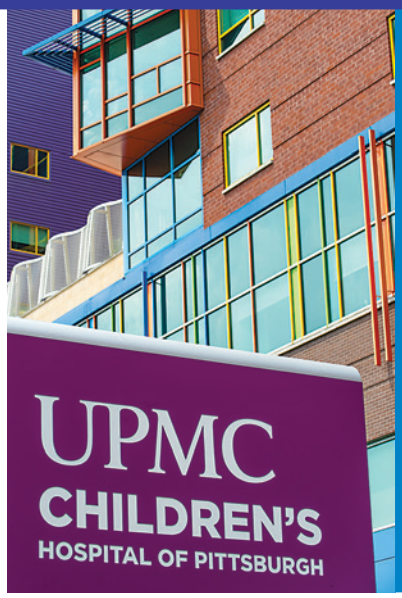

About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 13th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2017).

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