

NIH R25 Grant Awarded to Mentor and Train Next Generation of Kidney Researchers

Researchers from the Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh and the adult Renal-Electrolyte Division at UPMC Presbyterian were awarded a National Institutes of Health R25 grant supporting the creation of a training program designed to mentor undergraduate students in kidney-based research.



Co-principal investigators of the grant include assistant professor of Pediatrics, **Sunder Sims-Lucas, PhD**, who studies the basic science of acute kidney injury

(AKI), and **Carlton M. Bates, MD**, Division chief of Pediatric Nephrology at UPMC Children's, whose research is focused on acute bladder injury.

The R25 award supports the development of an undergraduate training program called "Summer Research Internship Program Kidney Workshop (SRIP-Kid)."

The new training program allows undergraduate students interested in kidney-based research to travel to the University of Pittsburgh and take part in a 10-week program where they will perform research and receive didactic instruction on a range

of topics in nephrology from researchers and physicians in the Division of Pediatric Nephrology and collaborators in the adult Renal-Electrolyte Division and Department of Critical Care Medicine at the University of Pittsburgh School of Medicine. The program has a significant emphasis on recruiting undergraduate students from racial and ethnic groups that are under-represented as scientists.

"For many kidney conditions, like acute kidney injury that my laboratory studies, we still have yet to develop effective therapies. We continue to learn a great deal, but we need the next generation of researchers and doctors to join the cause and lead the science forward. Our new training program will afford a number of talented students the ability to work and learn alongside some of the most respected kidney researchers in the world and, we hope, inspire them to continue with a career in science and nephrology," says Dr. Sims-Lucas.

SRIP-Kid Program Highlights

The goals of the SRIP-Kid program will be achieved by providing novel didactics on renal topics and career advice to participants. Faculty members participating in the program

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An Often Unrecognized and Underappreciated Complication: Transient Hyperphosphatasemia in Pediatric Kidney Transplant Patients

Illustrative Case

A 5-year-old male underwent a successful living donor kidney transplantation as a result of focal segmental glomerulosclerosis. At the 6-month follow-up visit after the transplant, the patient exhibited an incidental finding of an extremely high serum alkaline phosphatase level of 2,800 IU/L without the presence of other laboratory abnormalities. Further testing confirmed the elevated alkaline phosphatase level. The patient's serum alkaline phosphatase level was within the normal range prior to his kidney transplant and within the context of a well-controlled metabolic bone disease.

Clinical Questions

- What is the most likely etiology of the elevated alkaline phosphatase in this patient?
- What further investigation should be done?
- How common is this condition in renal transplant patients, and what is the natural history of the disorder?

Transient hyperphosphatasemia (TH) is a benign condition in children characterized by laboratory findings of extremely elevated levels of serum alkaline phosphatase (> 1000 IU/L). Many physicians are unfamiliar with this condition, which can lead to unnecessary follow-up investigations and patient anxiety.

UPMC Children's Hospital of Pittsburgh Division of Pediatric Nephrology former fellow Elisabeth Cole, MD, in conjunction with medical director of the UPMC Children's Pediatric Kidney Transplant Program, **Michael L. Moritz, MD**, published findings from a new study¹ that for the first time investigated the prevalence and natural history of TH in a large series of pediatric kidney transplant patients. The incidence of TH in this patient population has garnered little attention in the past, and its incidence rate has been unclear.

Summary of Key Study Findings

The research team found 11 cases of TH in 178 pediatric kidney transplant cases conducted at UPMC Children's between the years 2008 and 2019. Interestingly, all of TH cases were in patients < 12 years of age (12.8%) with a median age of 5 years. The analysis showed that the median time from kidney transplant to diagnosis of TH was 7 months, and the median length of time that TH persisted was 6 months. The median peak alkaline phosphatase level was > 2300 IU/L. The median glomerular filtration rate at the time of diagnosis of TH was 84 mL/min/1.73m², and no patients had significant abnormalities of calcium and phosphorous metabolism or radiologic abnormalities. No patients had a recurrence of elevated alkaline phosphatase level following resolution.

The investigators conclude from their study that TH is a common transplant complication in young children that manifests without symptoms during the first year following a pediatric kidney transplant, and it will typically resolve within a year from onset without recurrence.

Key Learnings for the Clinician

- Transient hyperphosphatasemia (TH) is a relatively common benign finding following pediatric kidney transplantation.
- TH primarily occurs in prepubertal children with an incidence of approximately 13% in children < 12 years of age.
- TH typically presents within the first year after transplantation, and usually resolves within a year without recurrence.
- TH is a clinical diagnosis and therefore no metabolic or radiologic investigations are indicated.

Study Reference

- ¹ Cole EB, Anslow M, Fadakar P, Miyashita Y, Ganoza A, Moritz ML. Transient Hyperphosphatasemia Following Pediatric Kidney Transplant. *Cureus*. 2021 Sep 3; 13(9): e17697.

Guidelines for Administering 3% NaCl Infusions via PIVCs

UPMC Children’s Hospital of Pittsburgh Division of Pediatric Nephrology clinical director **Michael L. Moritz, MD, FASN**, co-authored a new review paper on the administration of 3% sodium chloride infusions via a peripheral intravenous catheter (PIVC) in emergent conditions.

The paper was published in February in the *Journal of Infusion Nursing* with co-author Norma A. Metheny, PhD, RN, FAAN, from the Trudy Busch Valentine School of Nursing at Saint Louis University.

In most instances, the use of 3% NaCl is restricted to administrations through a central vascular access device (CVAD) in order to avoid or limit the incidence of adverse infusion events. However, a small yet growing body of evidence is supportive of the safe administration of 3% NaCl via PIVC.

Drs. Moritz and Metheny reviewed nine studies in the literature comprising a total of 837 cases of 3% NaCl infusion via PIVC. They review the current indications, recommendations, and guidelines for the use of 3% NaCl through a PIVC.

The paper discusses management of symptomatic hyponatremia with the administration of PIVC 3% NaCl, and the authors provide a series of four brief case studies illustrating clinical care scenarios involving 3% NaCl infusions.

Of note, monitoring for neurologic status changes in patients is critical with the use of 3% NaCl. Vigilance for serum sodium concentrations and fluid status of the patient is mandatory.

“Administering 3% NaCl through a CVAD is the preferred approach, but it is not always possible, particularly in emergent conditions where time is of the essence, particularly in cases where neurologic complications are a potential. While the body of evidence we reviewed is small and most of the studies were retrospective nature, the limited evidence is supportive of safety and efficacy, but this area of study is one that will benefit greatly from larger controlled studies. However, clinicians and hospitals need to examine and keep current with their policies and practices for the use of 3% NaCl administered through a peripheral vein when circumstances arise indicative of its use,” says Dr. Moritz.

Reference

Metheny NA, Moritz ML. Administration of 3% Sodium Chloride Via A Peripheral Vein. *J Infusion Nursing*. 2021. DOI 10.1097/NAN.0000000000000420.



More About Dr. Moritz



Michael L. Moritz, MD, FASN, is professor of Pediatrics in the Division of Pediatric Nephrology at UPMC Children’s Hospital of Pittsburgh and the University of Pittsburgh School of Medicine. Dr. Moritz is the Division’s clinical director, as well as the medical

director of the Kidney Transplant Program and medical director of pediatric dialysis at UPMC Children’s. Dr. Moritz is a leading researcher and expert in the fields of sodium disorders and water metabolism.

Pediatric Acute Kidney Injury Diagnostic Tools and Practical Bedside Application

UPMC Children's Hospital of Pittsburgh Division of Pediatric Nephrology faculty, **Dana Y. Fuhrman, DO, MS**, assistant professor of Pediatrics and Critical Care Medicine, has published a new review article in the journal *Pediatric Nephrology* discussing the current research and development of predictive tools and biomarkers for pediatric acute kidney injury (AKI) that can provide recognition of the condition as it develops earlier in the processes.

AKI in the pediatric setting (as well as in adult patients) remains a condition for which definitive therapeutic approaches — curative or protective — remain elusive. A single AKI increases the risk for future AKI, and the effects of AKI on overall kidney health and progression to kidney disease are of significant clinical concern, particularly in vulnerable patient populations or those with underlying comorbid conditions.

Dr. Fuhrman's review, with an eye toward practical application at the bedside, discusses among other topics the current state of urinary and serum biomarkers research, stratification strategies, and models for predicting AKI risk in pediatric patient populations (e.g., critical care, congenital heart disease), and assessment of a patient's renal functional reserve and its impact on the progression of renal dysfunction or chronic kidney disease.

Reference

Fuhrman DY. The Use of Diagnostic Tools for Pediatric AKI: Applying The Current Evidence to the Bedside. *Pediatr Nephrol*. 2021 Nov; 36(11): 3529-3537. Review.

About Dr. Fuhrman



Dana Y. Fuhrman, DO, MS, is an assistant professor of Critical Care Medicine and Pediatrics at the University of Pittsburgh School of Medicine. She is an attending physician in the Division of Pediatric Nephrology at UPMC Children's

Hospital of Pittsburgh, and she also currently serves as the associate program director of the Pediatric Critical Care Medicine Fellowship. Dr. Fuhrman's research interests are in the areas of AKI and continuous renal replacement therapy. Currently, her research focuses on the prevention and early detection of AKI in children. She is interested in studying renal reserve as defined by the difference in a baseline and a protein stimulated glomerular filtration rate. Dr. Fuhrman's work seeks to better understand how children with lower renal reserve values are at a greater risk for AKI after cardiac surgery. Her work also involves investigations of cell cycle arrest biomarkers, tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein 7, as a means to predict AKI risk and diagnose the condition earlier.

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will meet weekly with all students to provide a one-hour didactic session on a renal topic followed by a 30-minute discussion on a pertinent paper and discuss career options as a nephrology researcher. The program also will provide research training under the mentorship of the world-class kidney researchers at the University of Pittsburgh. A multi-media platform specifically designed for this program will act as an interface for future, current, and past students. SRIP-Kid participants each will be matched with one of the training faculty to pursue a research project. Given the breadth of faculty research interests at the University of Pittsburgh, students will have the opportunity to work on a laboratory-based project or a patient-oriented research project. At the end of the 10-week program, the students will present their work as an oral presentation. Upon completion of the SRIP-Kid

summer program, students will have been exposed to a wide array of kidney-based research topics, nationally respected clinician-scientists and PhD scientists, and a specific kidney-based research project.

"Dr. Sims-Lucas was the driving force behind this project and its ultimate funding. We both share similar passions for and dedication to mentoring young researchers in the field of pediatric nephrology. To our knowledge, we are the only pediatric nephrology program in which an award like this one is centered, and we are excited to marshal the necessary resources and collaborations to make such a learning experience possible for young students. Our entire Division is tremendously excited to take part in the experience, and I congratulate Dr. Sims-Lucas for making it a reality," says Dr. Bates.

Faculty Members News & Notes

Division of Pediatric Nephrology Welcomes New Faculty Aidan W. Porter, MD



The Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh is pleased to welcome new faculty member **Aidan W. Porter, MD**. Dr. Porter began his tenure on July 1, but he is no stranger to the Division, having completed his pediatric residency and pediatric nephrology

fellowship training at UPMC Children's and the University of Pittsburgh School of Medicine.

Dr. Porter graduated magna cum laude from Amherst College and 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. Dr. Porter began his pediatric nephrology fellowship at UPMC Children's in 2018 and joined the Division faculty immediately upon concluding his training.

Research Focus

Dr. Porter's clinical emphasis and research are closely aligned, focusing on acute kidney injury (AKI) and various electrolyte disorders.

Dr. Porter has identified novel roles for proteins that regulate the unfolded protein response in the pathogenesis and treatment of AKI. His research is conducted in the Brodsky Laboratory and the Center for Protein Conformational Diseases, led by Jeffrey L. Brodsky, PhD, the Avinoff Chair in Biological Sciences at the University of Pittsburgh.

Specifically, Dr. Porter's research involves the study of glucose-regulated protein 170 (GRP-170), a molecular chaperone that functions to regulate protein folding in the endoplasmic reticulum (ER). Dr. Porter is examining GRP-170's role in the cells of nephrons.

"We know that the accumulation of misfolded proteins within the ER triggers a cell stress response, which if left unchecked can contribute to AKI. A better understanding of the cellular physiology linking protein homeostasis to kidney disease promises novel therapeutic strategies to treat AKI," says Dr. Porter. "AKI continues to be one of the great challenges to surmount in nephrology. I am hopeful that my research may one day help to develop a viable target and strategy to treat this common condition and its complications," says Dr. Porter.

Carlton Bates, MD, chief of the Division of Pediatric Nephrology at UPMC Children's says, "Dr. Porter and his group are the first to identify a connection between the unfolded protein response and ER stress to acute kidney injury.

Excitingly, they have small molecules that target this pathway that may offer novel therapies for patients with AKI, for which we have no targeted therapies presently."

New Pediatric Nephrology Fellows Join Division

The Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh welcomes its new fellowship class **Mohga M. Behairy, DO**, and **Lillian G. Mauroner, DO**.

Dr. Behairy earned her undergraduate degree in neuroscience from the University of Miami, and her medical degree from the Nova Southeastern University College of Osteopathic Medicine in Florida. She completed her pediatric residency at the Cleveland Clinic joining UPMC Children's to pursue a pediatric nephrology fellowship.

Dr. Mauroner graduated from Hendrix College in Arkansas with a degree in biochemistry and molecular biology, and then earned her medical degree from William Carey University College of Osteopathic Medicine. She subsequently completed a pediatric residency at the University of Texas Health Science Center at Houston and McGovern Medical School.

UPMC Children's Neonatal Fellow Wins SPR Fellows Basic Research Award



Jo Duara, MD, MPH, was awarded a 2021 Society for Pediatric Research Fellows Basic Research Award for her work studying bladder urothelial injury.

Dr. Duara currently is a second-year perinatal-neonatal fellow in the UPMC Newborn Medicine Program. She earned her medical degree from the University of Miami Miller School of Medicine and then completed her residency in pediatrics at the Holtz Children's Hospital, also at the University of Miami.

Dr. Duara's research interests have been focused in epithelial cell biology, with previous work during her residency investigating the cellular mechanisms of lung cell damage due to hyperoxia.

At UPMC Children's, Dr. Duara's research focus has centered on bladder urothelial injury, working in the Bates Laboratory, which is led by Division of Pediatric Nephrology chief **Carlton M. Bates, MD**. Dr. Bates and his laboratory focus primarily on the roles of fibroblast growth factor receptors (FGFRs) and their signaling adapter proteins in the kidney and lower urinary

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tract using animal models. In recent years, the laboratory has focused on how FGF7/FGFR2 signaling acts in the context of bladder urothelial injury. The laboratory has evidence that exogenous FGF7 blocks Cyclophosphamide-induced apoptotic death of deeper urothelial cells, accelerates regeneration of outer Superficial cells, and leads to faster and high-fidelity repair compared to vehicle-treated mice.

Dr. Duara's research in the laboratory continues this work studying the genetic deletion of FGFR2 in mouse bladder urothelium and how it leads to regenerative defects after cyclophosphamide induced injury led by pathological endoreplication in Basal urothelial cells. Dr. Duara's studies investigate if loss of ERK signaling downstream of FGFR2 is responsible for the pathological urothelial response to injury.

Dr. Duara presented an abstract of her work at the 2021 Pediatric Academic Societies Annual Meeting under the title, "The Role of FGFR2/ERK Signaling in Urothelial Regeneration After Cyclophosphamide."

NIH R25 Grant Expands Summer Internship Program



Sunder Sims-Lucas, PhD, assistant professor in the Division of Pediatric Nephrology, and **Juan C. Celedón, MD, DrPH, ATSF**, professor and chief of the Division of Pediatric Pulmonary Medicine, were the recipients of a National Institutes of Health (NIH) R25 grant to expand and diversify the Summer Research Internship Program (SRIP) at UPMC Children's Hospital of Pittsburgh by offering summer research experiences to underrepresented minority students in the fields of heart, lung, and blood research.



SRIP is an annual summer internship for undergraduate college students to obtain experience in research laboratories. Participants learn the rationale, design strategies, methods, and other aspects of biomedical research as research interns. Training is provided under the direct supervision of University of Pittsburgh faculty and research personnel within the Department of Pediatrics and several affiliated University of Pittsburgh School of Medicine programs. Weekly career development and research seminars are also offered to participants alongside "rounding" for those interested in clinical medicine.

The training program concludes with a required poster presentation where student interns discuss the results of their research with faculty, physicians, and staff from UPMC Children's and the Department of Pediatrics.

About the Nephrology Fellowship Program at UPMC Children's

The Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh offers a three-year ACGME-accredited Pediatric Nephrology Fellowship program that provides outstanding clinical training and world-class research opportunities. The pediatric renal transplant service is one of the largest in the country, providing innovative, state-of-the-art care. Fellows are trained in all modalities of renal replacement therapies across the lifespan of pediatrics. The robust inpatient, consult and outpatient service will allow the fellow to care for a broad spectrum of patients with kidney disorders.

The fellowship program offers superb and diverse training in clinical, translational and basic research across the University of Pittsburgh School of Medicine Campus. The Division has four research-based MDs and two PhDs, the majority of whom are engaged in NIH R01 funded research. Prior fellows' research projects have included: vesicoureteral reflux, transplant immunology, nephrotoxins and acute kidney injury, infections and acute kidney injury, urinary microbiome, monogenic causes of hypertension and health disparities in renal transplantation. Fellows will access to the wide array



of resources at the University of Pittsburgh School of Medicine, including a prestigious O'Brien Center award.

The fellowship program is led by director **Jacqueline Ho, MD, MSc**.

Drs. Sims-Lucas and Celedón R25 grant supports additional paid internship positions specifically to underrepresented minority students to participate in heart, lung, and blood pediatric subspecialties.

In 2021, Dr. Sims-Lucas, along with Pediatric Nephrology Division chief **Carlton M. Bates, MD**, was awarded another NIH R25 grant to develop an undergraduate training program called "Summer Research Internship Program Kidney Workshop," or SRIP-Kid, designed to mentor undergraduate students in kidney-based research.

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Pilot Study to Explore KGF Use to Mitigate Injury in Neuropathic Bladders

A new pilot grant will allow UPMC Children's Hospital of Pittsburgh researchers to explore whether keratinocyte growth factor (KGF) can aid in reducing bladder injury and urinary tract infections in patients with neuropathic or neurogenic bladders.



Catherine Forster, MD, MS, FAAP, assistant professor in the Paul C. Gaffney Division of Pediatric Hospital Medicine, and **Carlton M. Bates, MD**, professor and chief of the Division of Pediatric Nephrology, are co-investigators of the new study funded by the Institute for Infection, Inflammation & Immunity in Children (i4Kids) at the University of Pittsburgh.

The title of their study is "KGF to Reduce Bladder Injury and Susceptibility to Urinary Tract Infection in Neuropathic Bladders."

"What we know about children with spina bifida is that as a consequence of their condition and resultant bladder dysfunction, they are at very high risk for recurrent urinary tract infection (UTI) and more severe infections when they occur. These repetitive UTIs carry with them the potential for significant long-term renal morbidities and disruption in quality-of-life," says Dr. Forster. "At baseline, we know that our spina bifida patients have injured bladder urothelial cells. These perturbations of the urothelium, we hypothesize, are

what ultimately lead to an increased rate of UTIs in some children with spina bifida."

The main aim of Dr. Forster and Bates' study is to examine how KGF affects urothelial injury in a model of neuropathic bladder and whether KGF therapy decreases susceptibility to urinary tract infection.

Drs. Forster and Bates will first examine whether KGF mitigates urothelial injury in a mouse model of spina bifida. They will then examine how KGF-driven urothelial repair affects the response to induction of urinary tract infection in the same mouse model. They will examine the urothelium, bladder, and urine at various time points to look for signs of improvement in bladder histology, decreases in bladder bacterial counts, and a better immunologic response of the urothelium to the presence of bacteria in the KGF-treated mice.

"We hypothesize that the urothelium will show improvement after KGF therapy and that we will see fewer bacteria over time, signifying a more normal response of the urothelial tissues to the presence of bacterial invaders," says Dr. Forster. "If we can normalize the urothelium in these patients, we think we can prevent or potentially reduce susceptibility to UTI and many of the downstream effects associated with neuropathic bladder, the worst of which is repeated renal injury and chronic kidney disease."

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UPMC Children's Faculty Appointed to SPR Leadership Roles

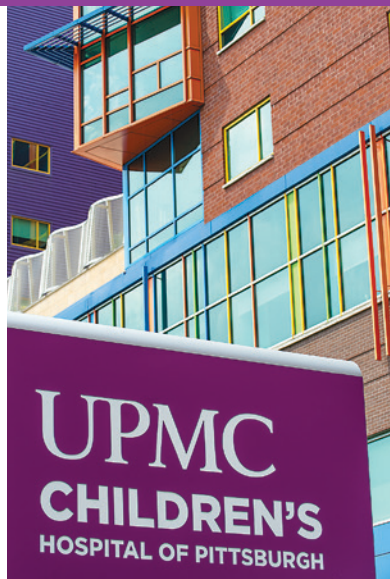
Carlton M. Bates, MD, Pediatric Nephrology Division chief at UPMC Children's Hospital of Pittsburgh was appointed to the role of Physician Scientist Development Lead on the Executive Committee of the Council for the Society for Pediatric Research (SPR). SPR is a leading national honorific organization devoted to creating a multidisciplinary network of diverse researchers to improve the health of children.

Dr. Bates has an extensive history with the Society for Pediatric Research, and a long-standing devotion to mentoring young and early-career physician-scientists. Dr. Bates was awarded membership into SPR in 2002, and in 2016, Dr. Bates was elected to the SPR Council for a three-year term. He has been a member of the Mentoring Work Group and the Finance Committee, and he has authored an SPR perspectives manuscript offering strategies for early-stage pediatric clinician-scientists (and their institutional leadership) to

increase their chances of success in obtaining external research funding. In 2017, Dr. Bates started a national K grant writing course for SPR Junior Section members, which has had vastly increasing numbers of applicants each year. Based on this work, he was awarded the Thomas A. Hazinski Distinguished Service Award from the SPR Council in 2019. In 2020, he was asked by SPR Council to become the first ever Lead for Pediatric Scientist Development. In this role, Dr. Bates is charged with expanding, developing, and implementing mentoring and career development programs for SPR Junior Section, often in collaboration with regional SPR organizations.

Of note, UPMC Children's Division of Pediatric Hematology-Oncology chief, **Linda M. McAllister-Lucas, MD, PhD**, also was elected to the SPR Council in 2020. **Catherine Forster, MD, MS, FAAP**, from the Hospital Medicine Division in the Department of Pediatrics at the University of Pittsburgh School of Medicine also is an SPR Council member and a member of the Executive Committee.

Affiliated with the University of Pittsburgh School of Medicine and ranked among the nation's best children's hospitals by *U.S. News & World Report*.



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 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2019) and ranking on *U.S. News & World Report's* Honor Roll of Best Children's Hospitals (2021-22).