Pediatric Insights

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT NEPHROLOGY 2017-18

Spring 2018

An Update from the Division of Pediatric Nephrology

About the Division

The Division of Pediatric Nephrology at Children's Hospital of PIttsburgh of UPMC provides a full range of services for the evaluation and management of children with simple or complex nephrologic or urologic disorders.

Division Faculty

Carlton M. Bates, MD – *Division Chief*
Rannar Airik, PhD
Demetrius Ellis, MD
Paul Fadakar, MD
Dana Y. Fuhrman, DO, MS
Jacqueline Ho, MD
Emily Joyce, MD
Yosuke Miyashita, MD – *Director, Pediatric Hypertension Clinic*
Michael Moritz, MD – *Clinical Director and Medical Director, Pediatric Dialysis*
Christina R. Nguyen, MD – *Medical Director, Pediatric Kidney Transplant*
Sunder Sims-Lucas, PhD
Agnieszka Swiatecka-Urban, MD

For a referral or consultation, please contact us at 412-692-5182. Visit us online at **CHP.edu/nephrology**.

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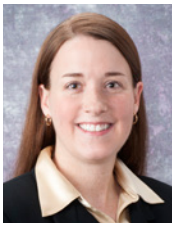
Children's Hospital of Pittsburgh of UPMC

Renal Disease Progression and AKI Research



Dana Fuhrman, DO, MS, joined the faculty of the Division of Pediatric Nephrology at Children's Hospital of Pittsburgh of UPMC in 2015. Completing fellowships in both pediatric nephrology and critical care medicine at the University of Rochester and University of Pittsburgh, respectively, Dr. Fuhrman's initial work and research had a focus on chronic kidney disease, leading to interesting recent published findings related to albuminuria and proteinuria and renal disease progression (see below for details). More recently, and likely to be the sole focus of Dr. Furhman's research career into the foreseeable future is the area of detection and prevention of acute kidney injury, specifically in young adults with congenital heart disease, and the use of biomarkers for early diagnosis and risk assessment of AKI.

Dr. Fuhrman's research interests lie in better understanding the risk of renal progression, and the risk of AKI when young adult congenital heart disease patients end up in the hospital for surgery or stays in the ICU. "This is a group of patients that really hasn't been studied from a kidney perspective. Fortunately, because of all of the advances that we have had in cardiology for congenital heart disease patients, they are living longer and longer. In fact, more people with congenital heart disease are adults now than are children. To me, though, the heartbreaking aspect is that for a portion of patients, they will get to adulthood and end up with kidney disease," says Dr. Fuhrman. So, the questions that follow are who is most at risk for kidney disease, why, and what can be done to prevent it. And these are exactly the avenues of investigation Dr. Fuhrman is beginning to examine.

Biomarker research and understanding a patient's underlying renal reserve are two research areas Dr. Fuhrman is currently involved in, having published on in the past and with several new manuscripts recently submitted for publication. "Unfortunately, at present, we do not have any viable direct clinical therapies for the treatment of AKI. This is why prevention and early detection are key aspects that we need to improve upon."

Albuminuria, Proteinuria, and Renal Disease Progression in Children with CKD

A new study published by Dr. Fuhrman and colleagues in 2017 examined and compared the abilities of proteinuria and urine protein-to-creatinine levels with albuminuria and albumin-to-creatinine levels to predict worsening of renal function or eventual need for renal replacement therapy in children with chronic kidney disease without diabetes. This study was completed within the context of, and used data from the NIH-funded Chronic Kidney Disease in Children (CKiD) observational study.

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Renal Disease Progression (Continued from Page 1)

Past studies in adults and children with diabetes have shown the utility of albuminuria in providing additional diagnostic and prognostic data for use by clinicians, but in cohort of children free of diabetes, the utility of the albuminuria testing versus, or in addition to the gold-standard proteinuria measurements for determining renal disease progression was not known. The study[1], published in June 2017, was the first to examine the association in a non-diabetic child population. "What we ultimately concluded is that in children with chronic kidney disease who do not have diabetes, the ability to predict renal progression using an initial protein to creatinine or albumin to creatinine study correlated very closely," says Dr. Fuhrman

Non-albumin protein levels were also examined and also correlated with the other two studies in terms of predictive value.

While one method was shown not be any better in predictive value than another for this patient cohort, it does lead to other possible conclusions, albeit not investigated as part of this study. "There may be potential cost savings involved by not ordering a urine albumin as part of routine diagnostics for non-diabetic children with CKD, however future cost effectiveness studies would be necessary to make that determination definitively," says Dr. Fuhrman.

References

[1] Fuhrman DY, et al. Albuminuria, Proteinuria, and Renal Disease Progression in Children with CKD. *Clin J Am Soc Nephrol.* 2017; 12: 912-920.

[2] Fuhrman DY, Kellum JA. Biomarkers for Diagnosis, Prognosis, and Intervention in Acute Kidney Injury. *Contrib Nephrol.* 2016; 187: 47-54.

[3] Joyce EL, Kane-Gill SL, Fuhrman DY, Kellum JA. Drug-associated Acute Kidney Injury: Who's at Risk? *Pediatr Nephrol.* 2016; 32(1): 59-69.

[4] Fuhrman DY, Kellum JA. Epidemiology and Pathophysiology of Cardiac Surgery-Associated Acute Kidney Injury. *Curr Opin Anaesthesiol.* 2017; 30(1): 60-65.

Department and Faculty News

Melissa Anslow, MD, is third year fellow in the Division of Pediatric Nephrology, who will be joining the Division as faculty in July 2018. Dr. Anslow's primary research interests revolve around congenital anomalies of the kidney and urinary tract. Dr. Anslow's nephrology fellowship was preceded by residency training at the Cleveland Clinic Children's hospital and medical school at Temple University. A native of Pittsburgh, Dr. Anslow competed her undergraduate education at the University of Pittsburgh.

Dr. Anslow was recently awarded a two-year K-12 institutional career development grant to pursue her research into how microRNAs (miRNAs) contribute to increased rates of vesicoureteral reflux (VUR). Dr. Anslow has created a transgenic mouse model with a knockout of the Dicer enzyme responsible for miRNA formation. miRNA regulates gene expression post-transcriptionally and they have been shown to be responsible for regulating many processes within the body. Preliminary work by Dr. Anslow with her animal model has shown significantly higher rates of VUR in the mice lacking the Dicer enzyme, implicating miRNAs for the first time in the development of VUR. Some of this work was presented as an oral abstract at the 2017 American Society of Nephrology annual meeting.

"We have good evidence for miRNAs role in VUR and in the broader spectrum of kidney development. My continuing research will be to try and pinpoint which miRNAs are responsible for VUR development and the signaling pathways in which they work. I'm excited to be joining the Division as a faculty member this year, and am equally excited to be working under the mentorship of Dr. Carlton Bates and Dr. Jaqueline Ho," says Dr. Anslow.

Fellowship Highlights

The Division of Pediatric Nephrology at Children's Hospital of Pittsburgh of UPMC — one of the largest in the country — offers a three-year ACGME-accredited fellowship program that features outstanding opportunities in both clinical care and research initiatives.

- Our robust inpatient, consult, and outpatient services allow direct patient contact across a wide spectrum of cases.
- The fellowship also offers diverse opportunities for clinical, translational, and basic research. It is one of only a handful in the country that has an NIH T32 fellowship training grant. There are currently six NIH-funded investigators within the division working on areas that include fluid management, renal development (genetic and epigenetic), vesicoureteral refux, obstructive nephropathy, polycystic kidney disease, tubular toxicity of albuminuria, transplant immunology/infection, podocyte biology, epithelial cell polarization, protein traffcking in epithelial cells, pyelonephritis, and neonatal hydronephrosis.
- Fellows have the opportunity to work with more than 30 NIH-funded investigators across the University of Pittsburgh.
- Since the inception of the fellowship program in 2009, we have graduated nine fellows in the past six years. The program currently has five fellows with two joining in 2018.

Unmasking the Medications Contributing to AKI in Cases of Critical Illness

Emily Joyce, MD, joined the Division of Pediatric Nephrology in July, 2017, after completing her residency and fellowship training at Children's Hospital of Pittsburgh of UPMC. Doctor 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 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 understand risk stratification, and how the risk of AKI can be minimized in certain medication scenarios. Dr. Joyce's initial investigations are probing antibiotic 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. "There's been some research along this front, and this combination of antimicrobial agents is something that is often prescribed in our PICU, so our goal is to really understand the nephrotoxicities of these agents alone and in combination to better guide our treatment decisions and if at all possible, reduce the risk of AKI from these agents with our patients," says Dr. Joyce.

Short- and Long-Term AKI Complications and Future Research

AKI acquired during critical care illness leads to short-term complications that include prolonged length of stay (LOS), higher associated costs of care, and increased mortality. Research in the field also is pointing more to long-term complications and consequences of acute kidney injury in these patient cohorts, and this is another aspect of Dr. Joyce's research, one that she plans to study longitudinally to better understand how an acquired AKI during critical illness may affect the longer-term outcomes for overt chronic kidney disease as well as indicators of renal dysfunction including masked hypertension and low-grade proteinuria, as well as how acute kidney injury affects other organ systems. There is also the possibility that having an AKI puts individuals at higher risk for another episode in the future, or a more chronic type of relapsing and remitting disease course. "Even if the patient recovers from their AKI and serum markers return to normal values, what we don't know is how or to what degree this injury predisposes these individuals to longer term renal dysfunction. Longitudinal studies are needed to help us understand who is at risk and how we might intervene to prolong their kidney health. This is one of my longer-term research goals, one which I hope to be studying for the next 10 to 20 years," says Dr. Joyce.

An Unbiased Search For Nephrotoxic Medications

While certain antibiotics are where Dr. Joyce and her colleagues research into medication nephrotoxicity has begun, there is much more to investigate and come in terms of future research. Because critically ill patients receive or are exposed to so many different medications during treatment, the landscape of knowing which ones are truly nephrotoxic (alone or in combination) is cloudy. Using their patient databases, Dr. Joyce and her colleagues hope to uncover associations of AKI and specific drugs in their current and expanding ICU data sets using various statistical methodologies. Their first studies will involve approximately 450 agents that have been used in the ICU more than 100 times in the patient cohort to see if they can find relationships between AKI and certain of these medications. "Untangling these associations will take time, and will start with small studies comparing 2 medication combinations." Dr. Joyce is also planning collaborations with the Center for Causal Discovery at the University of Pittsburgh to help understand and control for inherent indication bias in studying AKI. "Determining causality when you are just looking at observational studies is nearly impossible. My hope is that our collaborations can bring to bear different physical methodologies in these studies to better account for these biases and unlock, for example in a case of infection, is it the infection itself driving the AKI, or is it an antibiotic agent or combination of medications that is responsible," says Dr. Joyce.

References and Further Reading

Recently published papers by Dr. Joyce include the following:

1 Joyce EL, Kane-Gill SL, Fuhrman DY, Kellum JA. Drug-associated Acute Kidney Injury: Who's at Risk? *Pediatr Nephrol.* 2017; 32(1): 59-69.

2 Joyce E, Ho J, El-Gharbawy A, Salgado CM, Ranganathan S, Reyes-Mugica M. Value of Renal Biopsy in Diagnosing Infantile Nephropathic Cystinosis Associated With Secondary Nephrogenic Diabetes Insipidus. *Pediatr Dev Pathol.* 2017; 20(1): 72-75.

3 Joyce E, Glasner P, Ranganathan S, Swiatecka-Urban A. Tubulointerstitial Nephritis: Diagnosis, Treatment, and Monitoring. *Pediatr Nephrol.* 2017; 32(4): 577-587.

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Recent Publications

Below is a sampling of recent publications from faculty in the Division of Pediatric Nephrology.

Narla D, Slagle SB, **Schaefer CM**, **Bushnell DS**, **Puri P**, **Bates CM**. Loss of Peri-Wolffian Duct Stromal Frs2α Expression in Mice Leads to Abnormal Ureteric Bud Induction and Vesicoureteral Reflux. *Pediatr Res.* 2017 Dec;82(6):1022-1029.

Geramita MA, Hofer J, Cooper J, **Moritz ML**. Decreased severity of Shiga toxin-producing Escherichia coli haemolytic uraemic syndrome (STEC-HUS) in a child with type 1 von Willebrand disease. *BMJ Case Rep.* 2017; Epub ahead of print.

Squires J, **Nguyen C**. Complexity of Pre-emptive Liver Transplantation in Children With Primary Hyperoxaluria Type 1. *Pediatr Transplant.* 2016 Aug;20(5):604-6.

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Phua YL, **Ho J**. Insights into the Regulation of Collecting Duct Homeostasis by Small Noncoding RNAs. *J Am Soc Nephrol.* 2017 Dec 8. Epub ahead of print.

Ellis D. Pathophysiology, Evaluation, and Management of Edema in Childhood Nephrotic Syndrome. *Front Pediatr.* 2016 Jan 11;3:111. doi: 10.3389/fped.2015.00111. eCollection 2015. Review.

Swiatecka-Urban A. Endocytic Trafficking at the Mature Podocyte Slit Diaphragm. *Front Pediatr.* 2017 Feb 24; 5:32. doi: 10.3389/fped.2017.00032. eCollection 2017. Review.

Mukherjee E, **Maringer K**, **Papke E**, **Bushnell D**, **Schaefer C**, Kramann R, **Ho J**, Humphreys BD, **Bates C**, **Sims-Lucas S**. Endothelial Marker-Expressing Stromal Cells Are Critical for Kidney Formation. *Am J Physiol Renal Physiol.* 2017 Sep 1; 313(3):F611-F620.

Shukla S, Basu A, **Moritz ML**. Use of Hypotonic Maintenance Intravenous Fluids and Hospital-Acquired Hyponatremia Remain Common in Children Admitted to a General Pediatric Ward. *Front Pediatr.* 2016. Aug;4:90.

About Children's Hospital of Pittsburgh of UPMC

Regionally, nationally, and globally, Children's Hospital of Pittsburgh of UPMC 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, Children's Hospital has fulfilled this mission since its founding in 1890. Children's is named consistently to several elite lists of pediatric hospitals, including ranking No. 9 in the prestigious *U.S. News & World Report* annual Honor Roll of America's Best Children's Hospitals for 2017–2018 and ranking 10th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2016).