### Significant Accomplishments

**Improving Survival for Children on Dialysis**

Children with end stage kidney disease (ESKD) face enormous health hurdles, and a significantly shorter life expectancy. But a recent report shows that the outcome of dialysis treatment they require is dramatically improving. In a study published in the *Journal of the American Medical Association*, lead author Mark Mitsnefes, MD, MS, found that death rates among children and adolescents undergoing dialysis for ESKD in the United States have declined significantly over the past two decades. The study identified 23,401 children and adolescents in the United States who began ESKD treatment with dialysis between 1990 and 2010, and noted a significant decrease in mortality rates among the patients over that period. Children under age 5 who started dialysis in 1990-1994 had a mortality rate of 112.2 per 1,000 person-years. For those who began dialysis in 2005-2010, the rate fell to 83.4 per 1,000 person-years. Among those aged 5 and older, mortality rates declined from 44.6 per 1,000 person-years to 25.9. Significant decline also occurred in cardiovascular and infection-related mortality. Improved pre-dialysis care, advances in dialysis technology and greater experience of clinicians providing dialysis care may each have played a role in reducing the mortality rates.

**Controlling Cholesterol in Pediatric Kidney Transplant Recipients**

Cardiovascular disease is the leading cause of death for young adults who received a kidney transplant in childhood. High cholesterol is an important modifiable cardiovascular risk factor in these patients, yet research suggests that only about 50 percent of adolescents have even a single cholesterol test before they become adults, and fewer than 40 percent of adult transplant patients have controlled cholesterol. In a study published
in *Pediatrics*, David Hooper, MD, MS, and Jens Goebel, MD, demonstrated that using health information technology and reliable systems of care can dramatically improve outcomes. These more reliable systems led to 100 percent of eligible patients with high cholesterol being appropriately treated and 97 percent of kidney transplant patients with LDL cholesterol controlled below the recommended target of 130 mg/dl. Important components of their system redesign include: standardized protocols for personalized cholesterol monitoring based on risk; use of health information technology for decision support, population management and pre-visit planning; and well-defined roles and responsibilities among team members. This study demonstrates powerful techniques that can be used to improve important outcomes for children and adults with many chronic illnesses.

**Reducing Harm From Nephrotoxic Medication**

Nephrotoxic medication exposure is one of the most common causes of acute kidney injury (AKI) in hospitalized children. In a recent study published in *Pediatrics*, Stuart Goldstein, MD, Director of the Center for Acute Care Nephrology, demonstrated for the first time that the electronic health record can be programmed to reliably identify patients at-risk for nephrotoxic medication associated AKI. Through systematic kidney function assessment using a daily serum creatinine in at-risk patients, the research team found that 25 percent of all at-risk patients developed AKI. In addition, the team observed a 42 percent reduction in nephrotoxic medication associated AKI days, which translates to 900 AKI free days over a one year period.

**Research Highlights**

**Prasad Devarajan, MD**

Dr. Devarajan has continued with a wide spectrum of approaches to kidney health and disease processes, spanning from molecular, genomic and proteomic approaches to human observational and clinical trials. Dr. Devarajan is the Director of the newly NIH-funded P50 Center of Excellence in Nephrology, a unique multi-disciplinary research program designed to support basic, translational, and clinical research on critical pediatric kidney diseases that have major unmet needs. The proposal includes three Primary Research projects are proposed in the areas of acute kidney injury, proteinuric kidney disease, and lupus nephritis, with participation from recognized teams of investigators from multiple disciplines. Also included are high-resource Gene Expression, Proteomics, and Biomarker Cores with Core Leaders of international repute to support the study of the three focus areas. In addition, six Pilot and Feasibility projects will be funded in the three areas of research focus. Dr. Devarajan is the center PI and/or nephrology lead investigator for several NIH-funded prospective clinical studies. He has established a Kidney Biomarker Laboratory which now performs more than 40 distinct assays for acute and chronic kidney disease biomarkers. Dr. Devarajan’s ground-breaking research on biomarkers and new therapeutic targets in kidney diseases has yielded over 20 publications and several patent applications during the last fiscal year.

**Stuart L. Goldstein, MD**

Dr. Goldstein is the Director of the Center for Acute Care Nephrology (CACN), and has had a very productive research year, with achievements that spanned the scope of the Center’s research missions. The nephrotoxic medication acute kidney injury (AKI) reduction project, NINJA, resulted in a 33% reduction in AKI, and the associated manuscript was accepted for publication in *Pediatrics*. The CACN also is coordinating the international pediatric contribution to the DIRECT study, which is a genome wide association study for nephrotoxic medication associated AKI; currently 15 pediatric centers have signed on to this project. The
CACN is also coordinating the NICHD sponsored Pediatric Opportunistic Pharmacokinetic Study arm of the Pediatric Trials Network. Other ongoing research projects include validation of the Renal Angina risk stratification concept in the Pediatric ICU population, validation of novel AKI biomarkers in the ICU, and well as international multicenter AKI trials as part of the Prospective Pediatric AKI Research Group, which is housed in the CACN.

Elizabeth C. Jackson, MD

Dr. Jackson is the Director of the Healthy Bladder Clinic, and continues her active research program in optimizing the management of nocturnal enuresis. She is completing a randomized prospective trial comparing the effectiveness of the voice recordable alarm with the buzzer alarm for nocturnal enuresis. Preliminary results suggest that the voice alarm may lead to a lower dropout rate, and have been presented at national scientific meetings.

Bradley Dixon, MD

Dr. Dixon’s laboratory is focused on the mechanisms by which cells protect themselves from hyperosmolality in order to survive. One aspect of Dr. Dixon’s research is whether hyperosmolality of the bladder environment may interfere with the identification of damage to a cell’s DNA, leading to accumulation of mutations and ultimately an increased risk of cancer. Another aspect of Dr. Dixon’s laboratory research is studying how kidney cells can sense the degree of hyperosmolality around them in order to switch on vital cellular programs to withstand these conditions. Finally, Dr. Dixon is involved in clinical research with a focus on disorders of blood vessel inflammation and clotting known as thrombotic microangiopathies. Dr. Dixon is particularly interested in making clinical testing for the two major forms of thrombotic microangiopathy, aHUS and TTP, more efficient and meaningful as well as investigating new tests that can help to distinguish these two disease processes.

Mark Mitsnefes, MD, MS

Dr. Mitsnefes’ research interest has been to define biologic targets for interventions to prevent progression of cardiovascular disease in children with chronic kidney disease, through epidemiological and translational studies. Dr. Mitsnefes is a co-investigator and co-chair of the Cardiovascular Subcommittee in the multicenter NIH funded study of chronic kidney disease in children, the CKiD study. In one published study, the CKiD investigators examined the frequency of hypertension based on both office and 24-hour ambulatory blood pressure monitoring (ABPM). This study indicated that ABPM should be used to monitor blood pressure and guide treatment of hypertension in children with chronic kidney disease. Another published CKiD study provided evidence that children with chronic kidney disease are at increased cardiovascular risk, because the majority of these children were hypertensive and dyslipidemic, and over a quarter of them were either overweight or obese. In addition, these children had significantly greater carotid artery intima-medial thickness, an early marker of atherosclerosis.

Edward Nehus, MD, MS

Dr. Nehus’ research interest is in comparative effectiveness research with special emphasis on long-term outcomes of pediatric kidney transplant recipients. Other research interests include pharmacokinetic alterations that occur in children receiving continuous renal replacement therapy and the use of novel technologies for the estimation of kidney function. This past year, he completed the first nationwide study that investigated trends and graft outcomes of steroid avoidance in children who receive kidney transplants. Dr. Nehus’ research demonstrated that steroid avoidance can be safely practiced without conferring increased risk of graft failure, and therefore is an attractive option to avoid steroid-related morbidity. He also published two analyses.
evaluating cystatin C for the estimation of kidney function in high-risk patient populations.

Michael Bennett, PhD

Dr. Bennett is the Director of the Cincinnati Children's Hospital Medical Center Biomarker Laboratory and Co-Director of the Center of Excellence in Pediatric Nephrology Proteomics Core. His primary research interests include biomarkers and mechanisms of nephrotic syndrome and lupus nephritis. A major accomplishment this past year was the discovery of an investigational panel of biomarkers that can distinguish steroid sensitive from steroid resistant nephrotic syndrome. This panel has the potential to assist physicians in the early diagnosis of steroid resistance and help them to tailor more appropriate treatment plans for patients with this serious and progressive disease.

David Hooper, MD, MS

Dr. Hooper’s research interests lie in improving clinical outcomes for children with kidney disease through the design of reliable healthcare systems. His primary focus is to combine clinical outcomes research with quality improvement methodology to reliably prevent cardiovascular disease, the leading cause of long-term death and disability in children with kidney disease. During the past year, Dr. Hooper has published two important papers describing the variation in preventive cardiology care across six pediatric nephrology centers and demonstrating the ability to improve population cholesterol control by applying reliable systems of chronic disease management. Dr. Hooper has developed the capability to study the impact of care transformation on blood pressure control in kidney transplant recipients. Additionally, Dr. Hooper has helped design a sophisticated comprehensive web-based pre-visit planning tool that integrates medical record data, medication pharmacokinetic data and patient adherence data to provide decision support in kidney transplant care.

Rene Vandevoorde, MD

Dr. Vandevoorde is the Medical Director of Dialysis. His research interest lies in the different sequelae of chronic kidney disease in children with a focus on end stage renal disease and dialysis. He participates in multi-center studies or registry based analysis of interventions and outcomes. Particular areas of study include anemia management, bone and mineral disease, growth, psychosocial development, and associated morbidities of dialysis. He is the lead investigator for two current studies looking at the safety and efficacy of drugs in advanced chronic kidney disease: an intravenous iron supplement currently used in adults and a calcimimetic agent which binds the calcium-sensing receptor of the parathyroid gland. Our dialysis unit is also one of 27 pediatric units examining factors to reduce the rate of peritonitis in children receiving peritoneal dialysis. This project has shown a 27% reduction in infection rates so far after only one year of analysis. With this success, we are now embarking on applying similar interventions to reduce the rate of blood stream infections with hemodialysis catheters.

Jens Goebel, MD

Dr. Goebel is the Clinical Director of Nephrology and Medical Director of Kidney transplantation. His research interests focus on a better understanding of immune mechanisms affecting transplant outcomes. He has continued to advance knowledge about immunosuppressive agents used in pediatric kidney transplantation, and about renal issues in pediatric bone marrow transplantation. Examples for the former include the use of pharmacogenetics to better predict patients’ responses to drugs such tacrolimus or mycophenolate and the application of advanced immune phenotyping to further characterize possibly tolerogenic effects of sirolimus. Examples for the latter are ongoing work in pediatric bone marrow transplantation to further characterize the role of BK virus as a significant pathogen in that field and to develop novel insights into thrombotic
microangiopathy, a dreaded complication seen in patients who receive bone marrow transplants. Dr. Goebel also remains actively involved in work focusing on adherence and quality improvement in pediatric kidney transplantation, and he continues his role as center-PI for the CKID study, a large, NIH-sponsored effort to better understand the effects of chronic kidney disease in children over time.

**Significant Publications**


This study found that death rates among children and adolescents undergoing dialysis for ESKD in the United States have declined significantly over the past two decades. The study identified 23,401 children and adolescents in the United States who began ESKD treatment with dialysis between 1990 and 2010, and noted a significant decrease in mortality rates among the patients over that time period. Significant decline also occurred in both cardiovascular and infection-related mortality. Improved pre-dialysis care, advances in dialysis technology and greater experience of clinicians providing dialysis care may each have played a role.


This study demonstrated that the use of health information technology and reliable systems of care to achieve annual cholesterol monitoring in 95% of their patients can dramatically improve outcomes. These more reliable systems led to 100% of eligible patients with high cholesterol being appropriately treated with medical therapy and 97% of kidney transplant patients at Cincinnati Children’s with LDL cholesterol controlled below a recommended target of 130 mg/dl. This study demonstrates powerful techniques that can be used to improve important outcomes for children and adults with many chronic illnesses.


This prospective study showed that a panel of novel urinary biomarkers is strongly associated with specific tissue changes observed in conjunction with activity and chronicity of lupus nephritis. These urinary biomarkers are well-suited for use in noninvasive monitoring of lupus nephritis.


This prospective study examined for the first time the tolerance of the human kidney to ischemic injury. The study comprehensively showed that kidney structural, functional, and biomarker-related injuries are significantly milder than previously thought. The study showed that human kidneys can safely tolerate 30-60 minutes of controlled clamp ischemia with only mild structural changes and no acute functional loss.


This prospective study demonstrated that novel non-invasive urinary biomarkers such as NGAL can reliably differentiate between children with steroid sensitive versus steroid resistant nephrotic syndrome. Biomarker levels also correlate with disease severity in children with steroid resistant nephrotic syndrome.

**Division Publications**


34. Miller ER 3rd, Juraschek SP, Anderson CA, Guallar E, Henoch-Ryugo K, Charleston J, Turban S, Bennett MR, Appel LJ. The Effects of n-3 Long-Chain Polyunsaturated Fatty Acid Supplementation on


Faculty, Staff, and Trainees

Faculty Members

**Prasad Devarajan, MD,** Professor
Leadership Louise M. Williams Endowed Chair; Director, Division of Nephrology & Hypertension; Director, Clinical Nephrology Laboratory; CEO, Dialysis Unit; Director, Nephrology Fellowship Training Program

Research Interests Pathogenesis, biomarkers, and novel therapies of acute kidney injury; Pathogenesis and biomarkers of focal segmental glomerulosclerosis; Pathogenesis and biomarkers of lupus nephritis

Michael Bennett, PhD, Assistant Professor
Leadership Director, Biomarker Laboratory
Research Interests Biomarker discovery in acute and chronic kidney disease; focal segmental glomerulosclerosis

John J. Bissler, MD, Professor
Leadership Clark D. West Chair of Nephrology
Research Interests Polycystic kidney disease, renal tumors, tuberous sclerosis complex, Renal Cell Biology

Bradley P. Dixon, MD, Assistant Professor
Research Interests DNA damage and repair, cell biology of the augmented bladder, atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura

Jens Goebel, MD, Professor
Leadership Medical Director of Transplantation; Clinical Director, Nephrology
Research Interests Advancing basic and translational investigations into immunological aspects especially relevant to the field of transplantation

Stuart Goldstein, MD, Professor
Leadership Director, Center for Acute Care Nephrology; Medical Director, Pheresis Service
Research Interests Acute Kidney Injury, End Stage Renal Disease, Multi-Organ Dysfunction Syndrome, Continuous Renal Replacement Therapy, Cardio-Renal Syndrome, Nephrotoxic medication injury

Elizabeth Jackson, MD, Associate Professor
Leadership Director, Healthy Bladder Clinic
Research Interests Nocturnal enuresis, kidney stones, lower urinary tract dysfunction

Paul McEnery, MD, Professor Emeritus
Research Interests Glomerulonephritis; vitamin D resistant rickets; End Stage Renal Disease

Mark Mitsnerefs, MD, Professor
Leadership Program Director, Clinical Translational Research Center
Research Interests Cardiovascular abnormalities and risk factors for increased cardiac morbidity and mortality in children with CKD; evaluation of LVH; cIMT; hypertension

Edward Nehus, MD, Assistant Professor
Research Interests Comparative effectiveness research with special emphasis on long-term outcomes of pediatric kidney transplant recipients

C. Frederic Strife, MD, Professor Emeritus
Research Interests Clinical aspects of glomerulonephritis and dialysis

Rene Vandevoorde, MD, Assistant Professor
Leadership Medical Director, Dialysis Unit
Research Interests Chronic Kidney Disease; Dialysis including Infant Dialysis; Epidemiology of Renal
Diseases; Medical Education

David Hooper, MD, Assistant Professor

Research Interests Reliable and innovative chronic disease management, cardiovascular outcomes following kidney transplantation

Trainees

Ahmad Kaddourah, MD, PL-2
Donna Claes, MD, PL-2
Nianzhou Xiao, MD, PL-1
Stella Shin, MD, PL-1
LaTawnya Pleasant-Griffin, MD, PL-1

Division Collaboration

Heart Institute » Catherine Krawczeski
Co-investigator on studies entitled "Novel biomarkers in cardiac surgery to detect acute kidney injury", and "Ancillary Studies in the natural history of acute kidney injury" (Prasad Devarajan).

Rheumatology » Hermine Brunner
Co-investigator on studies entitled "Forecasters of progression of chronic kidney disease", and "Advanced Proteomics for the early prediction of lupus nephritis" (Prasad Devarajan).

Rheumatology » Hermine Brunner
Co-PI on study entitled "Biomarkers to distinguish classes of lupus nephritis", and Research Associate on "Advanced Proteomics for the early prediction of lupus nephritis" (Prasad Devarajan).

Developmental Biology » Steven Potter
Co-investigator on studies entitled "Glomerulosclerosis in human FSGS and mouse models" (Prasad Devarajan).

Hematology/Oncology » Sonata Jodele
Co-Investigator on study entitled "A Prospective Analysis of Clinical and Biochemical Markers for Pediatric Stem Cell Transplant-Associated Thrombotic Microangiopathy" (Prasad Devarajan).

Critical Care Medicine » Derek Wheeler
Use of Novel Urine and Blood Biomarkers to Optimize Fluid Dosing in Critically Ill Children with Acute Kidney Injury (Prasad Devarajan).

James M. Anderson Center for Health Systems Excellence » Peter A. Margolis
Reliable Individualized Monitoring Improves Cholesterol Control in Kidney Transplant Recipients (David K. Hooper, Jens Goebel).

James M. Anderson Center for Health Systems Excellence » Adam C. Carle
Quality of CVD Care in Adolescents (David K. Hooper, Mark Mitsnefes).

Clinical Pharmacology » Tsuyoshi Fukuda, Alexander Vinks, and Rhonda Gardiner
Risk of Tacrolimus Toxicity in CYP3A5 Non-Expressors Treated with Intravenous Nicardipine After Kidney Transplantation (David K. Hooper, Jens Goebel).

James M. Anderson Center for Health Systems Excellence » Ashwini Roy-Chaudhury
Risk of Tacrolimus Toxicity in CYP3A5 Non-Expressors Treated with Intravenous Nicardipine After Kidney Transplantation (David K. Hooper, Jens Goebel).

James M. Anderson Center for Health Systems Excellence; Behavioral Medicine and Clinical Psychology; Preventive Cardiology » Peter A. Margolis, Ahna Pai, and Elaine M. Urbina
A Reliable Blood Pressure Management System (David K. Hooper, Mark Mitsnefes, Jens Goebel).

Urology » William DeFoor, Pramod Reddy, and Paul Noh
Collect NGAL on hydronephrosis before and after repair (Prasad Devarajan).

Grants, Contracts, and Industry Agreements

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