New CAIRIBU GU Basic Science, Clinical/Translational, and Population Health Research Sept. 2022

BLADDER

Comparing clinical bladder diaries and recalled patient reports for measuring lower urinary tract symptoms in the symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

Flynn KE, Wiseman JB, Helmuth ME, Smith AR, Bradley CS, Cameron AP, Henry Lai H, Kirkali Z, Kreder KJ, Geynisman-Tan J, Merion RM, Weinfurt KP

Bladder diaries are a key source of information about lower urinary tract symptoms (LUTS); however, many patients do not complete them as instructed. Questionnaire-based patient-reported outcome measures (PROMs) are another option for reporting LUTS but may have recall bias. We assessed the strength of the associations between PROMs and a 3-day bladder diary. Symptomatic adults from 6 tertiary care sites completed a 3-day paper bladder diary and 3-, 7-, and 30-day electronic PROMs. We assessed the linear associations between mapped pairs of diary variables and responses to PROM items using biserial and polyserial correlation coefficients with 95% confidence intervals. Overall, Missing and unusable bladder diary data were common, highlighting the patient burden associated with this method of data collection. A questionnaire-based PROM is a reasonable alternative to a diary for reporting voiding frequency and may offer an easier option for reporting some symptoms.

Current Knowledge and Novel Frontiers in Lower Urinary Tract Dysfunction after Spinal Cord Injury: Basic Research Perspectives

Wada N, Karnup S, Kadekawa K, Shimizu N, Kwon J, Shimizu T, Gotoh D, Kakizaki H, de Groat WC, **Yoshimura N**

This review article aims to summarize the recent advancement in basic research on lower urinary tract dysfunction (LUTD) following spinal cord injury (SCI) above the sacral level. We particularly focused on the neurophysiologic mechanisms controlling the lower urinary tract (LUT) function and the SCI-induced changes in micturition control in animal models of SCI. The LUT has two main functions, the storage and voiding of urine, that are regulated by a complex neural control system. This neural system coordinates the activity of two functional units in the LUT: the urinary bladder and an outlet including bladder neck, urethra, and striated muscles of the pelvic floor. Following SCI, the bladder is initially areflexic but then becomes hyperreflexic due to the emergence of a spinal micturition reflex pathway. However, the bladder does not empty efficiently because coordination between the bladder and urethral sphincter is lost. In animal models of SCI, hyperexcitability of silent C-fiber bladder afferents is a major pathophysiological basis of neurogenic LUTD, especially detrusor overactivity. Reflex plasticity is associated with changes in the properties of neuropeptides, neurotrophic factors, or chemical receptors of afferent neurons. Not only C-fiber but also Aδ-fiber could be involved in the emergence of neurogenic LUTD such as detrusor sphincter dyssynergia following SCI. Animal research using disease models helps us to detect the different contributing factors for LUTD due to SCI and to find potential targets for new treatments.

Effect of Vitamin D Supplementation on Overactive Bladder and Urinary Incontinence Symptoms in Older Men: Ancillary Findings from a Randomized Trial

Markland AD, Vaughan C, **Huang AJ**, Kim E, Bubes VY, Tangpricha V, Buring J, Lee IM, Cook N, Manson JE, Grodstein F

The purpose of this study is to evaluate vitamin D supplementation for preventing or treating overactive bladder (OAB) and urinary incontinence (UI) in men. Ancillary study of men aged ≥55 years in the VITamin D and OmegA-3 TriaL (VITAL). Randomized treatments included: vitamin D3 (cholecalciferol), marine omega-3 fatty acids, or matching placebo. Structured UI questions measured the prevalence of OAB at year 5, and UI at years 2 and 5, along with incidence and progression of UI from years 2 to 5. Pre-specified subgroup analyses examined men with low baseline serum vitamin D [25(OH)D<20 ng/mL]. Overall, vitamin D supplementation did not improve OAB, or UI, compared to placebo. However, specific use of vitamin D in men with lower 25(OH)D levels had inconsistent findings.

Foundational science and mechanistic insights for a shared disease model: an expert consensus

Alperin M, Abramowitch S, Alarab M, Bortolini M, Brown B, Burnett LA, Connell KA, Damaser M, de Vita R, Gargett CE, Guess MK, Guler Z, Jorge RN, Kelley RS, Kibschull M, Miller K, Moalli PA, **Mysorekar IU**, Routzong MR, Shynlova O, Swenson CW, Therriault MA, Northington GM

Pelvic floor disorders (PFDs) are complex conditions that impact millions of women worldwide. It is estimated that PFDs will affect approximately 30%–50%of women older than 50 years and incur a 20%lifetime risk of undergoing at least 1 surgical procedure to repair either pelvic organ prolapse (POP) or stress urinary incontinence (SUI) by age 80 years. The surgical costs alone are estimated to exceed $10 billion annually, and this does not account for the cost of nonsurgical and conservative treatments. Although a large body of epidemiological literature provides important information regarding the risk factors for PFDs, the pathogenesis of POP and SUI continues to be poorly understood. Consequently, POP and SUI are associated with significant health care expenditure primarily due to lack of preventive measures, high failure rate of available interventions, and the need for retreatments. Furthermore, the long-standing gaps in mechanistic insights into the pathophysiology of POP and SUI represent one of the major barriers to the development of scientifically rational preventive and therapeutic strategies. Women's health across the life span depends on a better understanding of the anatomy and physiology of the female pelvic floor (PF) and the causal links between the multifactorial epidemiological risk factors and POP/SUI.

Gut-bladder axis enters the stage: Implication for recurrent urinary tract infections

Salazar AM, **Neugent ML**, **De Nisco NJ**, **Mysorekar IU**

The gut microbiome is a critical modulator of systemic physiology, including infectious disease susceptibility. Although this niche is a reservoir for uropathogenic Escherichia coli, knowledge of its role in urinary tract infections (UTIs) is limited. We discuss two recent studies, Thänert et al., 2022 and Worby et al., 2022, that interrogate the roles of the gut-bladder axis in UTIs.

Phenotyping of Urinary Urgency Patients without Urgency Incontinence, and Their Comparison to Urgency Incontinence Patients: Findings from the LURN Study

Lai HH, Wiseman JB, Helmuth ME, Smith AR, **Amundsen CL**, Cameron AP, Glaser AP, Hendrickson WK, Kirkali Z, Kenton K

The purpose of this study is to characterize patients with urinary urgency (UU) with and without urgency urinary incontinence (UUI) who presented to clinics actively seeking treatment for their symptoms. Participants who enrolled in the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN-I) were categorized into UU with versus without UUI. Participants were followed for 1 year; their urinary symptoms, urologic pain, psychosocial factors, bowel function, sleep disturbance, physical activity levels, physical function, and quality of life (QOL) were compared. Mixed effects linear regression models were used to examine the relationships between UUI and these factors. The conclusion showed that patients with UUI have severe storage symptoms, more psychosocial symptoms, poorer physical functioning, and worse QOL. Our data suggested UUI may be a more severe manifestation of UU, rather than UU and UUI being distinct entities.

Study protocol and methods for Easing Pelvic Pain Interventions Clinical Research Program (EPPIC): a randomized clinical trial of brief, low-intensity, transdiagnostic cognitive behavioral therapy vs education/support for urologic chronic pelvic pain syndrome (UCPPS)

Lackner JM, Jaccard J, Quigley BM, Ablove TS, Danforth TL, Firth RS, Gudleski GD, Krasner SS, Radziwon CD, Vargovich AM, **Clemens JQ**, Naliboff BD

Urologic chronic pelvic pain syndrome (UCPPS) encompasses several common, costly, diagnoses including interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome that are poorly understood and inadequately treated with conventional medical therapies. Behavioral strategies, recommended as a first-line treatment for managing symptoms, are largely inaccessible, time and labor intensive, and technically complex. The Easing Pelvic Pain Interventions Clinical Research Program (EPPIC) is a clinical trial examining the efficacy of low-intensity cognitive behavioral therapy (Minimal Contact CBT or MC-CBT) for UCPPS and its durability 3 and 6 months post treatment. Additional aims include characterizing the operative processes (e.g., cognitive distancing, context sensitivity, coping flexibility, repetitive negative thought) that drive MC-CBT-induced symptom relief and pre-treatment patient variables that moderate differential response.

Timing is everything: impact of development, ageing and circadian rhythm on macrophage functions in urinary tract infections

Wang AS, **Steers NJ**, Parab AR, Gachon F, Sweet MJ, **Mysorekar IU**

The bladder supports a diversity of macrophage populations with functional roles related to homeostasis and host defense, including clearance of cell debris from tissue, immune surveillance, and inflammatory responses. This review examines these roles with particular attention given to macrophage origins, differentiation, recruitment, and engagement in host defense against urinary tract infections (UTIs), where these cells recognize uropathogens through a combination of receptor-mediated responses. Time is an important variable that is often overlooked in many clinical and biological studies, including in relation to macrophages and UTIs. Given that ageing is a significant factor in urinary tract infection pathogenesis and macrophages have been shown to harbor their own circadian system, this review also explores the influence of age on macrophage functions and the role of diurnal variations in macrophage functions in host defense and inflammation during UTIs. We provide a conceptual framework for future studies that address these key knowledge gaps.

Urologic complications in diabetes

Blair Y, Wessells H, Pop-Busui R, Ang L, **Sarma AV**

Urologic complications such as bladder and sexual dysfunction among men and women with diabetes have received relatively little attention. This is despite emerging evidence that demonstrates that urologic complications increase with age in the general population and are more common in individuals with diabetes compared to those without diabetes. Here we summarize the latest information about the epidemiology of urologic complications in the setting of diabetes and the most recent findings regarding pathophysiology. In addition, we identify knowledge gaps and need for future funding to address these gaps that will reduce the burden of urologic complications in diabetes and optimize quality of life for all individuals affected by it.

Uropathogenic Escherichia coli subverts mitochondrial metabolism to enable intracellular bacterial pathogenesis in urinary tract infection

Beebout CJ, Robertson GL, Reinfeld BI, Blee AM, **Morales GH**, **Brannon JR**, Chazin WJ, Rathmell WK, Rathmell JC, Gama V, **Hadjifrangiskou M**

Urinary tract infections are among the most common human bacterial infections and place a significant burden on healthcare systems due to associated morbidity, cost and antibiotic use. Despite being a facultative anaerobe, uropathogenic Escherichia coli, the primary cause of urinary tract infections, requires aerobic respiration to establish infection in the bladder. Here, by combining bacterial genetics with cell culture and murine models of infection,

we demonstrate that the widely conserved respiratory quinol oxidase cytochrome bd is required for intracellular infection of urothelial cells. Through a series of genetic, biochemical and functional assays, we show that intracellular oxygen scavenging by cytochrome bd alters mitochondrial physiology by reducing the efficiency of mitochondrial respiration, stabilizing the hypoxia-inducible transcription factor HIF-1 and promoting a shift towards aerobic glycolysis. This bacterially induced rewiring of host metabolism antagonizes apoptosis, thereby protecting intracellular bacteria from urothelial cell exfoliation and preserving their replicative niche. These results reveal the metabolic basis for intracellular bacterial pathogenesis during urinary tract infection and identify subversion of mitochondrial metabolism as a bacterial strategy to facilitate persistence within the urinary tract.

Vitamin D supplements and prevalent overactive bladder in women from midlife through older ages

Vaughan CP, Markland AD, **Huang AJ**, Tangpricha V, Grodstein F

The objective of this study is to determine if vitamin D supplementation is associated with prevalent overactive bladder (OAB) in women across the aging spectrum. We used the Nurses' Health Study (NHS) I (initiated in 1976) and NHS II (initiated in 1989) cohorts to evaluate the association of vitamin D supplements with prevalent OAB, all of which were reported by participants in 2019 in both NHS cohorts. OAB was defined as the self-reported need to rush to toilet to urinate at least sometimes. Further, OAB/wet included incontinence at least monthly because of urgency, whereas OAB/dry included incontinence once per month or less, or stress-predominant incontinence. Multivariable-adjusted odds ratios and 95% confidence intervals of OAB/dry and OAB/wet subtypes were estimated using logistic regression models. The conclusions showed that OAB symptoms are highly prevalent across adult women, including the oldest old, who are often excluded from treatment trials. Despite interest in vitamin D supplementation as a low-cost strategy to address OAB, our findings indicate oral vitamin D is not associated with prevalent OAB in middle-aged and older women.

KIDNEY

Incorporating genetics services into adult kidney disease care

Bogyo K, Vena N, May H, **Rasouly HM**, Marasa M, **Sanna-Cherchi S**, Kiryluk K, Nestor J, **Gharavi A**

Studies have shown that as many as 1 in 10 adults with chronic kidney disease has a monogenic form of disease. However, genetic services in adult nephrology are limited. An adult Kidney Genetics Clinic was established within the nephrology division at a large urban academic medical center to increase access to genetic services and testing in adults with kidney disease. Between June 2019 and December 2021, a total of 363 patients were referred to the adult Kidney Genetics Clinic. Of those who completed genetic testing, a positive diagnostic finding was identified in 27.1%, a candidate diagnostic finding was identified in 6.7% of patients, and a nondiagnostic positive finding was identified in an additional 8.6% of patients, resulting in an overall yield of 42.4% for clinically relevant genetic findings in tested patients. A genetic diagnosis had implications for medical management, family member testing, and eligibility for clinical trials. With the utilization of telemedicine, genetic services reached a diverse geographic and patient population. Genetic education efforts were integral to the clinic's success, as they increased visibility and helped providers identify appropriate referrals. Ongoing access to genomic services will remain a fundamental component of patient care in adults with kidney disease.

The Prevalence and Clinical Significance of Congenital Anomalies of the Kidney and Urinary Tract in Preterm Infants

Hays T, Thompson MV, Bateman DA, Sahni R, Tolia VN, Clark RH, **Gharavi AG**

The prevalence and importance of congenital anomalies of the kidney and urinary tract (CAKUT) in preterm infants is unknown. The objective is to determine the prevalence of CAKUT in preterm infants and association with in-hospital morbidity and mortality. This cohort study included infants cared for in neonatal intensive care units managed by a large US network of hospitals and doctors. Eligible participants were infants born at 23 to 33 weeks' gestation between 2000 and 2020. Infants transferred from or to other health care facilities prior to discharge or death were excluded in analysis of outcomes. Data were analyzed from December 2021 until May 2022. The findings of this cohort study suggest that clinicians caring for preterm infants should have higher suspicion for CAKUT and consider screening, particularly those with extrarenal anomalies or genetic disorders, as preterm infants with CAKUT appear to be at significantly higher risk of death or severe illness. Detection of CAKUT can inform risk stratification and clinical decision making, and should also prompt clinicians to consider a genetic evaluation.

A user-friendly tool for cloud-based whole slide image segmentation with examples from renal histopathology

Lutnick B, Manthey D, Becker JU, Ginley B, Moos K, Zuckerman JE, Rodrigues L, Gallan AJ, Barisoni L, Alpers CE, Wang XX, Myakala K, Jones BA, Levi M, Kopp JB, Yoshida T, Zee J, Han SS, **Jain S**, Rosenberg AZ, Jen KY, Sarder P, **Barasch J**

Image-based machine learning tools hold great promise for clinical applications in pathology research. However, the ideal end-users of these computational tools (e.g., pathologists and biological scientists) often lack the programming experience required for the setup and use of these tools which often rely on the use of command line interfaces. We have developed Histo-Cloud, a tool for segmentation of whole slide images (WSIs) that has an easy-to-use graphical user interface. This tool runs a state-of-the-art convolutional neural network (CNN) for segmentation of WSIs in the cloud and allows the extraction of features from segmented regions for further analysis. By segmenting glomeruli, interstitial fibrosis and tubular atrophy, and vascular structures from renal and non-renal WSIs, we

demonstrate the scalability, best practices for transfer learning, and effects of dataset variability. Finally, we demonstrate an application for animal model research, analyzing glomerular features in three murine models. Histo-Cloud is open source, accessible over the internet, and adaptable for segmentation of any histological structure regardless of stain.

PROSTATE

Increased COX-1 expression in benign prostate epithelial cells is triggered by mitochondrial dysfunction

Hudson CN, **He K**, **Pascal LE**, **Liu T**, Myklebust LK, **Dhir R,** Srivastava P, **Yoshimura N**, **Wang Z**, **Ricke WA**, **DeFranco DB**

Prostatic inflammation is closely linked to the development and progression of benign prostatic hyperplasia (BPH). Clinical studies of non-steroidal anti-inflammatory drugs, which inhibit cyclooxygenase-2 (COX-2), targeting prostate inflammation patients with symptomatic BPH have demonstrated conflicting results, with some studies demonstrating symptom improvement and others showing no impact. Thus, understanding the role of the cyclooxygenases in BPH and prostatic inflammation is important. The expression of COX-1 was analyzed in a cohort of donors and BPH patients by immunohistochemistry and compared to previously determined characteristics for this same cohort. The impact of mitochondrial dysfunction on COX-1 and COX-2 was determined in experiments treating human benign prostate epithelial cell lines BPH-1 and RWPE-1 with rotenone and MitoQ. RWPE-1 cells were transfected with small interfering RNA specific to complex 1 gene NDUFS3. Our findings suggest COX-1 is elevated in BPH epithelial cells and is associated with increased presence of CD8+ cytotoxic T-cells. COX-1 can be induced in benign prostate epithelial cells in response to mitochondrial complex I inhibition, and knockdown of the complex 1 protein NDUFS3. COX-1 and mitochondrial dysfunction may play more of a role than previously recognized in the development of age-related benign prostatic disease.

STONES

Mechanisms of the intestinal and urinary microbiome in kidney stone disease

Miller AW, **Penniston KL**, Fitzpatrick K, Agudelo J, **Tasian G**, Lange D

Kidney stone disease affects ~10% of the global population and the incidence continues to rise owing to the associated global increase in the incidence of medical conditions associated with kidney stone disease including, for example, those comprising the metabolic syndrome. Considering that the intestinal microbiome has a substantial influence on host metabolism, that evidence has suggested that the intestinal microbiome might have a role in maintaining oxalate homeostasis and kidney stone disease is unsurprising. In addition, the discovery that urine is not sterile but, like other sites of the human body, harbours commensal bacterial species that collectively form a urinary microbiome, is an additional factor that might influence the induction of crystal formation and stone growth directly in the kidney. Collectively, the microbiomes of the host could influence kidney stone disease at multiple levels, including intestinal oxalate absorption and direct crystal formation in the kidneys.

- Jennifer Allmaras MPH, Muen Wang, 9/30/2022

Email cairibu@urology.wisc.edu to feature your newly published research in next month's communique