

BLADDER

D-Mannose reduces cellular senescence and NLRP3/GasderminD/IL-1 β -driven pyroptotic uroepithelial cell shedding in the murine bladder

Chetanchandra S Joshi, Arnold M Salazar, Caihong Wang, Marianne M Ligon, Rayvanth R Chappidi, **Bisiayo E Fashemi**, Paul A Felder, Amy Mora, Sandra L Grimm, Cristian Coarfa, **Indira U Mysorekar**

Aging is a risk factor for disease via increased susceptibility to infection, decreased ability to maintain homeostasis, inefficiency in combating stress, and decreased regenerative capacity. Multiple diseases, including urinary tract infection (UTI), are more prevalent with age; however, the mechanisms underlying the impact of aging on the urinary tract mucosa and the correlation between aging and disease remain poorly understood. Here, we show that, relative to young (8-12 weeks) mice, the urothelium of aged (18-24 months) female mice accumulates large lysosomes with reduced acid phosphatase activity and decreased overall autophagic flux in the aged urothelium, indicative of compromised cellular homeostasis. Aged bladders also exhibit basal accumulation of reactive oxygen species (ROS) and a dampened redox response, implying heightened oxidative stress. Furthermore, we identify a canonical senescence-associated secretory phenotype (SASP) in the aged urothelium, along with continuous NLRP3-inflammasome- and Gasdermin-D-dependent pyroptotic cell death. Consequently, aged mice chronically exfoliate urothelial cells, further exacerbating age-related urothelial dysfunction. Upon infection with uropathogenic *E. coli*, aged mice harbor increased bacterial reservoirs and are more prone to spontaneous recurrent UTI. Finally, we discover that treatment with D-mannose, a natural bioactive monosaccharide, rescues autophagy flux, reverses the SASP, and mitigates ROS and NLRP3/Gasdermin/interleukin (IL)-1 β -driven pyroptotic epithelial cell shedding in aged mice. Collectively, our results

demonstrate that normal aging affects bladder physiology, with aging alone increasing baseline cellular stress and susceptibility to infection, and suggest that mannose supplementation could serve as a senotherapeutic to counter age-associated urothelial dysfunction.

Integrated omics analysis unveils a DNA damage response to neurogenic injury

Ali Hashemi Gheinani, Bryan S Sack, Alex Bigger-Allen, Hatim Thaker, Hussein Atta, George Lambrinos, Kyle Costa, Claire Doyle, Mehrnaz Gharaee-Kermani, Susan Patalano, Mary Piper, Justin F Cotellessa, Dijana Vitko, Haiying Li, Manubhai Kadayil Prabhakaran, Vivian Cristofaro, John Froehlich, Richard S Lee, Wei Yang, Maryrose P Sullivan, **Jill A Macoska**, Rosalyn M Adam

Spinal cord injury (SCI) evokes profound bladder dysfunction. Current treatments are limited by a lack of molecular data to inform novel therapeutic avenues. Previously, we showed systemic inosine treatment improved bladder function following SCI in rats. Here, we applied multi-omics analysis to explore molecular alterations in the bladder and their sensitivity to inosine following SCI. Canonical pathways regulated by SCI included those associated with protein synthesis, neuroplasticity, wound healing, and neurotransmitter degradation. Upstream regulator analysis identified MYC as a key regulator, whereas causal network analysis predicted multiple regulators of DNA damage response signaling following injury, including PARP-1. Staining for both DNA damage (γ H2AX) and PARP activity (poly-ADP-ribose) markers in the bladder was increased following SCI, and attenuated in inosine-treated tissues. Proteomics analysis suggested that SCI induced changes in protein synthesis-, neuroplasticity-, and oxidative stress-associated pathways, a subset of which were shown in transcriptomics data to be inosine-sensitive. These findings provide novel insights into the molecular landscape of the bladder following SCI, and highlight a potential role for PARP inhibition to treat neurogenic bladder dysfunction.

Prolonged impacts of COVID-19-associated cystitis: A study on long-term consequences

Sophie Wittenberg, Jack Vercocke, **Michael Chancellor**, Sorabh Dhar, Aron Liaw, Steven Lucas, Nivedita Dhar

The Coronavirus Disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 virus is an international health concern with substantial morbidity and mortality. COVID-associated cystitis (CAC), presents as new onset or exacerbated urinary symptoms, resembling overactive bladder (OAB) symptoms. A cohort of 350 patients admitted to Detroit Hospitals with COVID-19 between May and December 2020, displaying CAC symptoms following discharge, was prospectively followed. Initial urologic evaluations occurred at 10-14 wk and were repeated at 21-28 mo post-discharge. Symptoms were managed conservatively, employing behavioral modifications and standard OAB medications. Participants completed surveys assessing urinary symptoms and quality of life (QoL) at both time points. The primary outcome was the Urology Care Foundation Overactive Bladder Assessment Tool. 87% of the final cohort (n = 310) reported symptom improvement at 21-28 mo post-discharge. Patients with new onset CAC symptoms showed a median decrease of 9-10 points in OAB and QoL scores, while those with existing symptoms experienced a decrease of 6 points. Overall, 95.4% of patients with new onset symptoms reported symptom improvement at follow-up, contrasting with 60.7% among those with existing symptoms. This study presents the first long-term follow-up of adult patients with CAC, revealing a promising prognosis with conservative management measures in the context of Long COVID. These findings provide reassurance to patients regarding symptom resolution and underscore the need for further research into this evolving aspect of COVID-19's impact on urological health.

Raising the alarm: fosfomycin resistance associated with non-susceptible inner colonies imparts no fitness cost to the primary bacterial uropathogen

Tomas A Bermudez, John R Brannon, Neha Dudipala, **Seth Reasoner**, **Grace Morales**, **Michelle Wiebe**, Mia Cecala, Michael DaCosta, **Connor Beebout**, Omar Amir, **Maria Hadjifrangiskou**

While fosfomycin resistance is rare, the observation of non-susceptible subpopulations among clinical *Escherichia coli* isolates is a common phenomenon during antimicrobial susceptibility testing (AST) in American and European clinical labs. Previous evidence suggests that mutations eliciting this phenotype are of high biological cost to the pathogen during infection, leading to current recommendations of neglecting non-susceptible colonies during AST. Here, we report that the most common route to fosfomycin resistance, as well as novel routes described in this work, does not impair virulence in uropathogenic *E. coli*, the major cause of urinary tract infections, suggesting a re-evaluation of current susceptibility guidelines is warranted.

STONES

Contribution of Hypersensitivity to Post-Ureteroscopy Ureteral Stent Pain: Findings from STENTS

H Henry Lai, Hongqui Yang, **Gregory E Tasian**, Jonathan D Harper, Alana C Desai, Rebecca D McCune, Ziya Kirkali, Hussein R Al-Khalidi, **Charles D Scales Jr**, Michele Curatolo; NIDDK Urinary Stone Disease Research Network (USDRN)

To examine the relationships between preoperative hypersensitivity to pain and central sensitization, and postoperative ureteral stent pain after ureteroscopy for urinary stones. Adults enrolled in the STudy to Enhance uNderstanding of sTent-associated Symptoms (STENTS) underwent quantitative sensory testing (QST) prior to ureteroscopy and stent placement. Hypersensitivity to mechanical pain was assessed using a pressure algometer. Participants rated their pain intensity to pressure applied to the ipsilateral flank area and lower abdominal quadrant on the side of planned stent placement, and the contralateral forearm (control). Pressure pain thresholds were also assessed.

Central sensitization was assessed by applying a pointed stimulator (pinprick) and calculating the temporal summation. Postoperative stent pain intensity and interference was assessed using PROMIS questionnaires. Data were analyzed using repeated-measures mixed-effects linear models. Among the 412 participants, the median age was 54.0 years, and 46% were female. Higher preoperative pain ratings to 2 kg and 4 kg mechanical pressure to the ipsilateral flank and abdominal areas were associated with higher postoperative stent pain intensity with the stent in situ. Greater degree of central sensitization preoperatively, manifesting as higher temporal summation, was associated with higher postoperative pain intensity. Factors associated with preoperative hypersensitivity on QST included female sex, presence of chronic pain conditions, widespread pain, and depression. Hypersensitivity to pain and central sensitization preoperatively was associated with postoperative ureteral stent pain, suggesting a physiologic basis for stent symptom variation. QST may identify patients more likely to develop stent pain after ureteroscopy and could inform selection for preventive and interventional strategies.

- Jennifer Allmaras MPH, Anna Barrett,
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BLADDER

[Survey of the infant male urobiome and genomic analysis of *Actinotignum spp*](#)

Seth A Reasoner, Viktor Flores, Gerald Van Horn, Grace Morales, Leslie M Peard, Benjamin Abelson, Carmila Manuel, Jessica Lee, Bailey Baker, Timothy Williams, Jonathan E Schmitz, Douglass B Clayton, Maria Hadjifrangiskou

The urinary bladder harbors a community of microbes termed the urobiome, which remains understudied. In this study, we present the urobiome of healthy infant males from samples collected by transurethral catheterization. Using a combination of enhanced culture and amplicon sequencing, we identify several common bacterial genera that can be further investigated for their effects on urinary health across the lifespan. Many genera were shared between all samples suggesting a consistent urobiome composition among this cohort. We note that, for this cohort, early life exposures including mode of birth (vaginal vs. Cesarean section), or prior antibiotic exposure did not influence urobiome composition. In addition, we report the isolation of culturable bacteria from the bladders of these infant males, including *Actinotignum spp.*, a bacterial genus that has been associated with urinary tract infections in older male adults. Herein, we isolate and sequence 9 distinct strains of *Actinotignum spp.* enhancing the genomic knowledge surrounding this genus and opening avenues for delineating the microbiology of this urobiome constituent. Furthermore, we present a framework for using the combination of culture-dependent and sequencing methodologies for uncovering mechanisms in the urobiome.

[Urinary symptoms and female sexual dysfunction in women with type 1 diabetes: the role of depression](#)

Golena Fernandez Moncaleano, Cody M Gibbons, Sarah Holt, Barbara Braffett, Rodica Pop-Busui, Alan Jacobson, Hunter Wessells, Aruna Sarma
Some reports suggest that women with type 1 diabetes (T1D) have a greater burden of female sexual dysfunction

(FSD) than women without T1D, but the etiology of this elevated risk is poorly understood. LUTS and UI symptoms were assessed in women with T1D who participated in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Multivariable logistic regression models estimated associations between FSD and UI/LUTS (overall and specific domains) and the impact of depression on these associations. FSD was measured with the Female Sexual Function Index-Reduced. In total, 499 self-reported sexually active women completed validated assessments of sexual and urinary function (mean \pm SD age, 47.7 \pm 7.6 years; T1D duration, 23.4 \pm 5.15 years). FSD was reported in 232 (46%) responders. The frequency of UI and LUTS was 125 (25.1%) and 96 (19.2%), respectively. Neither UI nor its subcategories (urge, stress) were associated with FSD. Although LUTS (odds ratio [OR], 1.75; 95% CI, 1.09-2.77) and its symptoms of urgency (OR, 1.99; 95% CI, 1.09-3.61) and incomplete emptying (OR, 2.44; 95% CI, 1.23-4.85) were associated with FSD, these associations were attenuated following adjustment for depression and antidepressant medication use. Depression indicators were independently associated with FSD overall and across domains. The complex interplay of voiding dysfunction, mental health, and sexual function warrants further investigation to understand the potential implications for patient assessment, goal setting, treatment, and care planning. Data are from a prospective study of individuals with T1D. These results are unable to explore cause-and-effect relationships among LUTS, UI, depression, and FSD. The sample may not be representative of the general population of women with T1D. Because participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study are mostly White, generalizing the findings to other races and to type 2 diabetes may not be appropriate. While

exclusion of sexually inactive women likely biases our findings toward the null, this design element permitted study of LUTS and UI in relation to aspects of FSD, the primary objective of this study. The significant associations between LUTS/UI and FSD among middle-aged women with T1D were greatly attenuated when depression was considered a mediating factor.

STONES

[Exploring optimal settings for safe and effective thulium fibre laser lithotripsy in a kidney model](#)

Arpit Mishra, Robert Medeiros, Junqin Chen, Francois Soto-Palou, Yuan Wu, Jodi Antonelli, Glenn M Preminger, Michael E Lipkin, Pei Zhong

To explore the optimal laser settings and treatment strategies for thulium fibre laser (TFL) lithotripsy, namely, those with the highest treatment efficiency, lowest thermal injury risk, and shortest procedure time. An in vitro kidney model was used to assess the efficacy of TFL lithotripsy in the upper calyx. Stone ablation experiments were performed on BegoStone phantoms at different combinations of pulse energy (EP) and frequency (F) to determine the optimal settings. Temperature changes and thermal injury risks were monitored using embedded thermocouples. Experiments were also performed on calcium oxalate monohydrate (COM) stones to validate the optimal settings. High EP /low F settings demonstrated superior treatment efficiency compared to low EP /high F settings using the same power. Specifically, 0.8 J/12 Hz was the optimal setting, resulting in a twofold increase in treatment efficiency, a 39% reduction in energy expenditure per unit of ablated stone mass, a 35% reduction in residual fragments, and a 36% reduction in total procedure time compared to the 0.2 J/50 Hz setting for COM stones. Thermal injury risk assessment indicated that 10 W power settings with high EP /low F combinations remained below the threshold for tissue injury, while higher power settings (>10 W) consistently exceeded the safety threshold. Our findings suggest that high EP /low F

settings, such as 0.8 J/12 Hz, are optimal for TFL lithotripsy in the treatment of COM stones. These settings demonstrated significantly improved treatment efficiency with reduced residual fragments compared to conventional settings while keeping the thermal dose below the injury threshold. This study highlights the importance of using the high EP /low F combination with low power settings, which maximizes treatment efficiency and minimizes potential thermal injury. Further studies are warranted to determine the optimal settings for TFL for treating kidney stones with different compositions.

[In vitro investigation of stone ablation efficiency, char formation, spark generation, and damage mechanism produced by thulium fiber laser](#)

Junqin Chen, Arpit Mishra, Robert Medeiros, Jodi Antonelli, Glenn M Preminger, Michael E Lipkin, Pei Zhong

To investigate stone ablation characteristics of thulium fiber laser (TFL), BegoStone phantoms were spot-treated in water at various fiber tip-to-stone standoff distances (SDs, 0.5 ~ 2 mm) over a broad range of pulse energy (Ep, 0.2 ~ 2 J), frequency (F, 5 ~ 150 Hz), and power (P, 10 ~ 30 W) settings. In general, the ablation speed (mm³/s) in BegoStone decreased with SD and increased with Ep, reaching a peak around 0.8 ~ 1.0 J. Additional experiments with calcium phosphate (CaP), uric acid (UA), and calcium oxalate monohydrate (COM) stones were conducted under two distinctly different settings: 0.2 J/100 Hz and 0.8 J/12 Hz. The concomitant bubble dynamics, spark generation and pressure transients were analyzed. Higher ablation speeds were consistently produced at 0.8 J/12 Hz than at 0.2 J/100 Hz, with CaP stones most difficult yet COM and UA stones easier to ablate. Charring was mostly observed in CaP stones at 0.2 J/100 Hz, accompanied by strong spark-generation, explosive combustion, and diminished pressure transients, but not at 0.8 J/12 Hz. By treating stones in parallel fiber orientation and leveraging the proximity effect of a ureteroscope, the

contribution of bubble collapse to stone ablation was found to be substantial (16% ~ 59%) at 0.8 J/12 Hz, but not at 0.2 J/100 Hz. Overall, TFL ablation efficiency is significantly better at high Ep/low F setting, attributable to increased cavitation damage with less char formation.

PROSTATE

[Beta-Sitosterol Alters Collagen Distribution in Prostate Fibroblasts](#)

Quentin D'Arcy, Marissa Sarna-McCarthy, Delaney Bowen, Fidias O Soto, Kourosh Zarringhalam, Jill A Macoska

Herbal supplements containing several types of plant sterols, vitamins, and minerals, are marketed for prostate health. In the majority of these supplements, the most abundant plant sterol is saw palmetto extract or its' principal component, beta-sitosterol. In terms of prostate health, previous work almost exclusively focused on the effects of beta-sitosterol on prostatic epithelium, with little attention paid to the effects on prostatic stroma. This omission is a concern, as the abnormal accumulation of collagen, or fibrosis, of the prostatic stroma has been identified as a factor contributing to lower urinary tract symptoms and dysfunction in aging men. To address whether beta-sitosterol may be promoting prostatic fibrosis, immortalized and primary prostate stromal fibroblasts were subjected to immunoblotting, immunofluorescence, qRT-PCR, ELISA, and image quantitation and analysis techniques to elucidate the effects of beta-sitosterol on cell viability and collagen expression and cellular localization. The results of these studies show that beta-sitosterol is nontoxic to prostatic fibroblasts and does not stimulate collagen production by these cells. However, beta-sitosterol alters collagen distribution and sequesters collagen within prostatic fibroblasts, likely in an age-dependent manner. This is a significant finding as prostate health supplements are used predominantly by middle aged and older men who may, then, be affected disproportionately by these effects.

[Genome-wide association study of prostate-specific antigen levels in 392,522 men identifies new loci and improves cross-ancestry prediction](#)

... Yu Jiang ... Stephen K Van Den Eeden ...

We conducted a multi-ancestry genome-wide association study of prostate-specific antigen (PSA) levels in 296,754 men (211,342 European ancestry; 58,236 African ancestry; 23,546 Hispanic/Latino; 3,630 Asian ancestry; 96.5% of participants were from the Million Veteran Program). We identified 318 independent genome-wide significant ($p \leq 5 \times 10^{-8}$) variants, 184 of which were novel. Most demonstrated evidence of replication in an independent cohort ($n=95,768$). Meta-analyzing discovery and replication ($n=392,522$) identified 447 variants, of which a further 111 were novel. Out-of-sample variance in PSA explained by our new polygenic risk score reached 16.9% (95% CI=16.1%-17.8%) in European ancestry, 9.5% (95% CI=7.0%-12.2%) in African ancestry, 18.6% (95% CI=15.8%-21.4%) in Hispanic/Latino, and 15.3% (95% CI=12.7%-18.1%) in Asian ancestry, and lower for higher age. Our study highlights how including proportionally more participants from underrepresented populations improves genetic prediction of PSA levels, with potential to personalize prostate cancer screening.

[Spatial transcriptomics identifies candidate stromal drivers of benign prostatic hyperplasia](#)

Anna S Pollack, Christian A Kunder, Noah Brazer, Zhewei Shen, Sushama Varma, Robert B West, Gerald R Cunha, Laurence S Baskin, James D Brooks, Jonathan R Pollack

Benign prostatic hyperplasia (BPH) is the nodular proliferation of the prostate transition zone in older men, leading to urinary storage and voiding problems that can be recalcitrant to therapy. Decades ago, John McNeal proposed that BPH originates with the "reawakening" of embryonic inductive activity by adult prostate stroma, which spurs new ductal proliferation and branching morphogenesis. Here, by laser microdissection and transcriptional profiling of the BPH stroma adjacent to hyperplastic branching ducts, we identified secreted factors likely

mediating stromal induction of prostate glandular epithelium and coinciding processes. The top stromal factors were Insulin Like Growth Factor 1 (IGF1) and CX-C Motif Chemokine Ligand 13 (CXCL13), which we confirmed by RNA in situ hybridization to be co-expressed in BPH fibroblasts, along with their cognate receptors (IGF1R and CXCR5) on adjacent epithelium. In contrast, IGF1 but not CXCL13 was expressed in human embryonic prostate stroma. Finally, we demonstrated that IGF1 is necessary for the generation of BPH-1 cell spheroids and patient-derived BPH cell organoids in three-dimensional culture. Our findings partially support historic speculations on the etiology of BPH, and provide what we believe to be new molecular targets for rational therapies directed against the underlying processes driving BPH.

KIDNEY

[Assessing GFR With Proenkephalin](#)

Remi Beunders, Leslie J Donato, Roger van Groenendaal, Birte Arlt, Cristiane Carvalho-Wodarz, Janin Schulte, Anton Cc Coolen, **John C Lieske**, Jeffrey W Meeusen, Allan S Jaffe, Peter Pickkers

In clinical practice, kidney (dys)function is monitored through creatinine-based estimations of glomerular filtration rate (eGFR: Modification of Diet in Renal Disease [MDRD], Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]). Creatinine is recognized as a late and insensitive biomarker of glomerular filtration rate (GFR). The novel biomarker proenkephalin (PENK) may overcome these limitations, but no PENK-based equation for eGFR is currently available. Therefore, we developed and validated a PENK-based equation to assess GFR. In this international multicenter study in 1354 stable and critically ill patients, GFR was measured (mGFR) through iothexol or iohalamate clearance. A generalized linear model with sigmoidal nonlinear transfer function was used for equation development in the block-randomized development set. Covariates were selected in a data-driven fashion. The novel equation was assessed for bias, precision (mean \pm SD), and accuracy (eGFR percentage within $\pm 30\%$ of mGFR, P30) in the validation set and compared with MDRD and CKD-EPI.

Results: Median mGFR was 61 [44-81] ml/min per 1.73 m². In order of importance, PENK, creatinine, and age were included, and sex or race did not improve performance. The PENK-based equation mean \pm SD bias of the mGFR was 0.5 ± 15 ml/min per 1.73 m², significantly less compared with MDRD (8 ± 17 , $P < 0.001$) and 2009 CKD-EPI (5 ± 17 , $P < 0.001$), not reaching statistical significance compared with 2021 CKD-EPI (1.3 ± 16 , $P = 0.06$). The P30 accuracy of the PENK-based equation was 83%, significantly higher compared with MDRD (68%, $P < 0.001$) and 2009 CKD-EPI (76%, $P < 0.001$), similar to 2021 CKD-EPI (80%, $P = 0.13$). Overall, the PENK-based equation to assess eGFR performed better than most creatinine-based equations without using sex or race.

PATIENT-CENTERED RESEARCH

[Comparing online crowdsourcing with clinic patient enrollment: Findings from the IP4IC Study on interstitial cystitis/bladder pain syndrome](#)

Joseph J Janicki, **Elijah P Ward**, Sarah N Bartolone, Laura E Lamb, Nitya Abraham, Melissa Laudano, Christopher P Smith, **Kenneth M Peters**, **Bernadette M Zwaans**, Michael B Chancellor

Interstitial cystitis/bladder pain syndrome (IC/BPS) manifests as urinary symptoms including urgency, frequency, and pain. The IP4IC Study aimed to establish a urine-based biomarker score for diagnosing IC/BPS. To accomplish this objective, we investigated the parallels and variances between patients enrolled via physician/hospital clinics and those recruited through online crowdsourcing. Through a nationwide crowdsourcing effort, we collected surveys from patients with history of IC/BPS. Study participants were asked to complete the validated instruments of Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), as well as provide demographic information. We then compared the survey responses of patients recruited through crowdsourcing with those recruited from three specialized tertiary care urology clinics engaged in clinical research.

Survey responses of 1300 participants were collected from all 50 states of the USA via crowdsourcing and 319 from a clinical setting. ICSI and ICPI were similar for IC/BPS patients diagnosed by the physicians in clinic and self-reported by subjects via crowdsourcing stating they have a history of previous physician diagnosis of IC/BPS. Surprisingly, ICSI and ICPI were significantly lower in crowdsourced control than in-clinic control subjects. The IP4IC Study provides valuable insights into the similarities and differences between patients recruited through clinics and those recruited through online crowdsourcing. There were no significant differences in disease symptoms among these groups. Individuals who express an interest in digital health research and self-identify as having been previously diagnosed by physicians with IC/BPS can be regarded as reliable candidates for crowdsourcing research.

[Referral and Prescription Patterns for Female Patients With Urinary Incontinence](#)

Marie C Luebke, Emily R W Davidson, Bradley H Crotty, Nicole Fergestrom, R Corey O'Connor, Emily Schmitt, Aaron N Winn, Kathryn E Flynn, Joan M Neuner

Although behavioral modifications, medications, and other interventions can improve urinary incontinence (UI), many women never receive them. To better characterize UI treatment patterns in primary care, we examined prescriptions and referrals to pelvic floor physical therapy (PFPT) and specialist physicians within a large Midwestern academic health system. Electronic health records were queried to identify a cohort of adult female patients receiving a new UI diagnosis during outpatient primary care visits from 2016 to 2020. Urinary incontinence referrals and referral completion were examined for the overall cohort, and medication prescriptions were examined for women with urgency or mixed UI. Logistic regression was used to assess the association of prescriptions and/or referrals with patient demographics, comorbidities, and UI diagnosis dates. In the year after primary care UI diagnosis, 37.2% of patients in the overall cohort (n

= 4,382) received guideline-concordant care. This included 20.6% of women who were referred for further management: 17.7% to urology/urogynecology and 3.2% to PFPT. Most women who were referred attended an initial appointment. Among those with urgency (n = 2,398) or mixed UI (n = 552), 17.1% were prescribed medication. Women with stress (odds ratio [OR], 3.10; 95% CI, 2.53-3.79) and mixed UI (OR, 6.17; 95% CI, 4.03-9.66) were more likely to be referred for further management, and women diagnosed during the COVID-19 pandemic were less likely to be referred for further care (OR, 0.39; 95% CI, 0.29, 0.48). Only slightly above 1 in 3 women with a new diagnosis of UI in primary care received guideline-based medications or referrals within 1 year, suggesting missed opportunities for timely care.

- Jennifer Allmaras MPH, Anna Barrett,
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BLADDER

Fibrin microthrombi in bladder urothelium after SARS-CoV-2 infection: Case report

Ly Hoang Roberts, Bernadette M Zwaans, Kausar Jabbar, Sarah N Bartolone, Priya Padmanabhan, Kenneth M Peters

A 45-year-old male with diabetes, hypertension and hyperlipidemia was referred to urology due to persistent symptoms of urinary frequency, urgency, nocturia, erectile dysfunction, and constant pain localized to the bladder, pelvis, and perineal area, 3-4 months after SARS-CoV-2 infection. A bladder biopsy showed urothelial mucosa and submucosa with hemorrhage and fibrin microthrombi in blood vessels. Hydrodistention of the bladder and pelvic floor physical therapy resolved symptoms, though bladder and pain symptoms returned upon reinfection with SARS-CoV-2. Urinalysis revealed elevated urinary interleukin-8, which may indicate localized bladder inflammation.

Financial strain across 25 years and women's bladder health: A life course perspective

Sonya S Brady, Andrés Arguedas, Jared D Huling, Gerhard Hellemann, Cora E Lewis, Cynthia S Fok, Stephen K Van Den Eeden, Alayne D Markland

A small number of cross-sectional studies have found that financial insecurity - a social determinant of health (SDOH) - is associated with lower urinary tract symptoms (LUTS). To examine (1) whether women in the Coronary Artery Risk Development in Young Adults study with higher levels of financial strain, assessed at seven time points across 25 years beginning in 1985-86, were more likely to report LUTS and impact after the 2010-11 financial strain assessment, and (2) whether healthcare access and comorbidities mediate potential associations. This prospective cohort study recruited Black and White participants aged 18-30 years at baseline (1985-86) from the populations of four United States cities. The analytic sample was comprised of women with complete data for analyses involving financial strain trajectories across 7 assessments

(n=841) and mediation tests of data collected at 4 assessments (n=886). The outcome variable was previously developed through a cluster analysis of urinary incontinence severity, urinary incontinence impact, other LUTS severity, and their impact at 2012-13, which yielded four LUTS/impact cluster categories: women with no or very mild symptoms and no impact versus mild, moderate, or severe symptoms and impact. Financial strain was defined as finding it "very hard," "hard," or "somewhat hard" (versus "not very hard") to pay for the very basics like food, heating, and medical care. Using proportional odds logistic regression, cluster categories were regressed on financial strain trajectory group, adjusting for age, race, education, and parity. For mediation analyses, separate financial strain variables (difficulty paying for the very basics like food and heating, difficulty paying for medical care) were created by combining 1995-96 and 2000-01 values. Two healthcare access variables (difficulty receiving care, underutilization of care) and a single comorbidity index (smoking, physical inactivity, body mass index, hypertension, diabetes, depressive symptoms) were created by combining 2005-06 and 2010-11 values. Regression analyses and structural equation modeling were used to test whether healthcare access and comorbidities mediated associations between financial strain and LUTS/impact cluster categories. In comparison to women who were consistently not financially strained, women who were consistently strained (OR=2.10, 95% CI: 1.13, 3.91), shifted into being strained (OR=2.00, 95% CI: 1.29, 3.10), or experienced more than one shift in strain (OR=1.99, 95% CI: 1.46, 2.71) had roughly twice the odds of reporting greater LUTS/impact. Underutilization of healthcare and comorbidities mediated the association between difficulty paying for medical care and LUTS/impact. In the structural equation model, difficulty paying for medical care and underutilization of care were associated ($\beta=.31$, $p<.01$), as was underutilization of care and greater

LUTS/impact ($\beta=.09$, $p<.01$). Difficulty paying for medical care and the comorbidity index also were associated ($\beta=.34$, $p<.01$), as was the comorbidity index and greater LUTS/impact ($\beta=.24$, $p<.01$). Collectively, these mediation pathways eliminated a direct association between difficulty paying for medical care and LUTS/impact. Underutilization of healthcare and comorbidities explained an association between financial strain (difficulty paying for medical care) and LUTS/impact. Research is needed to confirm findings and examine other mechanisms that may further explain the association. Accumulated evidence may inform future policies and practices.

Job strain, occupation, and bladder health among women

Sonya S Brady, Andrés Arguedas, Jared D Huling, Gerhard Hellemann, Cora E Lewis, Cynthia S Fok, Stephen K Van Den Eeden, Alayne D Markland

Lower urinary tract symptoms (LUTS) are common among employed women. An underexplored topic is whether characteristics of women's occupations may influence LUTS. The present study examined whether job strain and its individual components (psychological demands, decision latitude) were associated with greater LUTS and their impact and whether, compared to managerial and professional occupations, occupations characterized by manual labor, sales, service, nursing, and teaching were associated with greater LUTS and their impact. Coronary Artery Risk Development in Young Adults cohort study data were analyzed. Job strain and occupation were assessed in 1987-88 and 1995-96. In 2012-13, LUTS and their impact were assessed. LUTS/impact category (a composite variable ranging from bladder health to mild, moderate, and severe LUTS/impact) was regressed on job strain and occupation in separate analyses, adjusting for age, race, parity, education, and financial hardship ($n = 1006$). Job strain and its individual components were not associated with LUTS/impact. In comparison to managerial and professional occupations, service

occupations in 1987-88 and 1995-96 were both associated with greater odds of LUTS/impact in proportional odds logistic regression analyses. Employment as a nurse, health assistant, or health aide in 1995-96 was associated with greater odds of any LUTS/impact versus bladder health. Support positions in 1987-88 and sales positions in 1995-96 were associated with greater odds of moderate or severe LUTS/impact versus bladder health or mild LUTS/impact. Future research should examine characteristics of workplaces that may promote or constrain bladder health (e.g., time and autonomy to void when desired, infrastructure to void).

[Mouse and human studies support DSTYK loss of function as a low penetrance and variable expressivity risk factor for congenital urinary tract anomalies](#)

Jeremiah Martino ... Juntao Ke, Tze Y Lim ... Yask Gupta ... Hila Milo-Rasouly ... Cathy L Mendelsohn ... Ali G Gharavi, Simone Sanna-Cherchi

Previous work identified rare variants in DSTYK associated with human congenital anomalies of the kidney and urinary tract (CAKUT). Here, we present a series of mouse and human studies to clarify the association, penetrance, and expressivity of DSTYK variants. We phenotypically characterized Dstyk knockout mice of 3 separate inbred backgrounds, and re-analyzed the original family segregating the DSTYK c.654+1G>A splice-site variant (referred to as "SSV" below). DSTYK loss-of-function (LOF) and SSVs were annotated in individuals with CAKUT, Epilepsy, or amyotrophic lateral sclerosis (ALS) vs. controls. A Phenome-Wide Association Study (PheWAS) analysis was also performed using United Kingdom Biobank (UKBB) data. Results demonstrate ~20-25% penetrance of obstructive uropathy (OU), at least, in C57BL/6J and FVB/NJ Dstyk^{-/-} mice. Phenotypic penetrance increased to ~40% in C3H/HeJ mutants, with mild-to-moderate severity. Re-analysis of the original family segregating the rare SSV showed low penetrance (43.8%) and no alternative genetic causes for CAKUT. LOF DSTYK variants burden showed significant excess for CAKUT and Epilepsy vs. controls and an exploratory PheWAS

supported association with neurological disorders. These data support causality for DSTYK LOF variants and highlights the need for large-scale sequencing studies (here >200,000 cases) to accurately assess causality for genes and variants to lowly-penetrant traits with common population prevalence.

[Technical feasibility of uro-dynamic MRI study of voiding biomechanics: a pilot study](#)

Juan Pablo Gonzalez-Pereira, Cody John Johnson, Shane Wells, Wade Bushman, Alejandro Roldan-Alzate

Dynamic volumetric MRI was used to non-invasively assess voiding biomechanics in a healthy male volunteer. Using 3D Differential Subsampling with Cartesian Ordering (DISCO) Flex acquisition sequence, volumetric bladder images were obtained throughout the voiding effort. These were subsequently segmented using MIMICS. Segmented anatomical volumes were used to quantify total voided volume, post-void residual, volumetric displacement of urine over time, bladder neck angle, sphericity index, and prostatic urethral angle through the voiding effort. Bladder sphericity index correlated positively with flow rate. The greatest degree of bladder neck funneling correlated with the maximum urine flow rate. There was straightening of the prostatic urethral angle during voiding that also correlated positively with urine flow. This pilot study confirms the potential of dynamic MRI to provide non-invasive assessment of lower urinary tract anatomy and biomechanics during voiding.

STONES

[A Systematic Scoping Review of Comparative Effectiveness Studies in Kidney Stone Disease](#)

Pankaj Dangle, Gregory E Tasian, David I Chu, Rachel Shannon, Ryan Spiardi, Alice H Xiang, Aditya Jadhav, Juliana Arenas, Jonathan S Ellison

To review the status of comparative effectiveness studies for kidney stone disease with focus on study outcome, type, population, time trends, and patient centered approaches. A systematic scoping review was performed for articles published

between January 1, 2005, and March 30, 2021, using keywords relevant to kidney stone disease. Studies published in English that compared two or more alternative methods for prevention, diagnosis, treatment, monitoring or care delivery were included. Two reviewers independently reviewed abstracts and an arbitrator resolved discrepancies. Nine reviewers abstracted information from full-length studies. Descriptive statistics were summarized, and linear regression was performed to evaluate temporal trends of study characteristics. We reviewed 1773 abstracts and 707 full-length manuscripts focused on surgical intervention (440); medical expulsive therapy (MET) (152); analgesic control (80); and homeopathic, diagnostics, and/or prophylaxis (84). Randomized controlled trials were common across all outcome categories, including surgery (41.6%), MET (60.2%), analgesic control (81.3%), homeopathic (41.2%), diagnostic (47.6%), and prophylaxis (49.1%). Patient reported outcomes (PRO) were utilized in 71.7% and 95% of MET and analgesic control studies, respectively, but in the minority of all other study themes. Over time, meta-analyses and multi-center studies increased [P < 0.001]. Surgical and MET themes dominate published comparative literature in kidney stone disease. There is substantial variation in use of PROs across surgical themes. Multi-centered studies and those generating higher level evidence have increased over time but opportunities exist to improve collaborative, high-quality, and patient-centered research in kidney stone disease.

[Distinguishing characteristics of pediatric patients with primary hyperoxaluria type 1 in PEDSnet](#)

Gregory E Tasian, Kimberley Dickinson, Grace Park, Nicole Marchesani, Akanksha Mittal, Nathan Cheng, Christina B Ching, David I Chu, Ryan Walton, Karyn Yonekawa, Caroline Gluck, Samina Muneeruddin, Kathleen M Kan, William DeFoor, Kyle Rove, Christopher B Forrest

Primary hyperoxaluria type 1 (PH1) is an autosomal recessive inborn error of metabolism that causes oxalate deposition, leading to recurrent calcium oxalate kidney stones, chronic kidney

disease and systemic oxalosis, which produces a broad range of serious life-threatening complications. Patients with PH1 have delayed diagnosis due to the rarity of the disease and the overlap with early-onset kidney stone disease not due to primary hyperoxaluria. The objective of this study was to determine the clinical features of individuals <21 years of age with PH1 that precede its diagnosis. We hypothesized that a parsimonious set of features could be identified that differentiate patients with PH1 from patients with non-primary hyperoxaluria-associated causes of early-onset kidney stone disease. We determined the association between clinical characteristics and PH1 diagnosis in a case-control study conducted between 2009 and 2021 in PEDSnet, a clinical research network of eight US pediatric health systems. Each patient with genetically confirmed PH1 was matched by sex and PEDSnet institution to up to 4 control patients with kidney stones without PH of any type. We obtained patient characteristics and diagnostic test results occurring before to less than 6 months after study entrance from a centralized database query and from manual chart review. Differences were examined using standardized differences and multivariable regression. The study sample included 37 patients with PH1 and 147 controls. Patients with PH1 were younger at diagnosis (median age of 3 vs 13.5 years); 75 % of children with PH1 were less than 8 years-old. Patients with PH1 were more likely to have combinations of nephrocalcinosis on ultrasound or CT (43 % vs 3 %), lower eGFR at diagnosis (median = 52 mL/min/1.73 m² vs 114 mL/min/1.73 m²), and have normal mobility. Patients with PH1 had higher proportion of calcium oxalate monohydrate kidney stones than controls (median = 100 % vs 10 %). There were no differences in diagnosis of failure to thrive, stone size, or echocardiography results. Children with PH1 are characterized by presentation before adolescence, nephrocalcinosis, decreased eGFR at diagnosis, and calcium oxalate monohydrate stone composition. If externally validated, these

characteristics could facilitate earlier diagnosis and treatment of children with PH1.

[The impact of bilateral stone disease on patients' disease progression and health related quality of life](#)

Stefano Saliccia, Martina Maggi, Marco Frisenda, Lucia Finistauri Guacci, Sanie Hoxha, Leslie C Licari, Pietro Viscuso, Alessandro Gentilucci, Francesco Del Giudice, Ettore DE Berardinis, Susanna Cattarino, Gianna Mariotti, Antonio Tufano, Mauro DE Dominicis, Gian P Ricciuti, Alessandro Sciarra, Kristina L Penniston, Martina Moriconi Urolithiasis is a chronic condition, and it has been associated with a significant negative impact on patients' health-related quality of life (HRQOL). Several tools to assess patients' HRQOL have been validated in Italian, however disease-specific HRQOL instruments are still lacking. We aimed to develop and validate the Italian version of the WISQOL (I-WISQOL) in patients with urolithiasis. The Italian version of the WISQOL was developed in a multistep process involving primary translation, back-translation, and pilot testing among a group of patients (N.=10). Patients presenting with urolithiasis were prospectively recruited from the outpatient stone clinics and completed both questionnaire WISQOL and SF-36. Demographic information, as well as medical and surgical data, were obtained through an interview. Internal consistency of the I-WISQOL was obtained with Cronbach's α . Correlation of total scores of the I-WISQOL and SF36 was assessed to determine convergent validity using Spearman Rho. Correlations between clinical variables and results from the I-WISQOL were analyzed to descriptively assess the association of interest. A total of 93 participants were evaluated and completed the Italian version of the I-WISQOL. The I-WISQOL demonstrated excellent internal consistency (Cronbach's α 0.95) and good convergent validity with the validated SF-36 (Spearman Rho $r=0.70$, $P<0.001$). Using ANOVA analysis, a significant decline in WISQOL Score was noted with the increasing number of renal colics ($P=0.0543$), ER visits ($P=0.037$), number of inpatient hospitalization ($P=0.025$). At multivariate analysis, worse WISQOL

total score was predicted by a greater number of renal colic events ($\beta=-4.92$ [-8.81-1.04], $P=0.014$) and by a greater number inpatient hospitalization ($\beta=-7.31$ [-14.35 -0.26], $P=0.042$). The I-WISQOL is an internally consistent and valid instrument to assess HRQOL in Italian-speaking patients with kidney stones. Its use in clinical practice should be implemented in order to tailor the management of each patient.

[Oxalate disrupts monocyte and macrophage cellular function via Interleukin-10 and mitochondrial reactive oxygen species \(ROS\) signaling](#)

Parveen Kumar, Emma Laurence, David K Crossman, **Dean G Assimios**, Michael P Murphy, **Tanecia Mitchell**

Oxalate is a small compound found in certain plant-derived foods and is a major component of calcium oxalate (CaOx) kidney stones. Individuals that consume oxalate enriched meals have an increased risk of forming urinary crystals, which are precursors to CaOx kidney stones. We previously reported that a single dietary oxalate load induces nanocrystalluria and reduces monocyte cellular bioenergetics in healthy adults. The purpose of this study was to extend these investigations to identify specific oxalate-mediated mechanisms in monocytes and macrophages. We performed RNA-Sequencing analysis on monocytes isolated from healthy subjects exposed to a high oxalate (8 mmol) dietary load. RNA-sequencing revealed 1,198 genes were altered and Ingenuity Pathway Analysis demonstrated modifications in several pathways including Interleukin-10 (IL-10) anti-inflammatory cytokine signaling, mitochondrial metabolism and function, oxalic acid downstream signaling, and autophagy. Based on these findings, we hypothesized that oxalate induces mitochondrial and lysosomal dysfunction in monocytes and macrophages via IL-10 and reactive oxygen species (ROS) signaling which can be reversed with exogenous IL-10 or Mitoquinone (MitoQ; a mitochondrial targeted antioxidant). We exposed monocytes and macrophages to oxalate in an in-vitro setting which caused oxidative stress, a

decline in IL-10 cytokine levels, mitochondrial and lysosomal dysfunction, and impaired autophagy in both cell types. Administration of exogenous IL-10 and MitoQ attenuated these responses. These findings suggest that oxalate impairs metabolism and immune response via IL-10 signaling and mitochondrial ROS generation in both monocytes and macrophages which can be potentially limited or reversed. Future studies will examine the benefits of these therapies on CaOx crystal formation and growth in vivo.

[Role of Climate Change in Urologic Health: Kidney Stone Disease](#)

Ryan Spiardi, David S Goldfarb, Gregory E Tasian

Kidney stones are rising in incidence and prevalence worldwide. Given the temperature dependence of kidney stone presentations, climate change is projected to further increase the burden of disease for individuals and society. PATIENT SUMMARY: This mini-review reports current knowledge on climate change in relation to kidney stone disease. Kidney stones are more common in patients living in parts of the world that are hotter and more humid. Kidney stone problems are also more common after periods of high heat, which have a greater impact on men than on women. As temperatures rise with climate change, it is likely that the occurrence of kidney stones and the costs associated with their diagnosis and treatment will increase as well.

[Shock waves generated by toroidal bubble collapse are imperative for kidney stone dusting during Holmium:YAG laser lithotripsy](#)

Gaoming Xiang, Junqin Chen, Derek Ho, Georgy Sankin, Xuning Zhao, Yangyuanchen Liu, Kevin Wang, John Dolbow, Junjie Yao, Pei Zhong

Holmium:yttrium-aluminum-garnet (Ho:YAG) laser lithotripsy (LL) has been the treatment of choice for kidney stone disease for more than two decades, yet the mechanisms of action are not completely clear. Besides photothermal ablation, recent evidence suggests that cavitation bubble collapse is pivotal in kidney stone dusting when the Ho:YAG laser operates at low pulse energy (Ep) and high frequency (F). In this work, we

perform a comprehensive series of experiments and model-based simulations to dissect the complex physical processes in LL. Under clinically relevant dusting settings (Ep = 0.2 J, F = 20 Hz), our results suggest that majority of the irradiated laser energy (>90 %) is dissipated by heat generation in the fluid surrounding the fiber tip and the irradiated stone surface, while only about 1 % may be consumed for photothermal ablation, and less than 0.7 % is converted into the potential energy at the maximum bubble expansion. We reveal that photothermal ablation is confined locally to the laser irradiation spot, whereas cavitation erosion is most pronounced at a fiber tip-stone surface distance about 0.5 mm where multi foci ring-like damage outside the thermal ablation zone is observed. The cavitation erosion is caused by the progressively intensified collapse of jet-induced toroidal bubble near the stone surface (<100 µm), as a result of Raleigh-Taylor and Richtmyer-Meshkov instabilities. The ensuing shock wave-stone interaction and resultant leaky Rayleigh waves on the stone surface may lead to dynamic fatigue and superficial material removal under repeated bombardments of toroidal bubble collapses during dusting procedures in LL.

PROSTATE

[Aging-Related Mitochondrial Dysfunction is Associated with Fibrosis in Benign Prostatic Hyperplasia](#)

Alexis E Adrian, Teresa T Liu, Laura E Pascal, Scott R Bauer, Donald B DeFranco, William A Ricke

Age is the greatest risk factor for lower urinary tract symptoms attributed to benign prostatic hyperplasia (LUTS/BPH). While LUTS/BPH can be managed with pharmacotherapy, treatment failure has been putatively attributed to numerous pathological features of BPH (e.g., prostatic fibrosis, inflammation). Mitochondrial dysfunction is a hallmark of aging, however its impact on the pathological features of BPH remains unknown. Publicly available gene array data was analyzed. Immunohistochemistry examined mitochondrial proteins in human prostate. The effect of complex I

inhibition (rotenone) on a prostatic cell line was examined using qPCR, immunocytochemistry, and Seahorse assays. Oleic acid was tested as a bypass of complex I inhibition. Aged mice were treated with OA to examine its effects on urinary dysfunction. Voiding was assessed longitudinally, and a critical complex I protein measured. Mitochondrial function and fibrosis genes were altered in BPH. Essential mitochondrial proteins (i.e., VDAC1/2, PINK1 and NDUFS3) were significantly (P<0.05) decreased in BPH. Complex I inhibition in cultured cells resulted in decreased respiration, altered NDUFS3 expression, increased collagen deposition and gene expression. Oleic acid ameliorated these effects. Oleic acid treated aged mice had significantly (P<0.05) improved voiding function and higher prostatic NDUFS3 expression. Complex I dysfunction is a potential contributor to fibrosis and lower urinary tract dysfunction in aged mice. Oleic acid partially bypasses complex I inhibition and therefore should be further investigated as a mitochondrial modulator for treatment of LUTS/BPH. Hypotheses generated in this investigation offer a heretofore unexplored cellular target of interest for the management of LUTS/BPH.

KIDNEY

[The Clinical Utility of Genetic Testing in the Diagnosis and Management of Adults with Chronic Kidney Disease](#)

Neera K Dahl, Michelle S Bloom, Fouad T Chebib, Dinah Clark, Maggie Westemeyer, Sara Jandeska, Zhiji Zhang, Hila Milo-Rasouly, Victoria Kolupaeva, Maddalena Marasa, Varshasb Broumand, Richard A Fatica, Dominic S Raj, Zachary P Demko, Kyle Marshall, Sumit Punj, Hossein Tabriziani, Sangeeta Bhorade, Ali G Gharavi

Genetic testing in CKD has recently been shown to have diagnostic utility with many predicted implications for clinical management, but its effect on management has not been prospectively evaluated. Renasight Clinical Application, Review, and Evaluation (RenaCARE) (ClinicalTrials.gov NCT05846113) is a single-arm, interventional, prospective, multicenter study that evaluated the utility of genetic testing with a broad, 385 gene panel (the Renasight™ test) on the diagnosis and management of

adult patients with CKD recruited from 31 US-based community and academic medical centers. Patient medical history and clinical CKD diagnosis were collected at enrollment. Physician responses to questionnaires regarding patient disease categorization and management were collected before genetic testing and 1 month after the return of test results. Changes in CKD diagnosis and management after genetic testing were assessed. Of 1623 patients with CKD in 13 predefined clinical disease categories (ages, 18-96; median, 55 years), 20.8% (n = 338) had positive genetic findings spanning 54 genes. Positive genetic findings provided a new diagnosis or reclassified a prior diagnosis in 48.8% of those patients. Physicians reported that genetic results altered the management of 90.7% of patients with a positive genetic finding, including changes in treatment plan, which were reported in 32.9% of these patients. Genetic testing with a CKD-focused 385 gene panel substantially refined clinical diagnoses and had widespread implications for clinical management, including appropriate treatment strategies. These data support the utility of broader integration of panels of genetic tests into the clinical care paradigm for patients with CKD.

[Mayo Clinic consensus report on membranous nephropathy: proposal for a novel classification](#)

... John C Lieske ...

Membranous nephropathy (MN) is a pattern of injury caused by autoantibodies binding to specific target antigens, with accumulation of immune complexes along the subepithelial region of glomerular basement membranes. The past 20 years have brought revolutionary advances in the understanding of MN, particularly via the discovery of novel target antigens and their respective autoantibodies. These discoveries have challenged the traditional classification of MN into primary and secondary forms. At least 14 target antigens have been identified, accounting for 80%-90% of cases of MN. Many of the forms of MN associated with these novel MN target antigens have distinctive clinical and pathologic

phenotypes. The Mayo Clinic consensus report on MN proposes a 2-step classification of MN. The first step, when possible, is identification of the target antigen, based on a multistep algorithm and using a combination of serology, staining of the kidney biopsy tissue by immunofluorescence or immunohistochemistry, and/or mass spectrometry methodology. The second step is the search for a potential underlying disease or associated condition, which is particularly relevant when knowledge of the target antigen is available to direct it. The meeting acknowledges that the resources and equipment required to perform the proposed testing may not be generally available. However, the meeting consensus was that the time has come to adopt an antigen-based classification of MN because this approach will allow for accurate and specific MN diagnosis, with significant implications for patient management and targeted treatment.

PATIENT-CENTERED RESEARCH

[Reimagining Ambulatory Care in Urology: Conversion of the Urology Clinic into a Procedure Center Improves Patient's Experience](#)

Fadi Hamouche, Nizar Hakam, Rei Unno, Justin Ahn, Heiko Yang, **David Bayne**, Marshall L Stoller, Susan Smith, Emily Finlayson, James Smith, **Thomas Chi**

The coronavirus disease 2019 (COVID-19) pandemic made it necessary to practice social distancing and limited in-person encounters in health care. These restrictions created alternative opportunities to enhance patient access to care in the ambulatory setting. We hypothesized that by transforming clinics into centers that prioritize procedures and transitioning ambulatory appointments to telehealth, we could establish a secure, streamlined, and productive method for providing patient care. Clinic templates were restructured to allow the use of the physical space to perform procedure-based clinics exclusively, while switching to virtual telemedicine for all nonprocedural encounters. Staff members were given specific roles to support one of the patient care modalities for a given day (Procedures vs. Telehealth). Performance and patient satisfaction

metrics were collected between two periods of time defined as P1 (February-June 2019) and P2 Post-COVID (February-June 2020) and compared. These served as proxies of periods when the clinic workflow and templates were structured in the traditional versus the emerging way. Statistical analysis was performed using bivariate analyses. The percentage of procedures performed among all in-person visits were higher in P2 compared to P1 (45% vs. 29%, $p < 0.001$). Although total charges and relative value units were lower in P2, the overall revenue generated was higher compared to P1 (\$4,597,846 vs. \$4,517,427\$, respectively). This increase in revenue was mainly driven by the higher relative income generated by procedures. Patient experience, reflected through patient-reported outcomes, was more favorable in P2 where patients seemed more likely to "Recommend this provider office" (90% vs. 85.7%, $p = 0.01$), report improved "Access overall" (56% vs. 49%, $p = 0.02$), and felt they were "Moving through your visit overall" (59% vs. 51%, $p = 0.007$). Our data suggest that reorganizing urology clinics into a space that is centered around outpatient procedures can represent a model that improves the patient's access to care and clinical experience, while simultaneously improving operational financial strength. This efficient care model could be considered for many practice settings and drive high-value outpatient care.

- Jennifer Allmaras MPH, Anna Barrett,
10/27/2023

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BLADDER

[Intravesical liposomal tacrolimus for hemorrhagic cystitis: a phase 2a multicenter dose-escalation study](#)

Jason Hafron, Benjamin N Breyer, Shreyas Joshi, Christopher Smith, Melissa R Kaufman, Janet Okonski, **Michael B Chancellor**

Hemorrhagic cystitis (HC) is an inflammatory disease of the bladder with sustained hematuria for which there is currently no approved drug treatment. We evaluated a liposomal tacrolimus preparation (LP-10) in patients with refractory moderate to severe sterile HC. This phase 2a dose-escalation study assessed the safety and efficacy of up to 2 intravesical instillations of LP-10 (2, 4, or 8 mg tacrolimus) in 13 patients with HC. Primary efficacy outcomes were changes from baseline in the number of bleeding sites on cystoscopy, microscopic urine analysis for red blood cells (RBCs), and hematuria on dipstick. Additional efficacy measures included urinary incontinence, frequency, and urgency on a 3-day diary and cystoscopy global response assessment (GRA). Blood samples for pharmacokinetic (PK) assessment were obtained in all patients. Intravesical LP-10 was well tolerated, with no treatment-related severe or serious adverse events (AEs) and only 3 drug-related AEs (artificial urinary sphincter malfunction, dysuria, and bladder spasms). LP-10 blood levels showed short durations of minimal systemic uptake. Treatment resulted in significant improvements in bleeding on cystoscopy, RBC counts in urine, hematuria on dipstick, and urinary incontinence. Bleeding on cystoscopy and urinary incontinence showed dose-dependent improvements that were more pronounced in the 4 mg and 8 mg dose groups. All dose groups showed a significant improvement in cystoscopy GRA. LP-10 was well tolerated, with clinically relevant efficacy seen in improvements in cystoscopic bleeding, hematuria, and urinary incontinence. The benefit-risk profile supports the further clinical development of LP-10 at a tacrolimus dose of 4 mg.

[Strategies to prevent catheter-associated urinary tract infections in acute-care hospitals: 2022 Update](#)

Payal K Patel, **Sonali D Advani**, Aaron D Kofman, Evelyn Lo, Lisa L Maragakis, David A Pegues, Ann Marie Pettis, Sanjay Saint, **Barbara Trautner**, Deborah S Yokoe, Jennifer Meddings

The intent of this document is to highlight practical recommendations in a concise format designed to assist physicians, nurses, and infection preventionists at acute-care hospitals in implementing and prioritizing their catheter-associated urinary tract infection (CAUTI) prevention efforts. This document updates the Strategies to Prevent Catheter-Associated Urinary Tract Infections in Acute-Care Hospitals published in 2014. It is the product of a collaborative effort led by SHEA, the Infectious Diseases Society of America (IDSA), the Association for Professionals in Infection Control and Epidemiology (APIC), the American Hospital Association (AHA), and The Joint Commission.

KIDNEY

[Native nephrectomy in advanced pediatric kidney disease: indications, timing, and surgical approaches](#)

Brendan Crawford, Sarah Kizilbash, **Vinaya P Bhatia**, Nazia Kulsum-Meccie, Shannon Cannon, Sharon M Bartosh

In pediatric kidney failure, native kidneys may pose a risk to successful transplant outcomes. The indications and timing of native nephrectomy represent a controversial management decision. A lack of high-quality, outcomes-based data has prevented development of evidence-based guidelines for intervention. In this article, we review the published literature on medical indications for native nephrectomy and current knowledge gaps. In addition, we provide a surgical perspective regarding timing and approach.

GENITOURINARY

[Management of partial Müllerian agenesis: staged McIndoe procedure for the creation of a neovagina and utero-neovaginal unification](#)

Alejandro Gómez-Viso, Bobby May, **Cassandra Kisby**

The objectives of this video are to provide a brief overview of Müllerian agenesis, discuss a case of partial vaginal agenesis with a functional uterus, and present the steps of a staged McIndoe procedure for the creation of a neovagina and utero-neovaginal unification. We give an overview of Mayer-Rokitansky-Küster-Hauser syndrome, and review its incidence, clinical presentation, diagnostic evaluation, and treatment options. We present the case of a 23-year-old woman with partial vaginal agenesis, and her clinical course through conservative management with hormonal suppression and dilator therapy leading up to urogynecological surgical treatment. We describe a staged surgical approach that highlights the value of cystoscopy and laparoscopy to better delineate our patient's anatomical variations. Additionally, a mini-laparotomy and placement of an intrauterine Malecot catheter allowed for the drainage of prominent hematometra, relief of menstrual outflow obstruction, and epithelialization of a tract between the uterus and the planned neovaginal space. Ultimately, a neovagina was created using a staged McIndoe technique, leading to utero-neovaginal unification and unobstructed menses. In conclusion, our approach should be considered a feasible option for anatomical restoration via the creation of a neovagina in patients with Müllerian anomalies, even in the presence of a functional uterus.

- Jennifer Allmaras MPH, Anna Barrett, 9/22/2023

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BLADDER

[Haemorrhagic cystitis: a review of management strategies and emerging treatments](#)

Kevin D Li, Charles P Jones, Nizar Hakam, Bradley A Erickson, Alex J Vanni, **Michael B Chancellor**, Benjamin N Breyer

Haemorrhagic cystitis (HC) is characterised by persistent haematuria and lower urinary tract symptoms following radiotherapy or chemotherapy. Its pathogenesis is poorly understood but thought to be related to acrolein toxicity following chemotherapy or fibrosis/vascular remodelling after radiotherapy. There is no standard of care for patients with HC, although existing strategies including fulguration, hyperbaric oxygen therapy, botulinum toxin A, and other intravesical therapies have demonstrated short-term efficacy in cohort studies. Novel agents including liposomal tacrolimus are promising targets for further research. This review summarises the incidence and pathogenesis of HC as well as current evidence supporting its different management strategies.

[Total and Free 25-hydroxyvitamin D Concentrations and Risk of Urinary Incontinence in Women Participating in Nurses Health Studies I & II.](#)

Vin Tangpricha, Alayne D Markland, Camille P Vaughan, **Alison J Huang**, Francine Grodstein
Urgency urinary incontinence (UUI) occurs in >40% of older women. Our objective was to examine the relationship of total and free plasma 25-hydroxyvitamin D (25(OH)D) and UUI to evaluate vitamin D status as a novel target for prevention of UUI. We conducted a nested case control study using the Nurses' Health Study (NHS) and NHS II. Using stored plasma samples from 2000, we measured total 25(OH)D, free 25(OH)D, and intact parathyroid hormone (PTH) levels and examined their relationship to incident UUI from 2000 to 2013. Plasma biomarker levels were categorized as quartiles. Multivariable-adjusted odds ratios of UUI were estimated by conditional logistic regression models (with

matching by age) across categories of each biomarker and covariates. The analytic sample included 398 cases of incident UUI and 398 matched controls with a mean age of 50 years. We found a strong correlation of plasma levels of total 25(OH)D with free 25(OH)D ($r=0.5$). Plasma total 25(OH)D and free 25(OH)D concentrations were negatively correlated with PTH ($r=-0.08$ AND -0.09 , respectively). Overall, we found no evidence that levels of total plasma 25(OH)D, free 25(OH)D, or PTH were related to incident UUI after adjustment for obesity, physical activity, cigarette smoking, menopausal status, hypertension, and type 2 diabetes. Free plasma 25(OH)D by quartile, as well as total plasma 25(OH)D, was not associated with incident UUI in women. We found that plasma total and free 25(OH)D were highly correlated with each other and inversely correlated with PTH. Plasma free 25(OH)D did not provide additional predictive value in determining risk of UUI.

[Treatment of neurogenic detrusor overactivity and overactive bladder with Botox \(onabotulinumtoxinA\): Development, insights, and impact](#)

Victor Nitti, Cornelia Haag-Molkenteller, Michael Kennelly, **Michael Chancellor**, Brenda Jenkins, Brigitte Schurch

Neurogenic detrusor overactivity (NDO) is a complication of multiple sclerosis, spinal cord injury (SCI), stroke, head injury, and other conditions characterized by damage to the upper motor neuronal system. NDO often leads to high bladder pressure that may cause upper urinary tract damage and urinary incontinence (UI). Prior to the use of onabotulinumtoxinA, oral anticholinergics and surgical augmentation cystoplasty were the treatment options. Overactive bladder (OAB) is non-neurogenic and affects a much larger population than NDO. Both NDO and OAB negatively impact patients' quality of life (QOL) and confer high health care utilization burdens. Early positive results from pioneering investigators who injected

onabotulinumtoxinA into the detrusor of patients with SCI caught the interest of Allergan, which then initiated collaborative clinical trials that resulted in FDA approval of onabotulinumtoxinA 200U in 2011 for NDO and 100U in 2013 for patients with OAB who inadequately respond to or are intolerant of an anticholinergic. These randomized, double-blind, placebo-controlled trials for NDO showed significant improvements in UI episodes, urodynamic parameters, and QOL; the most frequent adverse events were urinary tract infection (UTI) and urinary retention. Similarly, randomized, double-blind, placebo-controlled trials of onabotulinumtoxinA 100U for OAB found significant improvements in UI episodes, treatment benefit, and QOL; UTI and dysuria were the most common adverse events. Long-term studies in NDO and OAB showed sustained effectiveness and safety with repeat injections of onabotulinumtoxinA, the use of which has profoundly improved the QOL of patients failing anticholinergic therapy and has expanded the utilization of onabotulinumtoxinA into smooth muscle.

PROSTATE

[Histologic inflammation and collagen content are not positively correlated in human BPH](#)

Andrew J Schneider, Emily C Serrell, **Matthew Grimes**, Sijian Wang, **Wade Bushman**

Recent clinical studies have implicated prostate inflammation and fibrosis in the development of bladder outlet obstruction and lower urinary tract symptoms (LUTS). Studies utilizing rodent models, including work in our laboratory, have shown prostate fibrosis to occur as a consequence of inflammation. However, the relationship between collagen content and inflammation in human tissue samples obtained from surgical treatment of benign prostatic hyperplasia (BPH)/LUTS has not to our knowledge been previously examined. Prostate tissue specimens from 53 patients (ages

47-88, mean 65.1) treated by open simple prostatectomy or transurethral resection of the prostate for BPH/LUTS were stained to quantitatively assess prostate inflammation and collagen content. Patients with prostate cancer present in greater than 5% of the surgical specimen were excluded. Prostate volume was determined from pelvic CT scan obtained within 2 years of surgery. Analysis of the data showed that inflammation was inversely correlated with collagen content ($r = -0.28$, $p = 0.04$). In men with prostates less than 75 cm³ inflammation increases and collagen content decreases with prostate volume ($p = 0.002$ and $p = 0.03$, respectively) while in men with prostate volume over 75 cm³ inflammation decreases and collagen content increases with prostate volume ($p = 0.30$ and $p = 0.005$, respectively). Our data do not support the assumed positive association of prostate inflammation with collagen content. Coordinated analysis of scatter plots of inflammation and collagen content with prostate volume revealed a subset of prostates with volumes >50 cm³ prostate characterized by intense inflammation and low collagen content and it is this subgroup that appears most responsible for the inverse correlation of inflammation and collagen.

KIDNEY

[An atlas of healthy and injured cell states and niches in the human kidney](#)

Blue B Lake, Rajasree Menon, Seth Winfree, Qiwen Hu, Ricardo Melo Ferreira, Kian Kalhor, Daria Barwinska, Edgar A Otto, Michael Ferkowicz, Dinh Diep, Nongluk Plongthongkum, Amanda Knoten, Sarah Urata, Laura H Mariani, Abhijit S Naik, Sean Eddy, Bo Zhang, Yan Wu, Diane Salamon, James C Williams, Xin Wang, Karol S Balderrama, Paul J Hoover, Evan Murray, Jamie L Marshall, Teia Noel, Anitha Vijayan, Austin Hartman, Fei Chen, Sushrut S Waikar, Sylvia E Rosas, Francis P Wilson, Paul M Palevsky, Krzysztof Kiryluk, John R Sedor, Robert D Toto, Chirag R Parikh, Eric H Kim, Rahul Satija, Anna Greka, Evan Z Macosko, Peter V Kharchenko, Joseph P Gaut, Jeffrey B Hodgins; KPMP Consortium; **Michael T Eadon**, Pierre C Dagher, Tarek M El-Achkar, Kun Zhang, Matthias Kretzler, **Sanjay Jain** Understanding kidney disease relies on defining the complexity of cell types and states, their associated molecular profiles and interactions within tissue neighbourhoods¹. Here we applied

multiple single-cell and single-nucleus assays (>400,000 nuclei or cells) and spatial imaging technologies to a broad spectrum of healthy reference kidneys (45 donors) and diseased kidneys (48 patients). This has provided a high-resolution cellular atlas of 51 main cell types, which include rare and previously undescribed cell populations. The multi-omic approach provides detailed transcriptomic profiles, regulatory factors and spatial localizations spanning the entire kidney. We also define 28 cellular states across nephron segments and interstitium that were altered in kidney injury, encompassing cycling, adaptive (successful or maladaptive repair), transitioning and degenerative states. Molecular signatures permitted the localization of these states within injury neighbourhoods using spatial transcriptomics, while large-scale 3D imaging analysis (around 1.2 million neighbourhoods) provided corresponding linkages to active immune responses. These analyses defined biological pathways that are relevant to injury time-course and niches, including signatures underlying epithelial repair that predicted maladaptive states associated with a decline in kidney function. This integrated multimodal spatial cell atlas of healthy and diseased human kidneys represents a comprehensive benchmark of cellular states, neighbourhoods, outcome-associated signatures and publicly available interactive visualizations.

[Implementation and Feasibility of Clinical Genome Sequencing Embedded Into the Outpatient Nephrology Care for Patients With Proteinuric Kidney Disease](#)

Maddalena Marasa, Dina F Ahram, Atteeq U Rehman, Adele Mitrotti, Avinash Abhyankar, Namrata G Jain, Patricia L Weng, Stacy E Piva, Hilda E Fernandez, Natalie S Uy, Debanjana Chatterjee, Byum H Kil, Jordan G Nestor, Vanessa Felice, Dino Robinson, Dilys Whyte, **Ali G Gharavi**, Gerald B Appel, Jai Radhakrishnan, Dominick Santoriello, Andrew Bomback, Fangming Lin, Vivette D D'Agati, Vaidehi Jobanputra, **Simone Sanna-Cherchi**

The diagnosis and management of proteinuric kidney diseases such as focal segmental glomerulosclerosis (FSGS) are challenging. Genetics holds the promise to improve clinical decision making for

these diseases; however, it is often performed too late to enable timely clinical action and it is not implemented within routine outpatient nephrology visits. We sought to test the implementation and feasibility of clinical rapid genome sequencing (GS) in guiding decision making in patients with proteinuric kidney disease in real-time and embedded in the outpatient nephrology setting. We enrolled 10 children or young adults with biopsy-proven FSGS (9 cases) or minimal change disease (1 case). The mean age at enrollment was 16.2 years (range 2-30). The workflow did not require referral to external genetics clinics but was conducted entirely during the nephrology standard-of-care appointments. The total turn-around-time from enrollment to return-of-results and clinical decision averaged 21.8 days (12.4 for GS), which is well within a time frame that allows clinically relevant treatment decisions. A monogenic or APOL1-related form of kidney disease was diagnosed in 5 of 10 patients. The genetic findings resulted in a rectified diagnosis in 6 patients. Both positive and negative GS findings determined a change in pharmacological treatment. In 3 patients, the results were instrumental for transplant evaluation, donor selection, and the immunosuppressive treatment. All patients and families received genetic counseling. Clinical GS is feasible and can be implemented in real-time in the outpatient care to help guiding clinical management. Additional studies are needed to confirm the cost-effectiveness and broader utility of clinical GS across the phenotypic and demographic spectrum of kidney diseases.

[Strong protective effect of the APOL1 p.N264K variant against G2-associated focal segmental glomerulosclerosis and kidney disease](#)

Yask Gupta ... Juntao Ke ... Tze Y Lim ... Jeremiah Martino ... Miguel Verbitsky ... **Ali G Gharavi** ... **Simone Sanna-Cherchi**

Black Americans have a significantly higher risk of developing chronic kidney disease (CKD), especially focal segmental glomerulosclerosis (FSGS), than

European Americans. Two coding variants (G1 and G2) in the APOL1 gene play a major role in this disparity. While 13% of Black Americans carry the high-risk recessive genotypes, only a fraction of these individuals develops FSGS or kidney failure, indicating the involvement of additional disease modifiers. Here, we show that the presence of the APOL1 p.N264K missense variant, when co-inherited with the G2 APOL1 risk allele, substantially reduces the penetrance of the G1G2 and G2G2 high-risk genotypes by rendering these genotypes low-risk. These results align with prior functional evidence showing that the p.N264K variant reduces the toxicity of the APOL1 high-risk alleles. These findings have important implications for our understanding of the mechanisms of APOL1-associated nephropathy, as well as for the clinical management of individuals with high-risk genotypes that include the G2 allele.

- Jennifer Allmaras MPH, Anna Barrett,
8/24/2023

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BLADDER

[Assessing the Utility of Tamsulosin in Delaying Progression to Clean Intermittent Catheterization and End-stage Renal Disease in Patients With Posterior Urethral Valves: Are We Postponing the Inevitable?](#)

Jin K Kim, Adree Khondker, Michael E Chua, Dheidan Alshammari, Juliane Richter, Joana Dos Santos, Natasha Brownrigg, Neeta D'Souza, John Weaver, **Gregory Tasian**, Armando J Lorenzo, Mandy Rickard

We reviewed a prospective institutional database containing posterior urethral valves patients treated between January 2000 and January 2022. After assessing baseline characteristics, Kaplan-Meier survival curves and log-rank tests were generated to assess differences in clinically significant outcomes (progression to CIC, dialysis, or kidney transplantation) between those prescribed tamsulosin and those who were not. Results: A total of 179 patients were included. Fifty-nine patients received tamsulosin prior to initiation of CIC (group 1), and 120 did not (group 2). The baseline characteristics were similar between the two groups, except for anticholinergic use (tamsulosin group - 35/59 vs no tamsulosin - 32/120, $P < .001$). The median age at tamsulosin initiation was 26.0 months (IQR 15.5-48.6) and the median time from initiation of tamsulosin to progression to CIC was 52.6 months (IQR 10.1-69.3). Kaplan-Meier survival curves showed that patients on tamsulosin were less likely to progress to CIC ($P = .021$), however, there was no difference in progression to dialysis or kidney transplantation. A Cox-regression analysis controlling for baseline characteristics, including age, anticholinergic use, vesicoureteral reflux severity, and CKD stage at 1-year of life, showed a consistent effect of tamsulosin in delaying progression to CIC (HR 0.444 95%CI 0.218-0.902, $P = .025$). While tamsulosin may delay CIC, it does not appear to delay progression to end-stage renal disease. Additional studies exploring specific patient factors are required to determine the timing and

subset who may benefit the most from tamsulosin.

[High Prevalence of Dysplastic Development of Sacral Vertebral Arches in Pediatric Enuresis](#)

Hideo Ozawa, Takakuki Shibano, Isao Tanaka, Toshitaka Taniguchi, **Michael B Chancellor**, Naoki Yoshimura

This is the first report to compare 3-dimensional computed tomography (3D-CT) images between pediatric patients with enuresis and children without lower urinary tract symptoms who underwent pelvic CT for other reasons. Forty-seven children (33 boys and 14 girls) with primary enuresis underwent 3D-CT of sacrococcygeal bones. The control group consisted of 138 children (78 boys and 60 girls) who underwent pelvic CT for other reasons. First, we determined the presence or absence of unfused sacral arches at the L4-S3 levels in both cohorts. Subsequently, we compared the fusion of sacral arches in age- and sex-matched children from these 2 groups. Dysplastic sacral arches, characterized by lack of fusion at 1 or more levels of the S1-3 arches, were observed in nearly all patients in the enuresis group. In the control group ($n=138$), 54 of 79 children over 10 years old (68%) exhibited fused sacral arches at 3 S1-3 levels. All 11 control children under 4 years old displayed at least 2 unfused sacral arches at the S1-3 levels. In a comparative study of age- and sex-matched patients with enuresis and control children aged 5 to 13 years ($n=32$ for each group, with 21 boys and 11 girls; mean age, 8.0 ± 2.2 years [range, 5-13 years]), only 1 patient (3%) in the enuresis group exhibited fusion of all S1-3 arches. In contrast, 20 of 32 control group participants (63%) had 3 fused sacral arches ($P < 0.0001$). Sacral vertebral arches typically fuse by the age of 10 years. However, in this study, children with enuresis exhibited a significantly elevated prevalence of unfused sacral arches, suggesting that dysplastic development of sacral vertebral arches may play a pathological role in enuresis.

[Mapping Niche-specific Two-Component System Requirements in Uropathogenic Escherichia coli](#)

John R Brannon, **Seth A Reasoner**, Tomas A Bermudez, Taryn L Dunigan, **Michelle A Wiebe**, **Connor J Beebout**, Tamia Ross, Adebisi Bamidele, **Maria Hadjifrangiskou**

Sensory systems allow pathogens to differentiate between different niches and respond to stimuli within them. A major mechanism through which bacteria sense and respond to stimuli in their surroundings is two-component systems (TCSs). TCSs allow for the detection of multiple stimuli to lead to a highly controlled and rapid change in gene expression. Here, we provide a comprehensive list of TCSs important for the pathogenesis of uropathogenic *Escherichia coli* (UPEC). UPEC accounts for >75% of urinary tract infections (UTIs) worldwide. UTIs are most prevalent among people assigned female at birth, with the vagina becoming colonized by UPEC in addition to the gut and the bladder. In the bladder, adherence to the urothelium triggers *E. coli* invasion of bladder cells and an intracellular pathogenic cascade. Intracellular *E. coli* are safely hidden from host neutrophils, competition from the microbiota, and antibiotics that kill extracellular *E. coli*. To survive in these intimately connected, yet physiologically diverse niches *E. coli* must rapidly coordinate metabolic and virulence systems in response to the distinct stimuli encountered in each environment. We hypothesized that specific TCSs allow UPEC to sense these diverse environments encountered during infection with built-in redundant safeguards. Here, we created a library of isogenic TCS deletion mutants that we leveraged to map distinct TCS contributions to infection. We identify - for the first time - a comprehensive panel of UPEC TCSs that are critical for infection of the genitourinary tract and report that the TCSs mediating colonization of the bladder, kidneys, or vagina are distinct.

[Multidrug Resistance of Escherichia coli From Outpatient Uncomplicated Urinary Tract Infections in a Large United States Integrated Healthcare Organization](#)

Jennifer H Ku, Katia J Bruxvoort, S Bianca Salas, Cara D Varley, Joan A Casey, **Eva Raphael**, Sarah C Robinson, Keeve E Nachman, Bruno J Lewin, Richard Contreras, Rong X Wei, Magdalena E Pomichowski, Harpreet S Takhar, Sara Y Tartof

Urinary tract infections (UTIs) cause significant disease and economic burden. Uncomplicated UTIs (uUTIs) occur in otherwise healthy individuals without underlying structural abnormalities, with uropathogenic *Escherichia coli* (UPEC) accounting for 80% of cases. With recent transitions in healthcare toward virtual visits, data on multidrug resistance (MDR) (resistant to ≥ 3 antibiotic classes) by care setting are needed to inform empiric treatment decision making. We evaluated UPEC resistance over time by care setting (in-person vs virtual), in adults who received outpatient care for uUTI at Kaiser Permanente Southern California between January 2016 and December 2021. We included 174 185 individuals who had ≥ 1 UPEC uUTI (233 974 isolates) (92% female, 46% Hispanic, mean age 52 years [standard deviation 20]). Overall, prevalence of UPEC MDR decreased during the study period (13% to 12%) both in virtual and in-person settings (P for trend $< .001$). Resistance to penicillins overall (29%), coresistance to penicillins and trimethoprim-sulfamethoxazole (TMP-SMX) (12%), and MDR involving the 2 plus ≥ 1 antibiotic class were common (10%). Resistance to 1, 2, 3, and 4 antibiotic classes was found in 19%, 18%, 8%, and 4% of isolates, respectively; 1% were resistant to ≥ 5 antibiotic classes, and 50% were resistant to none. Similar resistance patterns were observed over time and by care setting. We observed a slight decrease in both class-specific antimicrobial resistance and MDR of UPEC overall, most commonly involving penicillins and TMP-SMX. Resistance patterns were consistent over time and similar in both in-person and virtual settings. Virtual healthcare may expand access to UTI care.

[MV140 mucosal bacterial vaccine improves uropathogenic *E. coli* clearance in an experimental model of urinary tract infection](#)

Marianne Ligon, Carmen Diez-Rivero, Diego García-Ayuso, Soumitra Mohanty, Laura Conejero, Annelie Brauner, José Subiza, **Indira Mysorekar**, Paula Saz-Leal

MV140 is a mucosal vaccine of inactivated whole bacteria (*E. coli*, *K. pneumoniae*, *E. faecalis*, *P. vulgaris*) with clinical efficacy against recurrent urinary tract infections (UTIs). Here, MV140 was evaluated in a murine model of acute uropathogenic *E. coli* (UPEC)-induced UTI using the UTI89 strain. MV140 vaccination resulted in UPEC clearance, concomitant with increased influx of myeloid cells in urine, CD4+ T cells in the bladder, and a systemic adaptive immune response to both MV140-containing *E. coli* and UTI89.

[Neurobiology and long-term impact of bladder-filling pain in humans: a Multidisciplinary Approach to the Study of Chronic Pelvic Pain \(MAPP\) research network study](#)

Andrew D Schrepf, Ishtiaq Mawla, Bruce D Naliboff, Bob Gallop, Robert M Moldwin, Frank Tu, Priyanka Gupta, Steven Harte, John N Krieger, Claire Yang, Catherine Bradley, Larissa Rodriguez, David Williams, Vincent Magnotta, Eric Ichesco, Richard E Harris, **Quentin Clemens**, **Chris Mullins**, Jason J Kutch

Pain with bladder filling remains an unexplained clinical presentation with limited treatment options. Here, we aim to establish the clinical significance of bladder filling pain using a standardized test and the associated neural signature. We studied individuals diagnosed with urologic chronic pelvic pain syndrome (UCPPS) recruited as part of the multidisciplinary approach to the study of chronic pelvic pain (MAPP) study. Patients with urologic chronic pelvic pain syndrome ($N = 429$) and pain-free controls ($N = 72$) underwent a test in which they consumed 350 mL of water and then reported pain across an hour-long period at baseline and 6 months. We used latent class trajectory models of these pain ratings to define UCPPS subtypes at both baseline and 6 months. Magnetic resonance imaging of the brain postconsumption was used to examine neurobiologic differences between the

subtypes. Healthcare utilization and symptom flare-ups were assessed over the following 18 months. Two distinct UCPPS subtypes were identified, one showing substantial pain related to bladder filling and another with little to no pain throughout the test. These distinct subtypes were seen at both baseline and 6 month timepoints. The UCPPS subtype with bladder-filling pain (BFP+) had altered morphology and increased functional activity in brain areas involved in sensory and pain processing. Bladder-filling pain positive status predicted increased symptom flare-ups and healthcare utilization over the subsequent 18 months when controlling for symptom severity and a self-reported history of bladder-filling pain. These results both highlight the importance of assessing bladder filling pain in heterogeneous populations and demonstrate that persistent bladder-filling pain profoundly affects the brain.

[Posterior urethral valves in patients with trisomy 21: Similar renal outcomes and rates of volitional voiding](#)

Alice Xiang, John Weaver, Iqra Nadeem, Neeta D'Souza, Mandy Rickard, Dana Weiss, Karen Milford, Lynn Woo, Jessica Hannick, Armando Lorenzo, **Gregory Tasian**, Christopher Long

Posterior urethral valves (PUV) occur in patients with Down Syndrome (DS) at a rate of 3-4%; far higher than the general population. Our understanding of the relationship between PUVs and DS is in its infancy, with the majority of the literature consisting of case reports. In this study, we present the largest known series of DS patients with PUVs. We hypothesized that patients with DS and PUVs would have worse functional bladder outcomes and renal outcomes when compared to PUV patients without DS. We queried our prospectively managed multi-institutional database of PUV patients from 1990 to 2021. We identified patients with a concomitant diagnosis of DS and PUV. In addition, we performed a systematic review of the literature describing the presentation of children with PUV and DS. Patient demographics, renal outcomes, voiding habits, surgical interventions, and radiologic images were aggregated and

analyzed. Out of the 537 patients in our PUV database, we identified 18 patients with a concomitant diagnosis of PUV and DS, as well as 14 patients with a concomitant diagnosis of PUV and DS from the literature. DS and non-DS patients had a similar age at presentation, 31.5 days (2-731) and 17 (4-846), and length of follow up 6.32 years (2-11.2) and 6.98 (1-13). Both groups had similar nadir creatinines DS 0.43 (0.4-0.8), non-DS 0.31 (0.2-0.5) and similar rates of renal failure (DS 11.1% and non-DS 14.5%). With respect to bladder outcomes, a similar percentage of patients were volitionally voiding at last follow up (DS 72.2% and non-DS 72.3%). Our literature review corroborated these findings. Patients with DS and PUV have similar renal outcomes to other PUV patients in terms of renal function, progression to renal failure, and probability of volitional voiding with continence. Given the increased rate of PUVs in the DS population, physicians should have a high index of suspicion for PUV when patients with DS present with voiding dysfunction.

[Proteomics analysis of urine and catheter-associated biofilms in spinal cord injury patients](#)

Fernando J Garcia-Marques, Elissa Zakrasek, Abel Bermudez, **Alexandra L Polasko**, Shiqin Liu, Tanya Stoyanova, **James D Brooks**, John Lavelle, Sharon J Pitteri

After spinal cord injury (SCI), use chronic urinary catheters for bladder management is common, making these patients especially vulnerable to catheter-associated complications. Chronic catheterization is associated with bacterial colonization and frequent catheter-associated urinary tract infections (CAUTI). One determinant of infection success and treatment resistance is production of catheter-associated biofilms, composed of microorganisms and host- and microbial-derived components. To better understand the biofilm microenvironment, we performed proteomics analysis of catheter-associated biofilms and paired urine samples from four people with SCI with chronic indwelling urinary catheters. We

developed a novel method for the removal of adhered cellular components on catheters that contained both human and microbial homologous proteins. Proteins from seven microbial species were identified including: *Escherichia coli*, *Klebsiella* species (spp), *Enterococcus* spp, *Proteus mirabilis*, *Pseudomonas* spp, *Staphylococcus* spp, and *Candida* spp. Peptides identified from catheter biofilms were assigned to 4,820 unique proteins, with 61% of proteins assigned to the biofilm-associated microorganisms, while the remainder were human-derived. Contrastingly, in urine, only 51% were assigned to biofilm-associated microorganisms and 4,554 proteins were identified as a human-derived. Of the proteins assigned to microorganisms in the biofilm and paired urine, *Enterococcus*, *Candida* spp, and *P. mirabilis* had greater associations with the biofilm phase, whereas *E. coli* and *Klebsiella* had greater associations with the urine phase, thus demonstrating a significant difference between the urine and adhered microbial communities. The microbial proteins that differed significantly between the biofilm and paired urine samples mapped to pathways associated with amino acid synthesis, likely related to adaptation to high urea concentrations in the urine, and growth and protein synthesis in bacteria in the biofilm. Human proteins demonstrated enrichment for immune response in the catheter-associated biofilm. Proteomic analysis of catheter-associated biofilms and paired urine samples has the potential to provide detailed information on host and bacterial responses to chronic indwelling urinary catheters and could be useful for understanding complications of chronic indwelling catheters including CAUTIs, urinary stones, and catheter blockages.

[Spatial clusters of extended-spectrum beta-lactamase-producing *Escherichia coli* causing community-onset bacteriuria due to repeat infections: cluster analysis from a large urban medical center, San Francisco, 2014-2020](#)

Eva Raphael, Pushkar P Inamdar, Cheyenne Belmont, Salma Shariff-Marco, **Alison Huang**, Henry Chambers

Urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (ESBL-*E. coli*) may occur as outbreaks due to common-source exposures. Yet, it is currently unknown if they cluster geographically as would be expected as part of an outbreak. We collected electronic health record data on all patients living in San Francisco with culture-documented community-onset *E. coli* bacteriuria in a safety-net public healthcare system from January 2014 to March 2020 (diagnosed < 48 hours after hospital admission or in outpatient clinical settings without a hospitalization in the past 90 days). We assessed the presence of spatial clusters of (1) ESBL-*E. coli* bacteriuria episodes, and (2) individuals with any ESBL-*E. coli* bacteriuria episode, with Global and Local Moran's I. We evaluated differences in prevalence of bacteriuria recurrence by ESBL-production by Poisson regression. Out of 4,304 unique individuals, we identified spatial clusters of ESBL-*E. coli* bacteriuria episodes (n = 461) compared to non-ESBL-*E. coli* bacteriuria episodes (n = 5477; Global Moran's p < 0.001). Spatial clusters of individuals with any bacteriuria caused by ESBL-*E. coli* were not identified (p = 0.43). Bacteriuria recurrence was more likely to occur with ESBL-*E. coli* (odds ratio [OR] 2.78, 95% confidence interval [95%CI] 2.10, 3.66, p < 0.001), particularly after an initial ESBL-*E. coli* bacteriuria episode (OR 2.27, 95% CI 1.82, 2.83, p < 0.001). We found spatial clusters of ESBL-*E. coli* bacteriuria episodes. However, this was partly explained by clustering within individuals more than between individuals, as having an ESBL-*E. coli* bacteriuria was associated with recurrence with ESBL-*E. coli*.

KIDNEY

Clinical and postoperative characteristics of stentless ureteroscopy patients: a prospective analysis from ReSKU

Fadl Hamouche, Rei Unno, Nizar Hakam, Leslie Bernal Charondo, Heiko Yang, Justin Ahn, **David B Bayne**, Marshall L Stoller, **Thomas Chi**

Materials and methods: This was a prospective case cohort study utilizing data collected in the Registry for Stones of the Kidney and Ureter (ReSKU) from a single institution between October 2015 and December 2020. We identified all consecutive patients undergoing URS for stone disease and analyzed data encompassing demographics, medical history, intra and postoperative characteristics, including complications and postoperative symptoms. Univariate and multivariate logistic regression analyses were performed based on the presence or absence of an indwelling ureteral stent. A total of 470 patients were included for analysis, 92 patients in the stentless group (19.5%). Factors associated with stentless ureteroscopy were a lower stone burden ($p < 0.001$), the pre-existence of a ureteral stent (37.4% vs. 27.9% $p = 0.011$), absence of an access sheath (14.6% vs. 69.5% $p < 0.001$), and a shorter operative time (31 vs. 58 min $p < 0.001$). Postoperative gross hematuria and lower urinary tract symptoms (LUTS) were reported less frequently in stentless patients ($p = 0.02$, $p = 0.01$, respectively). There was no difference in postoperative complications between both groups (15.2% vs. 12.0%, $p = 0.385$). On multivariate analysis, the risk of postoperative complications was associated with obesity, stone burden ≥ 1 cm, and positive preoperative urine culture. There was no patient who required emergent stent placement in the stentless group. Our data show that, in well selected patients, omitting ureteral stent placement after URS can decrease postoperative gross hematuria and LUTS without increasing postoperative complications.

Performance of Nuclear Magnetic Resonance-Based Estimated Glomerular Filtration Rate in a Real-World Setting

Amauri Schwäble Santamaria, Marcello Grassi, Jeffrey W Meeusen, **John C Lieske**, Renee Scott, Andrew Robertson, Eric Schiffer

An accurate estimate of glomerular filtration rate (eGFR) is essential for proper clinical management, especially in patients with kidney dysfunction. This prospective observational study evaluated the real-world performance of the nuclear magnetic resonance (NMR)-based GFRNMR equation, which combines creatinine, cystatin C, valine, and myo-inositol with age and sex. We compared GFRNMR performance to that of the 2021 CKD-EPI creatinine and creatinine-cystatin C equations (CKD-EPI2021Cr and CKD-EPI2021CrCys), using 115 fresh routine samples of patients scheduled for urinary iothalamate clearance measurement (mGFR). Median bias to mGFR of the three eGFR equations was comparably low, ranging from 0.4 to 2.0 mL/min/1.73 m². GFRNMR outperformed the 2021 CKD-EPI equations in terms of precision (interquartile range to mGFR of 10.5 vs. 17.9 mL/min/1.73 m² for GFRNMR vs. CKD-EPI2021CrCys; $p = 0.01$) and accuracy (P15, P20, and P30 of 66.1% vs. 48.7% [$p = 0.007$], 80.0% vs. 60.0% [$p < 0.001$] and 95.7% vs. 86.1% [$p = 0.006$], respectively, for GFRNMR vs. CKD-EPI2021CrCys). Clinical parameters such as etiology, comorbidities, or medications did not significantly alter the performance of the three eGFR equations. Altogether, this study confirmed the utility of GFRNMR for accurate GFR estimation, and its potential value in routine clinical practice for improved medical care.

Polygenic risk affects the penetrance of monogenic kidney disease

Atlas Khan, Ning Shang, Jordan G Nestor, Chunhua Weng, George Hripacsak, Peter C Harris, **Ali G Gharavi**, Krzysztof Kiryluk

Chronic kidney disease (CKD) is a genetically complex disease determined by an interplay of monogenic, polygenic, and environmental risks. Most forms of monogenic kidney diseases have incomplete penetrance and variable

expressivity. It is presently unknown if some of the variability in penetrance can be attributed to polygenic factors. Using the UK Biobank (N=469,835 participants) and the All of Us (N=98,622 participants) datasets, we examined two most common forms of monogenic kidney disorders, autosomal dominant polycystic kidney disease (ADPKD) caused by deleterious variants in the PKD1 or PKD2 genes, and COL4A-associated nephropathy (COL4A-AN) caused by deleterious variants in COL4A3, COL4A4, or COL4A5 genes). We used the eMERGE-III electronic CKD phenotype to define cases (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m² or kidney failure) and controls (eGFR > 90 mL/min/1.73m² in the absence of kidney disease diagnoses). The effects of the genome-wide polygenic score (GPS) for CKD were tested in monogenic variant carriers and non-carriers using logistic regression controlling for age, sex, diabetes, and genetic ancestry. As expected, the carriers of known pathogenic and rare predicted loss-of-function variants in PKD1 or PKD2 had a high risk of CKD (OR meta= 17.1, 95% CI: 11.1-26.4, $P = 1.8E-37$). The GPS was comparably predictive of CKD in both ADPKD variant carriers (OR meta= 2.28 per SD, 95% CI: 1.55-3.37, $P = 2.6E-05$) and non-carriers (OR meta= 1.72 per SD, 95% CI= 1.69-1.76, $P < E-300$) independent of age, sex, diabetes, and genetic ancestry. Compared to the middle tertile of the GPS distribution for non-carriers, ADPKD variant carriers in the top tertile had a 54-fold increased risk of CKD, while ADPKD variant carriers in the bottom tertile had only a 3-fold increased risk of CKD. Similarly, the GPS was predictive of CKD in both COL4A-AN variant carriers (OR meta= 1.78, 95% CI= 1.22-2.58, $P = 2.38E-03$) and non-carriers (OR= 1.70, 95% CI: 1.68-1.73 $P < E-300$). The carriers in the top tertile of the GPS had a 2.5-fold higher risk of CKD while the risk for carriers in the bottom tertile was similar to the middle tertile of non-carriers. Variable penetrance of kidney disease in ADPKD and COL4A-AN is partially explained by differences in polygenic risk profiles. Accounting for polygenic factors has the potential to improve risk stratification in monogenic

kidney disease and may have implications for genetic counseling.

[Their last will and testament: dying immune cells protect the urinary system with extracellular DNA traps](#)

Nicholas J Steers, Jonathan Barasch

Like most epithelial organs, the bladder and kidney can be directly accessed by bacteria evolved for invasion. Epithelia and immune cells attempt to stymie this infection with biophysical and chemical mechanisms. Goldspink et al. connected the Na⁺ gradient in the kidney medulla with an immune defense mounted by dead cells (namely, the explosive death of neutrophils and macrophages), resulting in extracellular DNA traps. The pathway from Na⁺ concentration to immune death is depicted.

STONES

[End Point Considerations for Clinical Trials in Enteric Hyperoxaluria](#)

Craig B Langman, **Dean Assimos**, Melanie Blank, Juan Calle, Andreas Grauer, Annamaria Kausz, Dawn Milliner, Lama Nazzal, Kimberly Smith, **Greg Tasian**, Aliza Thompson, **Kyle D Wood**, Elaine Worcester, Sixun Yang, Meaghan A Malley, Felix Knauf, **John C Lieske**; Rare Kidney Stone Consortium (RKSC) Kidney Health Initiative (KHI) Oxalosis and Hyperoxaluria Foundation Enteric Hyperoxaluria Workgroup (OHF EH Workgroup)

Enteric hyperoxaluria is a medical condition characterized by elevated urinary oxalate excretion due to increased gastrointestinal oxalate absorption. Causative features include fat malabsorption and/or increased intestinal permeability to oxalate. Enteric hyperoxaluria has long been known to cause nephrolithiasis and nephrocalcinosis, and, more recently, an association with CKD and kidney failure has been shown. Currently, there are no US Food and Drug Administration-approved therapies for enteric hyperoxaluria, and it is unclear what end points should be used to evaluate the efficacy of new drugs and biologics for this condition. This study represents work of a multidisciplinary group convened by the Kidney Health Initiative to review the evidence supporting potential end points for clinical trials in enteric hyperoxaluria. A potential clinical outcome is symptomatic kidney stone events. Potential surrogate end points

include (1) an irreversible loss of kidney function as a surrogate for progression to kidney failure, (2) asymptomatic kidney stone growth/new stone formation observed on imaging as a surrogate for symptomatic kidney stone events, (3) urinary oxalate and urinary calcium oxalate supersaturation as surrogates for the development of symptomatic kidney stone events, and (4) plasma oxalate as a surrogate for the development of the clinical manifestations of systemic oxalosis. Unfortunately, because of gaps in the data, this Kidney Health Initiative workgroup was unable to provide definitive recommendations. Work is underway to obtain robust information that can be used to inform trial design and medical product development in this space.

[Development of an optically transparent kidney model for laser lithotripsy research](#)

Sabrina Tran, **Junqin Chen**, Gunnar Kozel, Eric T Chang, Trina Phung, Yanxi Peng, **Zachary Dionise**, Yuan Wu, W Neal Simmons, **Michael E Lipkin**, **Glenn M Preminger**, **Pei Zhong**

Ureteroscopy with laser lithotripsy (LL) has become the treatment of choice for kidney stones of all compositions, while leading the technology development in the surgical management of urinary stone disease. In recent years, dusting treatment that leverages low pulse energy (Ep) and high frequency (F) has gained widespread clinical acceptance over traditional fragmenting treatment that utilizes high Ep and low F, due to the smaller fragments produced and shortened overall procedure time. Concomitant to the paradigm shift in the treatment mode, recent laboratory studies have demonstrated that the mechanism of stone damage in holmium (Ho):yttrium-aluminum-garnet (YAG) LL may change from predominantly photothermal ablation in fragmenting mode to cavitation damage in dusting mode. Yet, these new observations need to be validated under clinically relevant conditions and thus demanding improvements for in vitro models, including (I) being able to mimic the functional morphology of human kidney, (II) having a transparent tissue boundary that allows researchers to capture the

bubble dynamics during the treatment, and (III) easy assembly of the model for stone implantation and retrieval of fragments. Motivated by those requirements, we introduce a simple fabrication process of an optically transparent, anatomically realistic, and hydrogel-based kidney phantom.

[Model-based simulations of pulsed laser ablation using an embedded finite element method](#)

Yangyuanchen Liu, Susanne Claus, Pierre Kerfriden, **Junqin Chen**, **Pei Zhong**, **John E Dolbow**

A model of thermal ablation with application to multi-pulsed laser lithotripsy is presented. The approach is based on a one-sided Stefan-Signorini model for thermal ablation, and relies on a level-set function to represent the moving interface between the solid phase and a fictitious gas phase (representing the ablated material). The model is discretized with an embedded finite element method, wherein the interface geometry can be arbitrarily located relative to the background mesh. Nitsche's method is adopted to impose the Signorini condition on the moving interface. A bound constraint is also imposed to deal with thermal shocks that can arise during representative simulations of pulsed ablation with high-power lasers. We report simulation results based on experiments for pulsed laser ablation of wet BegoStone samples treated in air, where BegoStone has been used as a phantom material for kidney stone. The model is calibrated against experimental measurements by adjusting the percentage of incoming laser energy absorbed at the surface of the stone sample. Simulation results are then validated against experimental observations for the crater area, volume, and geometry as a function of laser pulse energy and duration. Our studies illustrate how the spreading of the laser beam from the laser fiber tip with concomitantly reduced incident laser irradiance on the damaged crater surface explains trends in both the experimental observations and the model-based simulation results.

[Natural history of urine and plasma oxalate in children with primary hyperoxaluria type 1](#)

David J Sas, Kristin Mara, Ramila A Mehta, Barbara M Seide, Carly J Banks, David S Danese, Tracy L McGregor, **John C Lieske**, Dawn S Milliner

Primary hyperoxaluria type 1 (PH1) is a rare, severe genetic disease causing increased hepatic oxalate production resulting in urinary stone disease, nephrocalcinosis, and often progressive chronic kidney disease. Little is known about the natural history of urine and plasma oxalate values over time in children with PH1. For this retrospective observational study, we analyzed data from genetically confirmed PH1 patients enrolled in the Rare Kidney Stone Consortium PH Registry between 2003 and 2018 who had at least 2 measurements before age 18 years of urine oxalate-to-creatinine ratio (Uox:cr), 24-h urine oxalate excretion normalized to body surface area (24-h Uox), or plasma oxalate concentration (Pox). We compared values among 3 groups: homozygous G170R, heterozygous G170R, and non-G170R AGXT variants both before and after initiating pyridoxine (B6). Of 403 patients with PH1 in the registry, 83 met the inclusion criteria. Uox:cr decreased rapidly over the first 5 years of life. Both before and after B6 initiation, patients with non-G170R had the highest Uox:cr, 24-h Uox, and Pox. Patients with heterozygous G170R had similar Uox:cr to homozygous G170R prior to B6. Patients with homozygous G170R had the lowest 24-h Uox and Uox:cr after B6. Urinary oxalate excretion and Pox tend to decrease over time during childhood. eGFR over time was not different among groups. Children with PH1 under 5 years old have relatively higher urinary oxalate excretion which may put them at greater risk for nephrocalcinosis and kidney failure than older PH1 patients. Those with homozygous G170R variants may have milder disease. A higher resolution version of the Graphical abstract is available as Supplementary information.

[Pediatric Stone Disease: Current Trends and Future Directions](#)

Ching Man Carmen Tong, **Jonathan S Ellison**, **Gregory E Tasian**

Pediatric nephrolithiasis is less common in children than in adults but the incidence has been rising rapidly, and it is now a public health and economic burden in the United States. There are challenges unique to children that should be taken into consideration when evaluating and managing pediatric stone disease. In this review, we present the current research on risk factors, emerging new technologies for treatment of stones and recent investigations on prevention of stones in this population.

[The real world experience of pediatric primary hyperoxaluria patients in the PEDSnet clinical research network](#)

Christina B Ching, Kimberley Dickinson, John Karafilidis, Nicole Marchesani, Lisa Mucha, Nuno Antunes, Hanieh Razzaghi, Levon Utidjian, Karyn Yonekawa, Douglas E Coplen, Samina Muneeruddin, William DeFoor, Kyle O Rove, Christopher B Forrest, **Gregory E Tasian**

The rarity of primary hyperoxaluria (PH) challenges our understanding of the disease. The purpose of our study was to describe the course of clinical care in a United States cohort of PH pediatric patients, highlighting health service utilization. We performed a retrospective cohort study of PH patients < 18 years old in the PEDSnet clinical research network from 2009 to 2021. Outcomes queried included diagnostic imaging and testing related to known organ involvement of PH, surgical and medical interventions specific to PH-related renal disease, and select PH-related hospital service utilization. Outcomes were evaluated relative to cohort entrance date (CED), defined as date of first PH-related diagnostic code. Thirty-three patients were identified: 23 with PH type 1; 4 with PH type 2; 6 with PH type 3. Median age at CED was 5.0 years (IQR 1.4, 9.3 years) with the majority being non-Hispanic white (73%) males (70%). Median follow-up between CED and most recent encounter was 5.1 years (IQR 1.2, 6.8). Nephrology and Urology were the most common specialties involved in care, with low utilization of other sub-specialties (12%-36%). Most patients (82%) had diagnostic imaging used to evaluate kidney stones;

11 (33%) had studies of extra-renal involvement. Stone surgery was performed in 15 (46%) patients. Four patients (12%) required dialysis, begun in all prior to CED; four patients required renal or renal/liver transplant. Conclusion: In this large cohort of U.S. PH children, patients required heavy health care utilization with room for improvement in involving multi-disciplinary specialists. What is Known: Primary hyperoxaluria (PH) is rare with significant implications on patient health. Typical involvement includes the kidneys; however, extra-renal manifestations occur. Most large population studies describe clinical manifestations and involve registries. What is New: We report the clinical journey, particularly related to diagnostic studies, interventions, multispecialty involvement, and hospital utilization, of a large cohort of PH pediatric patients in the PEDSnet clinical research network. There are missed opportunities, particularly in that of specialty care, that could help in the diagnosis, treatment, and even prevention of known clinical manifestations.

PATIENT-CENTERED RESEARCH

[Relationships Between Urinary and Nonurinary Symptoms in Treatment-Seeking Women in LURN](#)

Abigail R Smith, Sarah A Mansfield, Catherine S Bradley, Kimberly S Kenton, Margaret E Helmuth, Anne P Cameron, Ziya Kirkali, C Emi Bretschneider, Victor Andreev, **Aruna Sarma**, **Giulia Lane**, Sarah A Collins, David Cella, **H Henry Lai**, Steven E Harte, James W Griffith; LURN Study Group

Physical health and psychological health represent modifiable factors in the causal pathway of lower urinary tract symptoms (LUTS). Adult women enrolled in the Symptoms of Lower Urinary Tract Dysfunction Research Network observational cohort study completed the LUTS Tool and Pelvic Floor Distress Inventory, including urinary (Urinary Distress Inventory), prolapse (Pelvic Organ Prolapse Distress Inventory), and colorectal anal (Colorectal-Anal Distress Inventory) subscales at baseline, 3 months, and 12 months. Physical functioning, depression, and sleep disturbance were measured using the Patient-Reported Outcomes

Measurement Information System (PROMIS) questionnaires; relationships were assessed using multivariable linear mixed models. Of 545 women enrolled, 472 had follow-up. Median age was 57 years; 61% and 78% reported stress urinary incontinence and overactive bladder, respectively; and 81% reported obstructive symptoms. The PROMIS depression scores were positively associated with all urinary outcomes (range, 2.5- to 4.8-unit increase per 10-unit increase in depression score; $P < 0.01$ for all). Higher sleep disturbance scores were associated with higher urgency, obstruction, LUTS Total Severity, Urinary Distress Inventory, and Pelvic Floor Distress Inventory (1.9- to 3.4-point increase per 10-unit increase, all $P < 0.02$). Better physical functioning was associated with less severe urinary symptoms except stress urinary incontinence (2.3- to 5.2-point decrease per 10-unit increase, all $P < 0.01$). All symptoms decreased over time; however, no association was detected between baseline PROMIS scores and trajectories of LUTS over time. Nonurologic factors demonstrated small to medium cross-sectional associations with urinary symptom domains, but no significant association was detected with changes in LUTS. Further work is needed to determine whether interventions targeting nonurologic factors reduce LUTS in women.

- Jennifer Allmaras MPH, Anna Barrett,
7/25/2023

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BLADDER

[Development and validation of models predicting treatment patterns in women with urinary urgency and/or urgency incontinence: A Symptoms of Lower Urinary Tract Dysfunction Research Network observational cohort study](#)

Bretschneider CE, Liu Q, Smith AR, Mansfield SA, Kirkali Z, Amundsen CL, Lai HH, Geynisman-Tan J, Kirby A, Jelovsek JE

The Symptoms of Lower Urinary Tract Dysfunction Research Network observational cohort study enrolled adult women with bothersome UU and/or UU incontinence using the lower urinary tract symptoms (LUTS) Tool who were seeking care for LUTS. Treatments for UU and/or urgency incontinence were ordered from least to most invasive. Ordinal logistic and Cox proportional hazard regression models were fit to predict the most invasive level of treatment during follow-up and overactive bladder (OAB) medication discontinuation, respectively. Binary logistic regression was performed to predict sling treatment during the study follow-up. Clinical tools were then created using the models listed above to predict treatment pattern over 12 months. Among 349 women, 281 reported UU incontinence, and 68 reported UU at baseline. The highest level of treatment during the study was as follows: 20% no treatment, 24% behavioral treatments, 23% physical therapy, 26% OAB medication, 1% percutaneous tibial nerve stimulation, 3% onabotulinumtoxin A, and 3% sacral neuromodulation. Slings were placed in 10% (n = 36) of participants before baseline and in 11% (n = 40) during study follow-up. Baseline factors associated with predicting the most invasive level of treatment included baseline level of treatment, hypertension, UU incontinence severity, stress urinary incontinence (SUI) severity, and anticholinergic burden score. Less severe baseline depression and less severe UU incontinence were associated with OAB medication discontinuation. UU and SUI

severity were associated with sling placement during the study period. Three tools are available to predict: (1) highest level of treatment; (2) OAB medication discontinuation; and (3) sling placement. OAB treatment prediction tools developed in this study can help providers individualize treatment plans and identify not only patients at risk for treatment discontinuation but also patients who may not be escalated to potentially beneficial OAB treatments, with the goal to improve clinical outcomes for patients suffering from this chronic and often debilitating condition.

[Effects of swelling and anatomical location on the viscoelastic behavior of the porcine urinary bladder wall](#)

Tuttle T, McClintock D, Roccabianca S.

The ability of the urinary bladder to perform its physiological function depends largely on its mechanical characteristics. Understanding the mechanics of this tissue is crucial to the development of accurate models of not just this specific organ, but of the pelvic floor overall. In this study, we tested porcine bladder to identify variations in the tissue's viscoelastic characteristics associated with anatomical locations and swelling. We investigated this relationship using a series of stress-relaxation experiments as well as a modified Maxwell-Wiechert model to aid in the interpretation of the experimental data. Our results highlight that tissue located near the neck of the bladder presents significantly different viscoelastic characteristics than the body of the organ. This supports what was previously observed and is a valuable contribution to the understanding of the location-specific properties of the bladder. We also tested the effect of swelling, revealing that the bladder's viscoelastic behavior is mostly independent of solution osmolarity in hypoosmotic solutions, but the use of a hyperosmotic solution can significantly affect its behavior. This is significant, since several urinary tract pathologies can lead to chronic inflammation and

disrupt the urothelial barrier causing increased urothelial permeability, thus subjecting the bladder wall to non-physiologic osmotic challenge.

[Lack of expression of miR-29a/b1 impairs bladder function in male mice.](#)

Wang Z, Spitz R, Vezina C, Hou J, Bjorling DE.

Lower urinary tract symptoms (LUTS) refer to various urological diseases, and incomplete bladder emptying is common among affected patients. Etiology of LUTS is largely unknown, and investigations of LUTS suggest that bladder fibrosis contributes to pathogenesis of LUTS. MicroRNAs (miRNAs) are short (~22 nucleotides), non-coding RNAs that repress target gene expression by a combination of mRNA degradation and translation inhibition. The miR-29 family is best known for its anti-fibrotic role in various organs. miR-29 was decreased in bladders of patients with outlet obstruction and a rat model of bladder outlet obstruction, suggesting that miR-29 may contribute to impaired bladder function subsequent to tissue fibrosis. We characterized bladder function in male mice lacking expression of MIR29A and MIR29B1 (miR-29a/b1). Lack of miR-29a/b1 resulted in severe urinary retention, increased voiding duration with reduced flow rate, and these mice failed to void or voided irregularly during anesthetized cytometry. Collagens and elastin were increased in bladders of mice lacking miR-29a/b1. These findings reveal an important role of miR-29 in bladder homeostasis and suggest therapeutic potential of miR-29 to improve symptoms in patients with LUTS.

[Male Akita mice develop signs of bladder underactivity independent of NLRP3 as a result of a decrease in neurotransmitter release from efferent neurons](#)

Hughes FM Jr, Alkanjari A, Odom MR, Mulcrone JE, Jin H, Purves JT.

Diabetic Bladder Dysfunction (DBD) is a prevalent diabetic complication that is recalcitrant to glucose control. Using the Akita mouse model (type 1) bred to be NLRP3^{+/+} or NLRP3^{-/-}, we previously found that females (mild hyperglycemia) progress from an overactive to an underactive bladder phenotype and this progression was dependent on NLRP3-induced inflammation. Here we examined DBD in the male Akita (severe hyperglycemia) and found by urodynamics only a compensated underactive-like phenotype (increased void volume and decreased frequency but unchanged efficiency). Surprisingly, this phenotype was still present in the NLRP3^{-/-} strain and so was not dependent on NLRP3 inflammasome-induced inflammation. Examining the cause of the compensated underactive-like phenotype, we assessed overall nerve density and afferent nerves (Aδ-fibers). Both were decreased in density during diabetes but denervation was absent in the diabetic NLRP3^{-/-} strain so it was deemed unlikely to cause the underactive-like symptoms. Changes in bladder smooth muscle (BSM) contractility to cell depolarization and receptor activation were also not responsible as KCl (depolarizing agent), carbachol (muscarinic agonist) and α , β -methylene-ATP (purinergic agonist) elicited equivalent contractions in denuded bladder strips in all groups. However, electrical field stimulation revealed a diabetes-induced decrease in contractility that was not blocked in the NLRP3^{-/-} strains suggesting that bladder compensated underactive-like phenotype in the male Akita is likely through a decrease in efferent neurotransmitter release.

[Personalized Pre-clinic Nursing Telemedicine Visit: An Efficient and Efficacious Approach for Bowel and Bladder Dysfunction in Children](#)

Jennika L Finup, **Vinaya P Bhatia**, Dana M Perry, Sarah J Truscott, Shannon T Cannon, Fardod O'Kelly, **Walid A Farhat**

To evaluate the effectiveness and efficacy of a Registered Nurse (RN) led educational pre-clinic telephone call on compliance and outcomes in children with bowel and bladder dysfunction

(BBD). Our novel RN-led pre-clinic telemedicine visit demonstrates excellent compliance and patient outcomes for children with BBD and can reduce the use of unnecessary imaging, medications, and time-consuming treatments such as biofeedback.

[Quantifying whole bladder biomechanics using the novel pentaplanar reflected image macroscopy system](#)

Hennig G, Saxena P, Broemer E, Herrera GM, Roccabianca S, Tykocki NR.

Optimal bladder compliance is essential to urinary bladder storage and voiding functions. Calculated as the change in filling volume per change in pressure, bladder compliance is used clinically to characterize changes in bladder wall biomechanical properties that associate with lower urinary tract dysfunction. But because this method calculates compliance without regard to wall structure or wall volume, it gives little insight into the mechanical properties of the bladder wall during filling. Thus, we developed Pentaplanar Reflected Image Macroscopy (PRIM): a novel ex vivo imaging method to accurately calculate bladder wall stress and stretch in real time during bladder filling. The PRIM system simultaneously records intravesical pressure, infused volume, and an image of the bladder in five distinct visual planes. Wall thickness and volume were then measured and used to calculate stress and stretch during filling. As predicted, wall stress was nonlinear; only when intravesical pressure exceeded ~ 15 mmHg did bladder wall stress rapidly increase with respect to stretch. This method of calculating compliance as stress vs stretch also showed that the mechanical properties of the bladder wall remain similar in bladders of varying capacity. This study demonstrates how wall tension, stress and stretch can be measured, quantified, and used to accurately define bladder wall biomechanics in terms of actual material properties and not pressure/volume changes. This method is especially useful for determining how changes in bladder biomechanics are altered in pathologies where profound

bladder wall remodeling occurs, such as diabetes and spinal cord injury.

[Understanding factors influencing primary treatment with intradetrusor onabotulinumtoxinA versus augmentation cystoplasty in patients with spina bifida](#)

Li B, Peard LM, Zhao S, Graham MK, Adams C, Taylor AS, Thomas JC, Pope JC, Adams MC, Brock JW, Clayton DB.

Surgical interventions in the urologic management of children with neurogenic bladder secondary to spina bifida aim to preserve upper tract function, prevent urinary tract infections, and optimize quality of life. However, since the introduction of intravesical onabotulinumtoxinA (Botox) in the management of these patients, the indications for choosing Botox over augmentation cystoplasty (AC) remain undefined. The objective of this study was to determine which factors lead patients to undergo Botox versus AC as a primary surgical treatment after failing medical management. We identified 14 and 50 myelomeningocele patients who underwent primary AC and primary Botox, respectively. We found no significant differences in age, sex, race, or history of reconstructive surgery (antegrade continence enema or catheterizable channel). For the 10 decision-making factors, desire for independence/continence ($p = <0.001$) and reduced capacity ($p = 0.002$) were significantly associated with AC, while trabeculation ($p = 0.006$), EFP ≥ 40 cm H₂O ($p = 0.029$), rising slope ($p = 0.019$), and physician-perceived hostility ($p = 0.012$) were significantly more common with Botox. At our institution, quality of life measures prompted AC over objective urodynamic or imaging findings before attempting Botox. These findings support a shared decision-making approach when considering surgical intervention for neurogenic bladder secondary to myelomeningocele.

GENITOURINARY

["Postoperative Outcomes Following Buried Penis Reconstruction: A Single-Institution Experience Using the Wisconsin Classification System"](#)

Allison J Seitz, Armin Edalatpour, Jacqueline S Israel, **Matthew D Grimes**, Daniel H Williams, Samuel O Poore

Adult acquired buried penis (AABP) is a complex condition often necessitating surgical intervention. This study seeks to examine the validity of the Wisconsin Classification System (WCS) in guiding the surgical management of AABP. Additionally, we aimed to identify which factors contribute to postoperative complications and persistent symptoms following AABP repair. The Wisconsin Classification System serves as a preoperative guide, an educational tool for patients, and provides a framework for the discussion of intraoperative maneuvers and the likelihood of complications. It is imperative to counsel patients on the surgical management of AABP and the postoperative course, as this may permit realistic patient expectations and optimize outcomes.

KIDNEY

[Automated Society of Fetal Urology \(SFU\) grading of hydronephrosis on ultrasound imaging using a convolutional neural network](#)

Ostrowski DA, Logan JR, Antony M, Broms R, Weiss DA, **Van Batavia J**, Long CJ, Smith AL, Zderic SA, Edwins RC, Pomerville RJ, Hannick JH, Woo LL, **Fan Y**, **Tasian GE**, Weaver JK.

Grading of hydronephrosis severity on postnatal renal ultrasound guides management decisions in antenatal hydronephrosis (ANH). Multiple systems exist to help standardize hydronephrosis grading, yet poor inter-observer reliability persists. Machine learning methods may provide tools to improve the efficiency and accuracy of hydronephrosis grading. To develop an automated convolutional neural network (CNN) model to classify hydronephrosis on renal ultrasound imaging according to the Society of Fetal Urology (SFU) system as potential clinical adjunct. We identified 710 patients with 4659

postnatal renal ultrasound series. Per radiologist grading, 183 were normal, 157 were SFU I, 132 were SFU II, 100 were SFU III, and 138 were SFU IV. The machine learning model predicted hydronephrosis grade with 82.0% (95% CI: 75-83%) overall accuracy and classified 97.6% (95% CI: 95-98%) of the patients correctly or within one grade of the radiologist grade. The model classified 92.3% (95% CI: 86-95%) normal, 73.2% (95% CI: 69-76%) SFU I, 73.5% (95% CI: 67-75%) SFU II, 79.0% (95% CI: 73-82%) SFU III, and 88.4% (95% CI: 85-92%) SFU IV patients accurately. Gradient class activation mapping demonstrated that the ultrasound appearance of the renal collecting system drove the model's predictions. The CNN-based model classified hydronephrosis on renal ultrasounds automatically and accurately based on the expected imaging features in the SFU system. Compared to prior studies, the model functioned more automatically with greater accuracy. Limitations include the retrospective, relatively small cohort, and averaging across multiple imaging studies per patient. An automated CNN-based system classified hydronephrosis on renal ultrasounds according to the SFU system with promising accuracy based on appropriate imaging features. These findings suggest a possible adjunctive role for machine learning systems in the grading of ANH.

[Estimating glomerular filtration rate with new equations: can one size ever fit all?](#)

Kasozi RN, Meeusen JW, **Lieske JC**.

Glomerular filtration rate (GFR) is thought to be the best overall indicator of kidney health. On an individual patient basis, a working knowledge of GFR is important to understand the future risk for chronic kidney disease (CKD) progression, enhanced risk for cardiovascular disease and death, and for optimal medical management including the dosing of certain drugs. Although GFR can be directly measured using exogenous compounds that are eliminated by the kidney, these methods

are not scalable for repeated and routine use in clinical care. Thus, in most circumstances GFR is estimated, termed estimated GFR (eGFR), using serum biomarkers that are eliminated by the kidney. Of these, serum creatinine, and to a lesser extent cystatin C, are most widely employed. However, the resulting number is simply a population average for an individual of that age and sex with a given serum creatinine and/or cystatin C, while the range of potential GFR values is actually quite large. Thus, it is important to consider characteristics of a given patient that might make this estimate better or worse in a particular case. In some circumstances, cystatin C or creatinine might be the better choice. Ultimately it is difficult, if not impossible, to have an eGFR equation that performs equally well in all populations. Thus, in certain cases it might be appropriate to directly measure GFR for high consequence medical decision-making, such as approval for kidney donation or prior to certain chemotherapeutic regimens. In all cases, the eGFR thresholds of CKD stage should not be viewed as absolute numbers. Thus, clinical care should not be determined solely by CKD stage as determined by eGFR alone, but rather by the combination of an individual patient's likely kidney function together with their current clinical situation.

[Genome-wide association analyses define pathogenic signaling pathways and prioritize drug targets for IgA nephropathy](#)

Kiryluk K, Sanchez-Rodríguez E, Zhou XJ, Zanon F, Liu L, Mladkova N, Khan A, Marasa M, Zhang JY, Balderes O, **Sanna-Cherchi S**,**Gharavi AG**.

IgA nephropathy (IgAN) is a progressive form of kidney disease defined by glomerular deposition of IgA. Here we performed a genome-wide association study of 10,146 kidney-biopsy-diagnosed IgAN cases and 28,751 controls across 17 international cohorts. We defined 30 genome-wide significant risk loci explaining 11% of disease risk. A total of 16 loci were new, including TNFSF4/TNFSF18, REL, CD28, PF4V1,

LY86, LYN, ANXA3, TNFSF8/TNFSF15, REEP3, ZMIZ1, OVOL1/RELA, ETS1, IGH, IRF8, TNFRSF13B and FCAR. The risk loci were enriched in gene orthologs causing abnormal IgA levels when genetically manipulated in mice. We also observed a positive genetic correlation between IgAN and serum IgA levels. High polygenic score for IgAN was associated with earlier onset of kidney failure. In a comprehensive functional annotation analysis of candidate causal genes, we observed convergence of biological candidates on a common set of inflammatory signaling pathways and cytokine ligand-receptor pairs, prioritizing potential new drug targets.

Rare Single Nucleotide and Copy Number Variants and the Etiology of Congenital Obstructive Uropathy: Implications for Genetic Diagnosis

Dina F Ahram, Tze Y Lim, Juntao Ke ... Miguel Verbitsky ... Thomas Hays ... James McKiernan ... Ali G Gharavi, ... Simone Sanna-Cherchi

Congenital obstructive uropathy (COU) is a prevalent human developmental defect with highly heterogeneous clinical presentations and outcomes. Genetics may refine diagnosis, prognosis, and treatment, but the genomic architecture of COU is largely unknown. Comprehensive genomic screening study of 733 cases with three distinct COU subphenotypes revealed disease etiology in 10.0% of them. We detected no significant differences in the overall diagnostic yield among COU subphenotypes, with characteristic variable expressivity of several mutant genes. Our findings therefore may legitimize a genetic first diagnostic approach for COU, especially when burdening clinical and imaging characterization is not complete or available. We established a genomic diagnosis in 10.0% of COU individuals. The findings underscore the urgent need to identify novel genetic susceptibility factors to COU to better define the natural history of the remaining 90% of cases without a molecular diagnosis.

The Site and Type of *CLCN5* Genetic Variation Impact the Resulting Dent Disease-1 Phenotype

Arnous MG, Arroyo J, Cogal AG, Anglani F, Kang HG, Sas D, Harris PC, Lieske JC.

Dent disease is an X-linked recessive disorder associated with low molecular weight proteinuria (LMWP), nephrocalcinosis, kidney stones, and kidney failure in the third to fifth decade of life. It consists of Dent disease 1 (DD1) (60% of patients) because of pathogenic variants in the *CLCN5* gene and Dent disease 2 (DD2) with changes in *OCRL*. A total of 110 patients had 51 different truncating (nonsense, frameshifting, large deletions, and canonical splicing) variants, whereas 52 patients had 31 different nontruncating (missense, in-frame, noncanonical splicing, and stop-loss) changes. Sixteen newly described pathogenic variants were found in our cohort. Among patients with truncating variants, lifetime stone events positively correlated with chronic kidney disease (CKD) evolution. Patients with truncating changes also experienced stone events earlier in life and manifested a higher albumin excretion rate than the nontruncating group. Nevertheless, neither age of nephrocalcinosis nor CKD progression varied between the truncating versus nontruncating patients. A large majority of nontruncating changes (26/31; 84%) were clustered in the middle exons that encode the voltage ClC domain whereas truncating changes were spread across the protein. Variants associated with kidney failure were restricted to truncating (11/13 cases), plus a single missense variant previously shown to markedly reduce ClC-5 functional activity that was found in the other 2 individuals. DD1 manifestations, including the risk of kidney stones and progression to kidney failure, may relate to the degree of residual ClC-5 function.

STONES

Effects of Delayed Surgical Intervention Following Emergency Department Presentation on Stone Surgery Complexity

Bayne D, Maru J, Srirangapatanam S, Hicks C, Neuhaus J, Scales C, Chi T, Stoller M.

Prior literature had demonstrated increased stone burden and higher rates of staged surgery in individuals of lower socioeconomic status (SES). Low SES individuals are more likely to experience delays in definitive stone surgery after initial presentation to the emergency department (ED) for kidney stones. This study aims to investigate the relationship between delays in definitive kidney stone surgery and the subsequent need for percutaneous nephrolithotomy (PNL) and/or staged surgical procedures using a statewide data set. A total of 1,816,093 billing encounters from 947,798 patients were screened, resulting in 44,835 patients with ED visits for kidney stones followed by a urologic stone procedure. Multivariable analysis revealed that relative to patients who underwent surgery within 1 month of initial ED visit for stone disease, patients were at increased odds of undergoing complex surgery if waiting ≥ 6 months (odds ratio [OR] 1.18, $p = 0.022$), ≥ 1 year (OR 1.29, $p < 0.001$), and ≥ 3 years (OR 1.43, $p < 0.001$). Delays in definitive stone surgery after initial ED encounter for stone disease were associated with increased likelihood of undergoing a complex stone treatment.

Endogenous Oxalate Synthesis and Urinary Oxalate Excretion

Sonia Fargue, Kyle D Wood, Joseph J Crivelli, Dean G Assimios, Robert A Oster, John Knight

Increased urinary oxalate excretion is a risk factor for developing calcium oxalate kidney stones and progression of CKD.1 Urinary oxalate is derived from dietary oxalate and endogenous oxalate synthesis (EOS). Endogenous oxalate metabolic pathways have been identified in healthy volunteers and those with primary hyperoxalurias, the latter characterized by excessive hepatic EOS. New small interfering RNA approaches for reducing EOS in primary hyperoxalurias type 1 have resulted in profoundly reduced urinary oxalate

excretion. Such treatments may potentially benefit others including those with calcium oxalate kidney stones and CKD, but our understanding of the role of EOS in these cohorts is lacking. To date, discordant rates of EOS have been reported using different analytical approaches. Thus, reliable methods to quantify EOS are needed. The objectives of this study were to determine EOS rates by continuous intravenous infusion of C2-oxalate and to identify surrogate methods of estimating EOS.

In pursuit of the optimal dusting settings with the Thulium Fiber Laser: an in vitro assessment

Soto-Palou FG, Chen J, Medeiros R, Zhong P, Antonelli JA, Preminger GM, Lipkin ME.

Low energy and high frequency settings are used in stone dusting for holmium lasers. Such settings may not be optimal for thulium fiber laser (TFL). With the seemingly endless combination of settings, we aim to provide guidance to the practicing urologists and assess the efficiency of the TFL platform in an automated in vitro "dusting model". Overall, SP provided greater ablation volume when compared to LP. Our dusting efficiency model demonstrated that the maximum stone ablation was achieved at the combination of high energy/low frequency settings ($p < 0.005$) and at a SD of 0.2mm. At all tested pulse energies, no stone phantoms were broken into fragments $> 1\text{mm}$. During stone dusting with TFL, SP offers superior ablation to LP settings. Optimal dusting at clinically relevant scanning speeds of 1mm/sec and 2mm/sec occurs at high energy/low frequency settings. Thulium lithotripsy with high pulse energy does not result in increased fragment size.

Ultrasound-Only Percutaneous Nephrolithotomy Is Safe and Effective Compared to Fluoroscopy-Directed Percutaneous Nephrolithotomy

Hosier GW, Hakam N, Hamouche F, Cortez X, Charondo L, Yang H, Chan C, Chang K, Unno R, Sui W, Bayne DB, Stoller ML, Chi T.

Outcomes after ultrasound-only percutaneous nephrolithotomy (PCNL), in which no fluoroscopy is used, are not well known. The goal of this study was to

compare outcomes of ultrasound-only and fluoroscopy-directed PCNL. Prospectively collected data from the Registry for Stones of the Kidney and Ureter database were reviewed for all patients who underwent PCNL at one academic center from 2015 to 2021. Primary outcomes were complications and stone-free rates (no residual fragments $\geq 3\text{ mm}$). Of the 141 patients who underwent ultrasound-only PCNL and 147 who underwent fluoroscopy-directed PCNL, there was no difference in complication rates (15% vs 16%, $p = 0.87$) or stone-free status (71% vs 65%, $p = 0.72$), respectively. After adjusting for body mass index, American Society of Anesthesiologists (ASA), stone size, and stone complexity by Guy score, ultrasound-only PCNL was not associated with any increased odds of complications (odds ratio [OR] 0.7, 95% confidence interval [CI] 0.3-1.6, $p = 0.41$) or residual stone fragments $\geq 3\text{ mm}$ (OR 1.0, 95% CI 0.5-1.9, $p = 0.972$) compared with fluoroscopy-directed PCNL. Ultrasound-only PCNL was associated with shorter operative time (median 99.5 vs 126 minutes, $p < 0.001$), and the use of ultrasound remained a significant predictor of short operative time (< 100 minutes) after controlling for supine positioning, stone size, and stone complexity by Guy score (OR 2.31, 95% CI 1.01-5.29, $p = 0.048$). Patients in the ultrasound-only group were spared a mean radiation exposure dose of 10 mGy per procedure. Ultrasound-only PCNL is safe and achieves similar stone-free rates compared with fluoroscopy-directed PCNL with the added benefit of avoidance of radiation.

- Jennifer Allmaras MPH, Anna Barrett,
6/22/2023

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BLADDER

[The mast cell stimulator Compound 48/80 causes urothelium-dependent increases in murine urinary bladder contractility](#)

B Malique Jones, Gerald C Mingin, Nathan R Tykocki

Mast cells and degranulation of pre-formed inflammatory mediators contribute to lower urinary tract symptoms. This study investigates pathways by which the mast cell stimulator Compound 48/80 alters urinary bladder smooth muscle contractility via mast cell activation. We hypothesized that: (1) mast cell degranulation will cause spontaneous urinary bladder smooth muscle contractions; and (2) these contractions are caused by urothelium-derived PGE₂. Urothelium intact and denuded urinary bladder strips were collected from mast cell sufficient (C57Bl/6) and deficient (B6.Cg-Kit^{w-sh}) mice to determine if Compound 48/80 altered urinary bladder smooth muscle (UBSM) contractility. Electrical field stimulation was used to assess the effects of Compound 48/80 on nerve-evoked contractions. Antagonists/inhibitors were utilized to identify prostanoid signaling pathways activated or if direct activation of nerves was involved. Compound 48/80 caused slow-developing contractions, increased phasic activity, and augmented nerve-evoked responses in both mast cell sufficient and deficient mice. Nerve blockade had no effect on these responses; however, they were eliminated by removing the urothelium. Blocking P2 purinoreceptors, cyclooxygenases, or G protein signaling abolished Compound 48/80 responses. However, only combined blockade of prostaglandin E₂ (EP1), prostaglandin F_{2α} (FP), and thromboxane A₂ (TP) receptors inhibited Compound 48/80 induced responses. Thus, the effects of compound 48/80 are urothelium dependent, but independent of mast cells. Further, these effects are mediated by druggable inflammatory pathways that may be used to manage

inflammatory non-neurogenic bladder hyperactivity. Finally, these data strongly suggest that great care must be taken when using Compound 48/80 to determine mast cell-dependent responses in the urinary bladder.

UTI

[The Role of Mobile Genetic Elements in Virulence Factor Carriage from Symptomatic and Asymptomatic Cases of *Escherichia coli* Bacteriuria](#)

Grace Morales, Benjamin Abelson, Seth Reasoner, Jordan Miller, Ashlee M Earl, Maria Hadjifrangiskou, Jonathan Schmitz

Uropathogenic *Escherichia coli* (UPEC) is extremely diverse genotypically and phenotypically. Individual strains can variably carry diverse virulence factors, making it challenging to define a molecular signature for this pathotype. For many bacterial pathogens, mobile genetic elements (MGEs) constitute a major mechanism of virulence factor acquisition. For urinary *E. coli*, the total distribution of MGEs and their role in the acquisition of virulence factors is not well defined, including in the context of symptomatic infection versus asymptomatic bacteriuria (ASB). In this work, we characterized 151 isolates of *E. coli*, derived from patients with either urinary tract infection (UTI) or ASB. For both sets of *E. coli*, we catalogued the presence of plasmids, prophage, and transposons. We analyzed MGE sequences for the presence of virulence factors and antimicrobial resistance genes. These MGEs were associated with only ~4% of total virulence associated genes, while plasmids contributed to ~15% of antimicrobial resistance genes under consideration. Our analyses suggests that, across strains of *E. coli*, MGEs are not a prominent driver of urinary tract pathogenesis and symptomatic infection. *Escherichia coli* is the most common etiological agent of urinary tract infections (UTIs), with UTI-associated strains designated

"uropathogenic" *E. coli* or UPEC. Across urinary strains of *E. coli*, the global landscape of MGEs and its relationship to virulence factor carriage and clinical symptomatology require greater clarity. Here, we demonstrate that many of the putative virulence factors of UPEC are not associated with acquisition due to MGEs. The current work enhances our understanding of the strain-to-strain variability and pathogenic potential of urine-associated *E. coli* and points toward more subtle genomic differences distinguishing ASB from UTI isolates.

LUTS

[Molecular Mechanisms of Neurogenic Lower Urinary Tract Dysfunction after Spinal Cord Injury](#)

Nobutaka Shimizu, Tetsuichi Saito, Naoki Wada, Mamoru Hashimoto, Takahiro Shimizu, Joonbeom Kwon, Kang Jun Cho, Motoaki Saito, Sergei Karnup, William C de Groat, Naoki Yoshimura

This article provides a synopsis of current progress made in fundamental studies of lower urinary tract dysfunction (LUTD) after spinal cord injury (SCI) above the sacral level. Animal models of SCI allowed us to examine the effects of SCI on the micturition control and the underlying neurophysiological processes of SCI-induced LUTD. Urine storage and elimination are the two primary functions of the LUT, which are governed by complicated regulatory mechanisms in the central and peripheral nervous systems. These neural systems control the action of two functional units in the LUT: the urinary bladder and an outlet consisting of the bladder neck, urethral sphincters, and pelvic-floor striated muscles. During the storage phase, the outlet is closed, and the bladder is inactive to maintain a low intravesicular pressure and continence. In contrast, during the voiding phase, the outlet relaxes, and the bladder contracts to facilitate adequate urine flow and bladder emptying. SCI disrupts the normal reflex circuits that regulate coordinated bladder and urethral sphincter

function, leading to involuntary and inefficient voiding. Following SCI, a spinal micturition reflex pathway develops to induce an overactive bladder condition following the initial areflexic phase. In addition, without proper bladder-urethral-sphincter coordination after SCI, the bladder is not emptied as effectively as in the normal condition. Previous studies using animal models of SCI have shown that hyperexcitability of C-fiber bladder afferent pathways is a fundamental pathophysiological mechanism, inducing neurogenic LUTD, especially detrusor overactivity during the storage phase. SCI also induces neurogenic LUTD during the voiding phase, known as detrusor sphincter dyssynergia, likely due to hyperexcitability of Aδ-fiber bladder afferent pathways rather than C-fiber afferents. The molecular mechanisms underlying SCI-induced LUTD are multifactorial; previous studies have identified significant changes in the expression of various molecules in the peripheral organs and afferent nerves projecting to the spinal cord, including growth factors, ion channels, receptors and neurotransmitters. These findings in animal models of SCI and neurogenic LUTD should increase our understanding of pathophysiological mechanisms of LUTD after SCI for the future development of novel therapies for SCI patients with LUTD.

[Trajectories of depressive symptoms over 20 years and subsequent lower urinary tract symptoms and impact among women](#)

Brady Sonya S, Shan Liang, Markland Alayne D, Huling Jared D, Arguedas Andrés, Fok Cynthia S, Van Den Eeden Stephen K, Lewis Cora E.

The aim of the study is to examine the association between depressive symptoms and subsequent lower urinary tract symptoms (LUTS) and impact (a composite outcome) among women (N = 1,119) from the Coronary Artery Risk Development in Young Adults study. The Center for Epidemiologic Studies-Depression Scale (CES-D) was administered in 1990–1991 and every 5 years through 2010–2011. In 2012–2013,

LUTS and impact data were collected for the first time. Accumulation of risk was examined in the following three ways: (1) mean CES-D score across 20 years (5 observations); (2) depressive symptom trajectory group, determined by group-based trajectory modeling; and (3) intercepts and slopes obtained from women's individual CES-D score trajectories through two-stage mixed effects modeling. For each approach, ordinal logistic regression analyses examined odds of having “greater LUTS/impact” for each unit change in a depressive symptom variable. (1) With each one-unit increase in mean CES-D score over the 20-year period, women were 9% more likely to report greater LUTS/impact (odds ratio [OR] = 1.09, 95% CI = 1.07–1.11). (2) In comparison with women with consistently low depressive symptoms, women with consistently threshold depression or consistently high depressive symptoms were twice (OR = 2.07, 95% CI = 1.59–2.69) and over five times (OR = 5.55, 95% CI = 3.07–10.06) as likely, respectively, to report greater LUTS/impact. (3) Women's individual symptom intercept and slope interacted. Increases in depressive symptoms across 20 years (greater slopes) were associated with greater LUTS/impact when women's initial CES-D score (intercept) was in the moderate-to-high range relative to the sample. Depressive symptoms over 20 years, examined with different degrees of nuance, were consistently associated with subsequently measured LUTS and impact.

STONES

[Examination of nutritional factors associated with urolithiasis risk in plant based meat alternatives marketed to children and infants](#)

Garrett N Ungerer, Christine W Liaw, Aaron M Potretzke, David J Sas, Patricio C Gargollo, Candace F Granberg, Kevin Koo

Introduction: The global prevalence of pediatric nephrolithiasis continues to rise amidst increased sodium and animal protein intake. Plant-based meat alternatives (PBMA) have recently gained popularity due to health benefits,

environmental sustainability, and increased retail availability. PBMA have the potential to reduce the adverse metabolic impact of animal protein on kidney stone formation. We analyzed PBMA targeted to children to characterize potential lithogenic risk vs animal protein. Methods: We performed a dietary assessment using a sample of PBMA marketed to or commonly consumed by children and commercially available at national retailers. Nutrient profiles for PBMA were compiled from US Department of Agriculture databases and compared to animal protein sources using standardized serving sizes. We also analyzed nutrient profiles for plant-based infant formulas against typical dairy protein-based formulas. Primary protein sources were identified using verified ingredient lists. Oxalate content was extrapolated from dietary data sources. Results: A total of 41 PBMA were analyzed: chicken (N = 18), hot dogs (N = 3), meatballs (N = 5), fish (N = 10), and infant formula (N = 5). Most products (76%) contained a high-oxalate ingredient as the primary protein source (soy, wheat, or almond). Average oxalate content per serving was substantially higher in these products (soy 11.6 mg, wheat 3.8 mg, almond 10.2 mg) vs animal protein (negligible oxalate). PBMA containing pea protein (24%) had lower average oxalate (0.11 mg). Most PBMA averaged up to six times more calcium and three times more sodium per serving compared to their respective animal proteins. Protein content was similar for most categories. Conclusions: Three-quarters of the examined plant-based meat products for children and infants contain high-oxalate protein sources. Coupled with higher per-serving sodium and calcium amounts, our findings raise questions about possible lithogenic risk in some PBMA, and further studies are needed to assess the relationship between PBMA and nephrolithiasis.

Outpatient Antibiotic Use is Not Associated with an Increased Risk of First-Time Symptomatic Kidney Stones

Charat Thongprayoon, Lisa E Vaughan, Erin F Barreto, Ramila A Mehta, **Kevin Koo**, Phillip J Schulte, **John C Lieske**, Andrew D Rule

Antibiotics modify gastrointestinal and urinary microbiomes, which may contribute to kidney stone formation. The current study examined whether an increased risk of a first-time symptomatic kidney stone episode follows antibiotic use. A population-based case-control study surveyed 1,247 chart-validated first-time symptomatic kidney stone formers with a documented obstructing or passed stone (cases) in Olmsted County, Minnesota, from 2008-2013 and 4,024 age- and sex-matched controls. All prescriptions for outpatient oral antibiotic use within 5 years prior to the onset of symptomatic stone for the cases and their matched controls were identified. Conditional logistic regression estimated the odds ratio (OR) of a first-time symptomatic kidney stone across time after antibiotic use. Analyses were also performed after excluding cases and controls with prior urinary tract infection or hematuria because urinary symptoms resulting in antibiotic prescription could have been warranted due to undiagnosed kidney stones. The risk of a symptomatic kidney stone was only increased during the 1-year period after antibiotic use (unadjusted OR=1.31, $p=0.001$), and this risk was attenuated after adjustment for comorbidities (OR=1.16, $p=0.08$). After excluding cases and controls with prior urinary symptoms, there was no increased risk of a symptomatic kidney stone during the 1-year period after antibiotic use (unadjusted OR=1.04, $p=0.70$). Findings were consistent across antibiotic classes and the number of antibiotic courses received. The increased risk of a first-time symptomatic kidney stone with antibiotic use appears largely due to both comorbidities and prescription of antibiotics for urinary symptoms. Under-

recognition of kidney stones that initially cause urinary symptoms resulting in antibiotic use may explain much of the perceived stone risk with antibiotics (i.e., reverse causality).

- Jennifer Allmaras MPH, Anna Barrett,
5/25/2023

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BLADDER

[Destroyed bladders: Characterization of progressive inflammatory cystitis](#)

Faris A, **Lane GI**, Mehra R, Dadhania V, Crescenze I, **Clemens JQ**, Romo PB, Stoffel J, Malaeb B, Blair Y, Goh M, Gupta P, Cameron AP

We identified a subset of patients with noninfectious cystitis who develop refractory symptoms marked by diffuse inflammatory changes, reduced bladder capacity, and vesicoureteral reflux (VUR), termed here as "progressive inflammatory cystitis" (PIC). Our objective was to describe the phenotype, disease outcomes, and pathologic findings of PIC. From 2008 to 2020, 46 patients with PIC were identified. The median age of symptom onset was 63 years old (interquartile range [IQR]: 56, 70) and the most common presenting symptoms were urinary urgency/frequency (54%) and incontinence (48%). Urodynamics showed a median maximum bladder capacity of 80 mL (IQR: 34, 152), commonly with VUR (68%) and hydronephrosis (59%). Ultimately 36 patients (78%) underwent urinary diversion at a median of 4.5 years (IQR: 2, 6.5) after symptom onset. Significant pathologic findings include presence of ulceration (52%), acute and chronic inflammation (68%), including eosinophils (80%), lymphoid follicles (56%), and mast cells in both lamina and muscularis propria (76%). PIC is a newly defined entity characterized by significantly diminished bladder capacity, upper tract changes, and relatively quick progression to urinary diversion. Larger prospective cohort studies are required to further characterize this severe phenotype of chronic noninfectious cystitis, aid earlier diagnosis, and guide management decisions.

[Disparities in central line-associated bloodstream infection and catheter-associated urinary tract infection rates: An exploratory analysis](#)

Erin B Gettler, Ibukunoluwa C Kalu, Nwora L Okeke, Sarah S Lewis, Deverick J Anderson, Becky A Smith, **Sonali D Advani**

This retrospective review of 4-year surveillance data revealed a higher

central line-associated bloodstream infection (CLABSI) rate in non-Hispanic Black patients and higher catheter-associated urinary tract infection (CAUTI) rates in Asian and non-Hispanic Black patients compared with White patients despite similar catheter utilization between the groups. Minoritized populations in the United States may be vulnerable to higher HAI rates. These data provide evidence that supports expanding NHSN data fields to include race and ethnicity and recommending their input for key quality measures. Mandated reporting could allow for better understanding of existing inequities in HAI incidence across different sociodemographic groups. Reported data could subsequently inform investigations into drivers of increased HAI rates and identify modifiable targets for novel interventions in groups experiencing the greatest disparities. Importantly, this work has implications for policy changes on a national level to inform corrective strategies and provide optimum, equitable care for all.

[Dynamic analysis of the individual patterns of intakes, voids, and bladder sensations reported in bladder diaries collected in the LURN study](#)

Andreev VP, Helmuth ME, Smith AR, Zisman A, Cameron AP, DeLancey JOL, **Bushman WA**

The goal of this study was to perform an in-depth dynamic analysis of individual bladder diaries to inform which behavioral modifications would best reduce lower urinary tract symptoms, such as frequency and urgency. Three-day bladder diaries containing data on timing, volumes, and types of fluid intake, as well as timing, volumes, and bladder sensation at voids were analyzed for 197 participants with lower urinary tract symptoms. A novel dynamic analytic approach to bladder diary time series data was proposed and developed, including intra-subject correlations between time-varying variables: rates of intake, bladder filling rate, and urge growth rate. Grey-box models of bladder

filling rate and multivariable linear regression models of urge growth rate were developed for individual diaries. These models revealed that bladder filling rate, rather than urine volume, was the primary determinant of urinary frequency and urgency growth rate in the majority of participants. Simulations performed with the developed models predicted that the most beneficial behavioral modifications to reduce the number of urgency episodes are those that smooth profiles of bladder filling rate, which might include behaviors such as exclusion of caffeine and alcohol and/or other measures, e.g., increasing number and decreasing volumes of intakes.

[Interpersonal Stressors and Resources for Support: Associations with Lower Urinary Tract Symptoms and Impact Among Women](#)

Brady SS, Arguedas A, Huling JD, Shan L, Lewis CE, Fok CS, **Van Den Eeden SK**, Markland AD

This study utilizes Coronary Artery Risk Development in Young Adults (CARDIA) data to examine whether women's perceived emotional support and interpersonal stressors are associated with lower urinary tract symptoms (LUTS) and their impact on quality of life. Emotional support was assessed at baseline/year 0 (1985-86), year 2 (1987-88), year 15 (2000-01), and year 20 (2005-06); interpersonal stressors were assessed at years 15 and 20. In 2012-13, LUTS and impact were assessed. LUTS/impact category (a composite variable ranging from bladder health to mild, moderate, and severe LUTS/impact) was regressed on trajectory groups of emotional support from years 0 to 20. Separately, LUTS/impact was regressed on mean emotional support and interpersonal stressors across years 15-20. Analyses were adjusted for age, race, education, and parity (n = 1104). In the CARDIA cohort, quality of women's interpersonal relationships, assessed between 1985-86 and 2005-06, was associated with LUTS/impact assessed in 2012-13. Additional research collecting LUTS/impact data at multiple time points

is needed to test potential bidirectional associations of emotional support and interpersonal stressors with LUTS/impact, as well as potential mechanisms of association.

[Intraoperative Predictors of Sacral Neuromodulation Implantation and Treatment Response-Results from the ROSETTA Trial](#)

Gill BC, Thomas S, Barden L, Jelovsek JE, Meyer I, Chermansky C, Komesu YM, Menefee S, Myers D, Smith A, Mazloomdoost D, **Amundsen CL**

The purpose of this study is to determine the utility of intraoperative data in predicting sacral neuromodulation (SNM) outcomes in urgency urinary incontinence (UUI). Intraoperative details of SNM Stage 1 were recorded during the prospective, randomized, multi-center ROSETTA trial, including responsive electrodes, amplitudes, and response strengths (motor and sensory Likert scales). Stage 2 implant was performed for Stage 1 success on 3-day diary with 24 month follow-up. An intraoperative amplitude-response score for each electrode was calculated ranging from 0 (no response) to 99.5 (maximum response, 0.5 V). Predictors for Stage 1 success and improvement at 24 months were identified by stepwise logistic regression confirmed with LASSO and stepwise linear regression. The conclusion showed specific parameters routinely assessed intraoperatively during Stage 1 SNM for UUI show limited utility in predicting both acute and long-term outcomes. However, lead position as it relates to the trajectory of the sacral nerve root appears to be important.

[Therapeutic effects of p38 mitogen-activated protein kinase inhibition on hyperexcitability of capsaicin sensitive bladder afferent neurons in mice with spinal cord injury](#)

Suzuki T, Shimizu T, Karnup S, Shimizu N, Ni J, de Groat WC, **Yoshimura N**

Nerve growth factor (NGF) has been implicated as a key molecule of pathology-induced changes in C-fiber afferent nerve excitability, which contributes to the emergence of neurogenic detrusor overactivity due to spinal cord injury (SCI). It is also known that the second messenger signaling

pathways activated by NGF utilize p38 Mitogen-Activated Protein Kinase (MAPK). We examined the roles of p38 MAPK on electrophysiological properties of capsaicin sensitive bladder afferent neurons with SCI mice. We used female C57BL/6 mice and transected their spinal cord at the Th8/9 level. Two weeks later, continuous administration of p38 MAPK inhibitor (0.51 µg/h, i.t. for two weeks) was started. Bladder afferent neurons were labelled with a fluorescent retrograde tracer, Fast-Blue (FB), injected into the bladder wall three weeks after SCI. Four weeks after SCI, freshly dissociated L6-S1 dorsal root ganglion neurons were prepared and whole cell patch clamp recordings were performed in FB-labelled neurons. After recording action potentials or voltage-gated K⁺ currents, the sensitivity of each neuron to capsaicin was evaluated. P38 MAPK plays an important role in hyperexcitability of capsaicin-sensitive bladder afferent neurons due to the reduction in KA channel activity in SCI mice.

[Treating Incontinence for Underlying Mental and Physical Health \(TRIUMPH\): a study protocol for a multicenter, double-blinded, randomized, 3-arm trial to evaluate the multisystem effects of pharmacologic treatment strategies for urgency-predominant urinary incontinence in ambulatory older women](#)

Huang AJ, Walter LC, Yaffe K, Vittinghoff E, Kornblith E, Schembri M, Chang A, Subak LL

Urgency-type urinary incontinence affects one in four older community-dwelling women and overlaps with other common aging-associated health syndromes such as cognitive impairment, physical mobility impairment, and depression. Observational studies have raised concern about potentially higher rates of delirium and dementia in older adults taking anticholinergic bladder medications, but few prospective data are available to evaluate the effects of these and other pharmacologic treatments for urgency incontinence on cognition and other multisystem

functional domains important to older women. The TRIUMPH study is a randomized, double-blinded, 3-arm, parallel-group trial comparing the multisystem effects of anticholinergic versus beta-3-adrenergic agonist bladder therapy and versus no active bladder anti-spasmodic pharmacotherapy in older women with urgency incontinence. Women aged 60 years and older (target N = 270) who have chronic urgency-predominant urinary incontinence and either normal or mildly impaired cognition at baseline are recruited from the community by investigators based in northern California, USA. The TRIUMPH trial addresses the need for rigorous evidence to guide counseling and decision-making for older women who are weighing the potential multisystem benefits and risks of pharmacologic treatments for urgency incontinence in order to preserve their day-to-day functioning, quality of life, and independence in older age.

KIDNEY

[Genomic Disorders in CKD across the Lifespan](#)

Miguel Verbitsky, Sarathbabu Krishnamurthy, Priya Krithivasan, Daniel Hughes, Atlas Khan, Maddalena Marasà, Natalie Vena, **Pavan Khosla**, Junying Zhang, **Tze Y Lim**, Joseph T Glessner, Chunhua Weng, Ning Shang, Yufeng Shen, George Hripsak, Hakon Hakonarson, Iuliana Ionita-Laza, Brynn Levy, Eimear E Kenny, Ruth J F Loos, Krzysztof Kiryluk, **Simone Sanna-Cherchi**, David R Crosslin, Susan Furth, Bradley A Warady, Robert P Igo Jr, Sudha K Iyenga, Craig S Wong, Afshin Parsa, Harold I Feldman, **Ali G Gharavi**

Pathogenic structural genetic variants, also known as genomic disorders, have been associated with pediatric CKD. This study extends those results across the lifespan, with genomic disorders enriched in both pediatric and adult patients compared with controls. In the Chronic Renal Insufficiency Cohort study, genomic disorders were also associated with lower serum Mg, lower educational performance, and a higher risk of death. A phenome-wide association study confirmed the link between kidney disease and genomic disorders in an unbiased way. Systematic detection of genomic disorders can provide a molecular diagnosis and refine prediction of risk and prognosis.

Undiagnosed GDs are detected both in children and adults with CKD. Identification of GDs in these patients can enable a precise genetic diagnosis, inform prognosis, and help stratify risk in clinical studies. GDs could also provide a molecular explanation for nephropathy and comorbidities, such as poorer neurocognition for a subset of patients.

Multi-population genome-wide association study implicates immune and non-immune factors in pediatric steroid-sensitive nephrotic syndrome

Barry A, McNulty MT, Jia X, Gupta Y, Debiec H, Luo Y, Nagano C, Horinouchi T, Jung S, Colucci M, Ahram DF, Mitrotti A, Sinha A, Teeninga N, Jin G, Shril S, Caridi G, Bodria M, Lim TY, Westland R, Zanoni F, Marasa M, Turudic D, Giordano M, Gesualdo L, Magistroni R, Pisani I, Fiaccadori E, Reiterova J, Maringhini S, Morello W, Montini G, Weng PL, Scolari F, Saraga M, Tasic V, Santoro D, van Wijk JAE, Milošević D, Kawai Y, Kiryluk K, Pollak MR, **Gharavi A**, Lin F, Simoes E Silva AC, Loos RIF, Kenny EE, Schreuder MF, Zurewska A, Dossier C, Ariceta G, Drozynska-Duklas M, Hogan J, Jankauskiene A, Hildebrandt F, Prikhodina L, Song K, Bagga A, Cheong H 2nd, Ghiggeri GM, Vachvanichsanong P, Nozu K, Lee D, Vivarelli M, Raychaudhuri S, Tokunaga K, **Sanna-Cherchi S**, Ronco P, Iijima K, Sampson MG

Pediatric steroid-sensitive nephrotic syndrome (pSSNS) is the most common childhood glomerular disease. Previous genome-wide association studies (GWAS) identified a risk locus in the HLA Class II region and three additional independent risk loci. But the genetic architecture of pSSNS, and its genetically driven pathobiology, is largely unknown. Here, we conduct a multi-population GWAS meta-analysis in 38,463 participants (2440 cases). We then conduct conditional analyses and population specific GWAS. We discover twelve significant associations-eight from the multi-population meta-analysis (four novel), two from the multi-population conditional analysis (one novel), and two additional novel loci from the European meta-analysis. Fine-mapping implicates specific amino acid haplotypes in HLA-DQA1 and HLA-DQB1 driving the HLA Class II risk locus. Non-HLA loci colocalize with eQTLs of monocytes and numerous T-cell subsets in independent datasets. Colocalization with kidney eQTLs is lacking but overlap with kidney cell open chromatin suggests an uncharacterized disease mechanism

in kidney cells. A polygenic risk score (PRS) associates with earlier disease onset. Altogether, these discoveries expand our knowledge of pSSNS genetic architecture across populations and provide cell-specific insights into its molecular drivers. Evaluating these associations in additional cohorts will refine our understanding of population specificity, heterogeneity, and clinical and molecular associations.

Nedosiran in primary hyperoxaluria subtype 3: results from a phase I, single-dose study (PHYOX4)

Goldfarb DS, **Lieske JC**, Groothoff J, Schalk G, Russell K, Yu S, Vrhnjak B

Nedosiran is an N-acetyl-D-galactosamine (GalNAc)-conjugated RNA interference agent targeting hepatic lactate dehydrogenase (encoded by the LDHA gene), the putative enzyme mediating the final step of oxalate production in all three genetic subtypes of primary hyperoxaluria (PH). This phase I study assessed the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of subcutaneous nedosiran in patients with PH subtype 3 (PH3) and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m². Single-dose nedosiran 3 mg/kg or placebo was administered in a randomized (2:1), double-blinded manner. Safety/tolerability, 24-h urinary oxalate (Uox) concentrations, and plasma nedosiran concentrations were assessed. The main PD endpoint was the proportion of participants achieving a $> 30\%$ decrease from baseline in 24-h Uox at two consecutive visits. Six participants enrolled in and completed the study (nedosiran, n = 4; placebo, n = 2). Nedosiran was well-tolerated and lacked safety concerns. Although the PD response was not met, 24-h Uox excretion declined 24.5% in the nedosiran group and increased 10.5% in the placebo group at Day 85. Three of four nedosiran recipients had a $> 30\%$ reduction in 24-h Uox excretion during at least one visit, and one attained near-normal (i.e., ≥ 0.46 to < 0.60 mmol/24 h; ≥ 1.0 to $< 1.3 \times$ upper limit of the normal reference range) 24-h Uox excretion from Day 29 to Day 85. Nedosiran displayed predictable plasma PK. The

acceptable safety and trend toward Uox lowering after single-dose nedosiran treatment enables further clinical development of nedosiran in patients with PH3 who currently have no viable therapeutic options. A plain language summary is available in the supplementary information.

STONES

Development and Preliminary Validation of the 6-Item Short Form of the Wisconsin Stone Quality of Life Questionnaire (WISQOL)

Li S, Knodler M, Hass C, Nakada SY, **Penniston KL**

The purpose of this study is to develop a short form of the Wisconsin Stone Quality of Life (WISQOL): 1) identify the smallest subset of items from WISQOL that accurately predict patients' health-related quality of life (HRQOL), and 2) in a clinical patient population, test these items - grouped together to form the WISQOL-short form (SF) - and assess its convergent validity. The items for the WISQOL-SF were identified based on classic item analysis theory. Patients who previously completed the original 28-item WISQOL were randomly split into 2 groups of equal size. Scores for the WISQOL were calculated for one group while those for the WISQOL-SF were calculated for the other. Cronbach's alpha coefficients were calculated. Impacts of demographic and clinical factors as well as stone and symptom status at the time of WISQOL completion were examined. Patients (n=740) who completed the WISQOL between 6/2017-11/2021 were included. Patients were 48% male, 54.1 \pm 14.6 years old, and had a BMI of 31.2 \pm 8.1. After item analysis and reduction, the six items ultimately included in the WISQOL-SF represented 2 of the 4 domains (social and emotional) of the original WISQOL. The internal consistency of the WISQOL-SF was similar to the original (Cronbach's alpha 0.943 vs. 0.973). No differences for HRQOL were found between groups (p=0.567). The conclusion showed that the WISQOL-SF demonstrated the expected differences for gender and between patients with and without stone-related symptoms at the time of WISQOL completion. The WISQOL-SF

showed good consistency and produced similar HRQOL scores to the full-form WISQOL.

Translation and validation of the Italian version of the Wisconsin Stone Quality of Life Questionnaire (I-WISQOL) for assessing quality of life in patients with urolithiasis

Salciccia S, Maggi M, Frisenda M, Finistauri Guacci L, Hoxha S, Licari LC, Viscuso P, Gentilucci A, Del Giudice F, DE Berardinis E, Cattarino S, Mariotti G, Tufano A, DE Dominicis M, Ricciuti GP, Sciarra A, Penniston KL, Moriconi M

Urolithiasis is a chronic condition, and it has been associated with a significant negative impact on patients' health-related quality of life (HRQOL). Several tools to assess patients' HRQOL have been validated in Italian, however disease-specific HRQOL instruments are still lacking. We aimed to develop and validate the Italian version of the WISQOL (I-WISQOL) in patients with urolithiasis. The Italian version of the WISQOL was developed in a multistep process involving primary translation, back-translation, and pilot testing among a group of patients (N.=10). Patients presenting with urolithiasis were prospectively recruited from the outpatient stone clinics and completed both questionnaire WISQOL and SF-36. Demographic information, as well as medical and surgical data, were obtained through an interview. Internal consistency of the I-WISQOL was obtained with Cronbach's α . Correlation of total scores of the I-WISQOL and SF36 was assessed to determine convergent validity using Spearman Rho. Correlations between clinical variables and results from the I-WISQOL were analyzed to descriptively assess the association of interest. The conclusion showed that the I-WISQOL is an internally consistent and valid instrument to assess HRQOL in Italian-speaking patients with kidney stones. Its use in clinical practice should be implemented in order to tailor the management of each patient.

PATIENT-CENTERED RESEARCH

Healthcare system contact following ureteroscopy: does discharge instruction readability matter?

Britton CJ, Potretzke AM, Liaw C, Ahmed ME, Manka MG, Wymer KM, Alom M, Linder BJ, Koo K, Klett DE

We aimed to assess the impact of discharge instruction (DCI) readability on 30-day postoperative contact with the healthcare system. There were 105 contacts to the healthcare system within 30 days of surgery: 78 communications, 14 ED visits and 13 clinic visits. There were no significant differences between cohorts in the proportion of patients with communications ($p = 0.16$), ED visits ($p = 1.0$) or clinic visits ($p = 0.37$). On multivariable analysis, older age and psychiatric diagnosis were associated with significantly increased odds of overall healthcare contact ($p = 0.03$ and $p = 0.04$) and communications ($p = 0.02$ and $p = 0.03$). Prior psychiatric diagnosis was also associated with significantly increased odds of unplanned clinic visits ($p = 0.003$). Overall, irDCI were not significantly associated with the endpoints of interest. The conclusion showed that increasing age and prior psychiatric diagnosis, but not irDCI, were significantly associated with an increased rate of healthcare system contact following CRULLS.

The Patient Voice - Stent Experiences after Ureteroscopy: Insights from In-Depth Interviews with Participants in the USDRN STENTS Nested Qualitative Cohort Study

Corneli A, Dombeck C, McKenna K, Harper JD, Antonelli JA, Desai A, Lai HH, Tasian G, Ziemba JB, McCune R, Piskator B, Al-Khalidi H, Maalouf N, Reese P, Wessells H, Kirkali Z, Scales CD

Ureteral stents are commonly used after ureteroscopy and cause significant discomfort, yet qualitative perspectives on patients' stent experiences remain unknown. We describe psychological, functional, and interpersonal effects of post-ureteroscopy stents and whether additional patient-reported assessments may be needed. All 39 participants experienced pain, although descriptions varied and differentiated between feelings of pain versus discomfort. Almost all experienced urinary

symptoms. Only a few reported other physical symptoms, although several psychological aspects were identified. In the areas of sleep, mood, life enjoyment, work, exercise, activities of daily living, driving, childcare, and leisure/social activities, the stent had little impact on daily living among participants placed in the minimal group ($n=12$) and far greater impact for participants in the substantial group ($n=8$). For patients in the moderate group ($n=19$), some daily activities were moderately or substantially affected, while other activities were minimally affected. The conclusion showed that counseling to better prepare patients for the impact of stent-associated symptoms may help mitigate symptom burden. While existing instruments adequately cover most symptoms, additional assessments for other domains, particularly psychological factors, may be needed.

- Jennifer Allmaras MPH, Muen Wang, 5/1/2023

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BLADDER

[Defining the Infant Male Urobiome and Moving Towards Mechanisms in Urobiome Research](#)

Hadjifrangiskou M, Reasoner S, Flores V, Horn GV, Morales G, Peard L, Abelson B, Manuel C, Lee J, Baker B, Williams T, Schmitz J, Clayton D

The urinary bladder harbors a community of microbes termed the urobiome, which remains understudied. In this study, we present the urobiome of healthy infant males from samples collected by transurethral catheterization. Using a combination of extended culture and amplicon sequencing, we identify several common bacterial genera that can be further investigated for their effects on urinary health across the lifespan. Many genera were shared between all samples suggesting a consistent urobiome composition among this cohort. We note that, for this cohort, early life exposures including mode of birth (vaginal vs. Caesarean section), or prior antibiotic exposure did not influence urobiome composition. In addition, we report the isolation of culturable bacteria from the bladders of these infant males, including *Actinotignum schaalii*, a bacterial species that has been associated with urinary tract infection in older male adults. Herein, we isolate and sequence 9 distinct strains of *A. schaalii* enhancing the genomic knowledge surrounding this species and opening avenues for delineating the microbiology of this urobiome constituent. Furthermore, we present a framework for using the combination of culture-dependent and sequencing methodologies for uncovering mechanisms in the urobiome.

[Evaluation of a clinical and translational research initiative: Developing and implementing a collaborative evaluation process in CAIRIBU](#)

Allmaras JM, Penniston KL, Rolland B

Funding for large research initiatives, such as those funded through the National Institutes of Health U mechanism, has increased since 2010;

however, there is little published research on how to evaluate the success of such initiatives. Here, we describe the collaborative evaluation planning process undertaken by the Interactions Core of the Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU) research community, a clinical and translational research initiative funded by the National Institute of Diabetes and Digestive and Kidney Diseases. Evaluation is necessary to measure the impact of our work and to allow for continuous improvement efforts of CAIRIBU activities and initiatives. We developed and implemented an iterative seven-step process that engaged the Interactions Core, NIDDK program staff, and grantees at each step of the planning process. Challenges faced in planning and implementing the evaluation plan included the time burden on investigators to submit new data for evaluations, finite time and resources for evaluation work, and the development of infrastructure for the evaluation plan. We call on funding agencies to include more explicit requirements for evaluation participation from grantees, as well as dedicated funding to support the evaluation process, in future funding opportunity announcements for large research consortia.

[The impact of short term, long term and intermittent E. coli infection on male C57BL/6J mouse prostate histology and urinary physiology](#)

Ruetten H, Sandhu SK, Fox O, Zhu J, Sandhu JK, Vezina CM

Prostatic inflammation and prostatic fibrosis are associated with lower urinary tract dysfunction in men. Prostatic inflammation arising from a transurethral uropathogenic *E. coli* infection is sufficient to increase prostatic collagen content in male mice. It is not known whether and how the sequence, duration and chronology of prostatic infection influence urinary function, prostatic inflammation and collagen content. We placed a transurethral catheter into adult male

C57BL/6J mice to deliver uropathogenic *E. coli* UTI189 two-weeks prior to study endpoint (to evaluate the short-term impact of infection), 10-weeks prior to study endpoint (to evaluate the long-term impact of infection), or two-, six-, and ten-weeks prior to endpoint (to evaluate the impact of repeated intermittent infection). Mice were catheterized the same number of times across all experimental groups and instilled with sterile saline when not instilled with *E. coli* to control for the variable of catheterization. We measured bacterial load in free catch urine, bodyweight and weight of bladder and dorsal prostate; prostatic density of leukocytes, collagen and procollagen 1A1 producing cells, and urinary function. Transurethral *E. coli* instillation caused more severe and persistent bacteriuria in mice with a history of one or more transurethral instillations of sterile saline or *E. coli*. Repeated intermittent infections resulted in a greater relative bladder wet weight than single infections. However, voiding function, as measured by the void spot assay, and the density of collagen and ProCOL1A1+ cells in dorsal prostate tissue sections did not significantly differ among infection groups. The density of CD45+ leukocytes was greater in the dorsal prostate of mice infected two weeks prior to study endpoint but not in other infection groups compared to uninfected controls.

[Nocturnal polyuria and nocturia](#)

Tyagi S, Chancellor MB

Nocturia is a common complaint that can have a significant impact on quality of life. The pathophysiology is usually multifactorial and can be due to poor sleep, nocturnal polyuria, or low bladder capacity alone or in combination. Nocturnal polyuria (NP) is the most common cause of nocturia in older adults. We hereby review the role of nocturnal polyuria in nocturia. To manage nocturia, a multipronged approach personalized to the patient's multifactorial etiology is warranted, with a focus on lifestyle modifications and behavioral approaches as first-line therapies. Pharmacologic treatment

should be considered based on underlying disease processes, and healthcare providers should be mindful of potential drug interactions and polypharmacy in older adults. Referral to specialists in sleep or bladder-related disorders may be necessary for some patients. With comprehensive and individualized management, patients with nocturia can achieve improved quality of life and overall health outcomes.

[Treating Lower Urinary Tract Symptoms in Older Adults: Intravesical Options](#)

Ganguly A, Tyagi S, Chermansky C, Kanai A, Beckel J, Hashimoto M, Cho KJ, Chancellor M, Kaufman J, Yoshimura N, Tyagi P

This article provides an overview of the diagnosis and the treatment of lower urinary tract symptoms in older adults complicated by the neurodegenerative changes in the micturition reflex and further confounded by age-related decline in hepatic and renal clearance raising the propensity of adverse drug reactions. The first-line drug treatment for lower urinary tract symptoms, orally administered antimuscarinics, fails to reach the equilibrium dissociation constant of muscarinic receptors even at their maximum plasma concentration and tends to evoke a half-maximal response at a muscarinic receptor occupancy of just 0.206% in the bladder with a minimal difference from exocrine glands, which raises the adverse drug reaction risk. On the contrary, intravesical antimuscarinics are instilled at concentrations 1000-fold higher than the oral maximum plasma concentration and the equilibrium dissociation constant erects a downhill concentration gradient that drives passive diffusion and achieves a mucosal concentration around ten-fold lower than the instilled concentration for a long-lasting occupation of muscarinic receptors in mucosa and sensory nerves. A high local concentration of antimuscarinics in the bladder triggers alternative mechanisms of action and is supposed to engage retrograde transport to nerve cell bodies for neuroplastic changes that underlie a long-lasting therapeutic effect, while an intrinsically lower systemic uptake of the

intravesical route lowers the muscarinic receptor occupancy of exocrine glands to lower the adverse drug reaction relative to the oral route. Chemodenervation by an intradetrusor injection of onabotulinumtoxinA is merited for patients with idiopathic overactive bladder discontinuing oral treatment because of a lack of efficacy. However, age-related peripheral neurodegeneration potentiates the adverse drug reaction risk of urinary retention that motivates the quest of liquid instillation, delivering larger fraction of onabotulinumtoxinA to the mucosa as opposed to muscle by an intradetrusor injection can also probe the neurogenic and myogenic predominance of idiopathic overactive bladder. Overall, the treatment paradigm of lower urinary tract symptoms in older adults should be tailored to individual's overall health status and the risk tolerance for adverse drug reactions.

[Using clinical decision support to improve urine testing and antibiotic utilization](#)

Michael E Yarrington, Staci S Reynolds, Tray Dunkerson, Fabienne McClellan, Christopher R Polage, Rebekah W Moehring, Becky A Smith, Jessica L Seidelman, Sarah S Lewis, Sonali D Advani
Urine cultures collected from catheterized patients have a high likelihood of false-positive results due to colonization. We examined the impact of a clinical decision support (CDS) tool that includes catheter information on test utilization and patient-level outcomes. CDS tools can aid in optimizing urine culture collection practices and can serve as a reminder for removal or exchange of long-term indwelling urinary catheters at the time of urine-culture collection.

[Using the COM-B model to identify barriers to and facilitators of evidence-based nurse urine-culture practices](#)

Sonali D Advani, Ali Winters, Nicholas A Turner, Becky A Smith, Jessica Seidelman, Kenneth Schmader, Deverick J Anderson, Staci S Reynolds
Our surveys of nurses modeled after the Capability, Opportunity, and Motivation Model of Behavior (COM-B model) revealed that opportunity and

motivation factors heavily influence urine-culture practices (behavior), in addition to knowledge (capability). Understanding these barriers is a critical step towards implementing targeted interventions to improving urine-culture practices. Focusing on knowledge alone is insufficient to improve evidence-based urine-culture (behavior) practices. Opportunity and motivation play key roles in influencing urine-culture (behavior) practices. Healthcare systems should include nurses in stewardship efforts and should consider interventions that target opportunity and motivation barriers to improve urine-culture practices.

GENITOURINARY

[Collagen is More Abundant and Structurally Altered in Lichen Sclerosis](#)

Eduardo M Miranda Mora, Melissa I Champer, Wei Huang, Paul J Campagnola, Matthew D Grimes

To test the hypothesis that genital skin and male urethra affected by lichen sclerosis (LS) has increased collagen content and altered collagen structure. LS tissues have greater collagen content compared to non-LS tissues. Quantitative assessment of collagen organization, using GLCM, revealed less homogeneity and more disorganization of collagen in LS compared to non-LS tissues. Taken together, our findings suggest that alterations in physical tissue properties seen in LS may be due to both increased collagen abundance and altered structure.

KIDNEY

[Impact of race-independent equations on estimating glomerular filtration rate for the assessment of kidney dysfunction in liver disease](#)

Stämmler F, Derain-Dubourg L, Lemoine S, Meeusen JW, Dasari S, Lieske JC, Robertson A, Schiffer E

Altered hemodynamics in liver disease often results in overestimation of glomerular filtration rate (GFR) by creatinine-based GFR estimating (eGFR) equations. Recently, we have validated a novel eGFR equation based on serum myo-inositol, valine, and creatinine

quantified by nuclear magnetic resonance spectroscopy in combination with cystatin C, age and sex (GFRNMR). We hypothesized that GFRNMR could improve chronic kidney disease (CKD) classification in the setting of liver disease. We conducted a retrospective multicenter study in 205 patients with chronic liver disease (CLD), comparing the performance of GFRNMR to that of validated CKD-EPI eGFR equations, including eGFRcr (based on creatinine) and eGFRcr-cys (based on both creatinine and cystatin C), using measured GFR as reference standard. GFRNMR outperformed all other equations with a low overall median bias (-1 vs. -6 to 4 ml/min/1.73 m² for the other equations; $p < 0.05$) and the lowest difference in bias between reduced and preserved liver function (-3 vs. -16 to -8 ml/min/1.73 m² for other equations). Concordant classification by CKD stage was highest for GFRNMR (59% vs. 48% to 53%) and less biased in estimating CKD severity compared to the other equations. GFRNMR P30 accuracy (83%) was higher than that of eGFRcr (75%; $p = 0.019$) and comparable to that of eGFRcr-cys (86%; $p = 0.578$). In conclusion, the addition of myo-inositol and valine to creatinine and cystatin C in GFRNMR further improved GFR estimation in CLD patients and accurately stratified liver disease patients into CKD stages.

[In Vivo Prediction of Kidney Stone Fragility Using Radiomics-Based Regression Models](#)

Sudhir Pillai P, Hsieh SS, Vercnocke AJ, Potretzke AM, Koo K, McCollough CH, Ferrero A

The surgical technique for urinary stone removal is partly influenced by its fragility, as prognosticated by the clinician. This feasibility study aims to develop a linear regression model from CT-based radiomic markers to predict kidney stone comminution time in vivo with two ultrasonic lithotrites. Patients identified by urologists at our institution as eligible candidates for percutaneous nephrolithotomy were prospectively enrolled. The active engagement time of the lithotrite in breaking the stone during surgery denoted the comminution time of each stone. The comminution rate was computed as the stone volume

disintegrated per minute. Stones were grouped into three fragility classes (fragile, moderate, hard), based on inverse of the comminution rates with respect to the mean. Multivariable linear regression models were trained with radiomic features extracted from clinical CT images to predict comminution times in vivo. The model with the least root mean squared error (RMSE) on comminution times and the fewest misclassification of fragility was finally selected. Twenty-eight patients with 31 stones in total were included in this study. Stones in the cohort averaged 1557 (± 2472) mm³ in volume and 5.3 (± 7.4) minutes in comminution time. Ten stones had nonmoderate fragility. Linear regression of stone volume alone predicted comminution time with an RMSE of 6.8 minutes and missed all 10 stones with nonmoderate fragility. A fragility model that included stone volume, internal morphology, shape-based radiomics, and device type improved RMSE to below 3.3 minutes and correctly classified 20/21 moderate and 6/10 nonmoderate stones. In conclusion, CT metrics-based fragility models may provide information to surgeons regarding kidney stone fragility and facilitate the selection of stone removal procedures.

PROSTATE

[Prosteria - National Trends and Outcomes of More Frequent Than Guideline Recommended Prostate Specific Antigen Screening](#)

Peterson DJ, Bhambhani HP, Baird DRW, Li S, Eisenberg ML, Brooks JD

The objective of this study is to characterize national trends in and associated outcomes of more often than annual prostate-specific antigen (PSA) screening, which we term "prosteria." Men in the Optum Clinformatics Data Mart with ≥ 2 years from first PSA test to censoring at the end of insurance or available data (January 2003 to June 2019) or following exclusionary diagnoses or procedures, such as PCa treatment, were included. PSAs within 90 days were treated as one PSA. Prosteria was defined as having ≥ 3 PSA testing intervals of ≤ 270 days. A total of

9,734,077 PSAs on 2,958,923 men were included. The average inter-PSA testing interval was 1.5 years, and 4.5% of men had prosteria, which increased by 0.53% per year. Educated, wealthy, non-White patients were more likely to have prosteria. Men within the recommended screening age (ie 55-69) had lower rates of prosteria. Prosteria patients had higher average PSA values (2.5 vs 1.4 ng/mL), but lower values at PCa diagnosis. Prosteria was associated with biopsy and PCa diagnosis; however, there were comparable rates of treatment within 2 years of diagnosis. To conclude, in this large cohort study, prosteria was common, increased over time, and was associated with demographic characteristics. Importantly, there were no clinically meaningful differences in PSA values at diagnosis or rates of early treatment, suggesting prosteria leads to both overdiagnosis and overtreatment. These results support current AUA and USPTF guidelines and can be used to counsel men seeking more frequent PSA screening.

STONES

[Characterization of Stone Events in Patients With Type 3 Primary Hyperoxaluria](#)

Amous MG, Vaughan L, Mehta RA, Schulte PJ, Lieske JC, Milliner DS

Hallmarks of primary hyperoxaluria type 3 are nephrolithiasis and hyperoxaluria. However, little is known about factors influencing stone formation in this disease. We characterized stone events and examined associations with urine parameters and kidney function in a primary hyperoxaluria type 3 population. We retrospectively analyzed clinical, and laboratory data of 70 primary hyperoxaluria type 3 patients enrolled in the Rare Kidney Stone Consortium Primary Hyperoxaluria Registry. Kidney stones occurred in 65/70 primary hyperoxaluria type 3 patients (93%). Among the 49 patients with imaging available, the median (IQR) number of stones was 4 (2, 5), with largest stone 7 mm (4, 10) at first imaging. Clinical stone events occurred in 62/70 (89%) with

median number of events per patient 3 (2, 6; range 1-49). Age at first stone event was 3 years (0.99, 8.7). Lifetime stone event rate was 0.19 events/year (0.12, 0.38) during follow-up of 10.7 (4.2, 26.3) years. Among 326 total clinical stone events, 139 (42.6%) required surgical intervention. High stone event rates persisted for most patients through the sixth decade of life. Analysis was available for 55 stones: pure calcium oxalate accounted for 69%, with mixed calcium oxalate and phosphate in 22%. Higher calcium oxalate supersaturation was associated with increased lifetime stone event rate after adjusting for age at first event (IRR [95%CI] 1.23 [1.16, 1.32]; $P < .001$). By the fourth decade, estimated glomerular filtration rate was lower in primary hyperoxaluria type 3 patients than the general population. In conclusion, stones impose a lifelong burden on primary hyperoxaluria type 3 patients. Reducing urinary calcium oxalate supersaturation may reduce event frequency and surgical intervention.

Dissimilar cavitation dynamics and damage patterns produced by parallel fiber alignment to the stone surface in holmium:yttrium aluminum garnet laser lithotripsy

Gaoming Xiang, Daiwei Li, Junqin Chen, Arpit Mishra, Georgy Sankin, Xuning Zhao, Yuqi Tang, Kevin Wang, Junjie Yao, Pei Zhong

Recent studies indicate that cavitation may play a vital role in laser lithotripsy. However, the underlying bubble dynamics and associated damage mechanisms are largely unknown. In this study, we use ultra-high-speed shadowgraph imaging, hydrophone measurements, three-dimensional passive cavitation mapping (3D-PCM), and phantom test to investigate the transient dynamics of vapor bubbles induced by a holmium:yttrium aluminum garnet laser and their correlation with solid damage. We vary the standoff distance (SD) between the fiber tip and solid boundary under parallel fiber alignment and observe several distinctive features in bubble dynamics. First, long pulsed laser irradiation and solid boundary interaction create an elongated "pear-shaped" bubble that

collapses asymmetrically and forms multiple jets in sequence. Second, unlike nanosecond laser-induced cavitation bubbles, jet impact on solid boundary generates negligible pressure transients and causes no direct damage. A non-circular toroidal bubble forms, particularly following the primary and secondary bubble collapses at $SD = 1.0$ and 3.0 mm, respectively. We observe three intensified bubble collapses with strong shock wave emissions: the intensified bubble collapse by shock wave, the ensuing reflected shock wave from the solid boundary, and self-intensified collapse of an inverted "triangle-shaped" or "horseshoe-shaped" bubble. Third, high-speed shadowgraph imaging and 3D-PCM confirm that the shock origins from the distinctive bubble collapse form either two discrete spots or a "smiling-face" shape. The spatial collapse pattern is consistent with the similar BegoStone surface damage, suggesting that the shockwave emissions during the intensified asymmetric collapse of the pear-shaped bubble are decisive for the solid damage.

Health-related quality of life disparities among Hispanic/Latinx patients with nephrolithiasis

Flores AR, Abedi G, Girgiss CB, Berger JH, Penniston KL, Li S, Friedlander DF, Bechis SK, Sur RL

It is documented that Hispanic/Latinx kidney stone formers have inferior health-related quality of life (HRQoL) compared to the general population. We hypothesized that socioeconomic factors drive HRQoL disparities. Specifically, we sought to determine if medical insurance type is associated with HRQoL disparities among Hispanic/Latinx stone formers. This was a prospective cohort observational study of patients with kidney stones across the University of San Diego Health Care System. Patients enrolled from June 2018 to August 2020 completed a validated Wisconsin Stone Quality of Life questionnaire (WISQoL). Patient characteristics and self-reported HRQoL were compared between Hispanic/Latinx and non-Hispanic/Latinx stone formers using MANCOVA and ordinal logistic regression. Matched group comparisons were performed

based on age, gender, body mass index, stone symptoms, and insurance type using MACOVA. A total of 270 patients were enrolled (Hispanic/Latinx $n = 88$; non-Hispanic/Latinx $n = 182$). Hispanic/Latinx stone formers had higher rates of public insurance at baseline ($p < 0.001$) with significantly lower HRQoL [social impact ($p = 0.007$)]. However, a matched cohort comparison demonstrated no differences. On multivariate analysis, private insurance increased the likelihood of having higher HRQoL (OR 2.21, $p = 0.021$), while stone symptoms (OR = 0.06, $p < 0.001$) and emergency department visits (OR = 0.04, $p = 0.008$) decreased chances of higher HRQoL. Ethnicity was not a significant factor in HRQoL scores on multivariate analysis. Our analysis suggests that differences in HRQoL among Hispanic/Latinx stone formers may be primarily driven by socioeconomic factors as opposed to clinical or racial differences. Specifically, source of insurance appears to have significant effect on HRQoL in this ethnic group.

Machine-Learning Model for Prediction of Cefepime Susceptibility in Escherichia coli from Whole-Genome Sequencing Data

Romney M Humphries, Eugene Bragin, Julian Parkhill, Grace Morales, Jonathan E Schmitz, Paul A Rhodes

The declining cost of performing bacterial whole-genome sequencing (WGS) coupled with the availability of large libraries of sequence data for well-characterized isolates have enabled the application of machine-learning (ML) methods to the development of nonlinear sequence-based predictive models. We tested the ML-based model developed by Next Gen Diagnostics for prediction of cefepime phenotypic susceptibility results in *Escherichia coli*. A cohort of 100 isolates of *E. coli* recovered from urine ($n = 77$) and blood ($n = 23$) cultures were used. The cefepime MIC was determined in triplicate by reference broth microdilution and classified as susceptible (MIC of ≤ 2 $\mu\text{g/mL}$) or not susceptible (MIC of ≥ 4 $\mu\text{g/mL}$) using the 2022 Clinical and Laboratory Standards Institute breakpoints. Five isolates generated both susceptible and not

susceptible MIC results, yielding categorical agreement of 95% for the reference method to itself. Categorical agreement of ML to MIC interpretations was 97%, with 2 very major (false, susceptible) and 1 major (false, not susceptible) errors. One very major error occurred for an isolate with blaCTX-M-27 (MIC mode, ≥ 32 $\mu\text{g/mL}$) and one for an isolate with blaTEM-34 for which the MIC cefepime mode was 4 $\mu\text{g/mL}$. One major error was for an isolate with blaCTX-M-27 but with a MIC mode of 2 $\mu\text{g/mL}$. These preliminary data demonstrated performance of ML for a clinically important antimicrobial-species pair at a caliber similar to phenotypic methods, encouraging wider development of sequence-based susceptibility prediction and its validation and use in clinical practice.

- Jennifer Allmaras MPH, Muen Wang,
4/13/2023

Email cairibu@urology.wisc.edu to
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next month's communique

BLADDER

[Adverse Childhood Experiences and Lower Urinary Tract Symptoms and Impact Among Women](#)

Brady SS, Arguedas A, Huling JD, Shan L, Lewis CE, Fok CS, Van Den Eeden SK, Markland AD

This study utilizes Coronary Artery Risk Development in Young Adults (CARDIA) cohort study data to examine whether (1) family-based adverse childhood experiences (ACEs), recalled by women aged 32 to 47, are associated with lower urinary tract symptoms (LUTS) and their impact, a composite variable with 4 levels (bladder health and mild, moderate, or severe LUTS/impact), and (2) extensiveness of women's social networks in adulthood attenuates an association between ACEs and LUTS/impact. Recall of more frequent family-based ACEs was associated with report of more LUTS/impact over 10 years later (OR=1.26, 95% CI=1.07, 1.48). Social networks during adulthood appeared to attenuate the association between ACEs and LUTS/impact (OR=0.64, 95% CI=0.41, 1.02). Among women with less extensive social networks, estimated probability of experiencing moderate or severe LUTS/impact versus bladder health or mild LUTS/impact was 0.29 and 0.21 for those reporting an ACEs frequency corresponding to more than "a little" versus "rarely or none of the time," respectively. Among women with more extensive social networks, estimated probabilities were 0.20 and 0.21, respectively.

[Clinically Important Differences for Pain and Urinary Symptoms in Urologic Chronic Pelvic Pain Syndrome: A MAPP Network Study](#)

Stephens-Shields AJ, Lai HH, Landis JR, Kreder K, Rodriguez LV, Naliboff BD, Afari N, Sutcliffe S, Moldwin R, Griffith JW, Clemens JQ, Bradley CS, Quallich S, Gupta P, Harte SE, Farrar JT

Symptom heterogeneity in interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, collectively termed urologic chronic pelvic pain syndrome (UCPPS), has resulted in difficulty in defining

appropriate clinical trial endpoints. We determine clinically important differences (CIDs) for 2 primary symptom measures, Pelvic Pain Severity (PPS) and Urinary Symptom Severity (USS), and evaluate subgroup differences. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain Symptom Patterns Study enrolled individuals with UCPPS. We defined CIDs by associating changes in PPS and USS over 3 to 6 months with marked improvement on a global response assessment using regression and receiver operating characteristic curves. We evaluated CIDs for absolute and percent change and examined differences in CIDs by sex-diagnosis, presence of Hunner lesions, pain type, pain widespreadness, and baseline symptom severity. The conclusion showed that a reduction of 30-50% in PSS is a clinically meaningful endpoint for future therapeutic trials in UCPPS. USS CIDs are more appropriately defined separately for male and female participants.

[Deep Learning of Videourodynamics to Classify Bladder Dysfunction Severity in Patients with Spina Bifida](#)

Weaver JK, Martin-Olenski M, Logan J, Broms R, Antony M, Van Batavia J, Weiss DA, Long CJ, Smith AL, Zderic SA, Huang J, Fan Y, Tasian GE

Urologists rely heavily on videourodynamics (VUDS) to identify patients with neurogenic bladders who are at risk of upper tract injury, but their interpretation has high interobserver variability. Our objective was to develop deep learning models of VUDS studies to categorize severity of bladder dysfunction. Among 306 VUDS studies, the accuracy and weighted kappa of the ensemble model classification of bladder dysfunction when at least 75% expected bladder capacity was reached were 70% (95% CI 66%, 76%) and 0.54 (moderate agreement), respectively. The performance of the clinical model built from data extracted by pediatric urologists was the poorest with an accuracy of 61% (55%, 66%) and a weighted kappa of 0.37. Our models built from urodynamic pressure-volume tracings and fluoroscopic images were

able to automatically classify bladder dysfunction with moderately high accuracy.

[Effects of aging on urinary tract epithelial homeostasis and immunity](#)

Ligon MM, Joshi CS, Fashemi BE, Salazar AM, Mysorekar IU

A global increase in older individuals creates an increasing demand to understand numerous healthcare challenges related to aging. This population is subject to changes in tissue physiology and the immune response network. Older individuals are particularly susceptible to infectious diseases, with one of the most common being urinary tract infections (UTIs). Postmenopausal and older women have the highest risk of recurrent UTIs (rUTIs); however, why rUTIs become more frequent after menopause and during old age is incompletely understood. In this review, we highlight our understanding of bladder innate and adaptive immunity and the impact of aging and hormones and hormone therapy on bladder epithelial homeostasis and immunity. In particular, we elaborate on how the cellular and molecular immune landscape within the bladder can be altered during aging as aged mice develop bladder tertiary lymphoid tissues (bTLT), which are absent in young mice leading to profound age-associated change to the immune landscape in bladders that might drive the significant increase in UTI susceptibility. Knowledge of host factors that prevent or promote infection can lead to targeted treatment and prevention regimens. This review also identifies unique host factors to consider in the older, female host for improving rUTI treatment and prevention by dissecting the age-associated alteration of the bladder mucosal immune system.

[Longitudinal urinary microbiome characteristics in women with urgency urinary incontinence undergoing sacral neuromodulation](#)

Mueller MG, Das P, Andy U, Brennaman L, Dieter AA, Dwarica D, Kirby AC, Shepherd JP, Gregory WT, Amundsen CL

The objective was to evaluate the stability of the urinary microbiome communities in women undergoing sacral neuromodulation (SNM) for urgency urinary incontinence (UUI). We hypothesized that clinical response to SNM therapy would be associated with changes in the urinary microbiome. Nineteen women who underwent SNM and provided both baseline and 3-month urine samples were included in this analysis. Women reported improvement in objective (number of UUI episodes) and subjective (symptom severity and health-related quality of life) measures. Ninety percent of the bacteria were classified as Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. No significant differences were observed in each subject's beta-diversity at 3 months compared with their baseline microbiome. Our descriptive pilot study of a cohort of women who had achieved objective and subjective improvements in UUI following SNM therapy demonstrates that the urinary microbiome remains relatively stable, despite variability amongst the cohort.

Primary ablation versus urinary diversion in posterior urethral valve: Systematic review and meta-analysis

Adree Khondker, Justin Yh Chan, Shamir Malik, Jin K Kim, Michael E Chua, Brittney Henderson, Priyank Yadav, Joana Dos Santos, Natasha Brownrigg, Bernarda Viteri, **Gregory E Tasian**, Mandy Rickard, Armando J Lorenzo

A systematic search was performed in March 2021. Comparative studies were evaluated according to Cochrane collaboration recommendations. Assessed measures included kidney outcomes (chronic kidney disease, end-stage renal disease, kidney function) and bladder outcomes. Odds ratios (OR) and mean difference (MD) with 95% confidence interval (CI) were extrapolated from available data for quantitative synthesis. Random-effects meta-analysis and meta-regression were performed according to study design, and potential covariates were assessed with subgroup analysis. The systematic review was prospectively registered on PROSPERO (CRD42021243967). Thirty unique studies describing 1547 boys with PUV were included in this synthesis.

Overall effect estimates demonstrate that patients undergoing primary diversion have significantly increased odds of developing renal insufficiency [OR 0.60, 95% CI 0.44, 0.80; $p < 0.001$]. However, when adjusting for baseline kidney function between intervention groups, there was no significant difference in long term kidney outcomes [$p = 0.09$, 0.35], or the development of bladder dysfunction or requiring clean-intermittent catheterization with primary ablation rather than diversion [OR 0.89, 95% CI 0.49, 1.59; $p = 0.68$]. Current low-quality evidence suggests that medium-term kidney outcomes in children are similar between primary ablation and primary diversion after adjusting for baseline kidney function, while bladder outcomes are highly heterogeneous. Further research with covariate control is warranted to investigate sources of heterogeneity.

Single-Use Ureteroscopes Are Associated with Decreased Risk of Urinary Tract Infection After Ureteroscopy for Urolithiasis Compared to Reusable Ureteroscopes

Rei Unno, Gregory Hosier, Fadl Hamouche, **David B Bayne**, Marshall L Stoller, **Thomas Chi**

Urinary tract infection (UTI) is a common complication after ureteroscopy. Despite sterilization, there is evidence that reusable ureteroscopes can still harbor bacteria. Whether this property is associated with increased risk of UTI is unknown. The objective of this study was to compare rates of postoperative UTI after ureteroscopy for urolithiasis performed with single-use ureteroscopes vs reusable ureteroscopes. Single-use ureteroscopes are associated with a twofold decreased risk of UTI and increased stone clearance rate after ureteroscopy for urolithiasis compared to reusable ureteroscopes.

The role of the bladder diary in phenotyping men with LUTS

Khosla L, Lee P, Farooq M, Rychik K, Daniel R, Vizgan G, Prishtina L, **Bushman W**, Weiss JP, Blaivas JG

The aim of this study was to compare the clinical characteristics of men with lower urinary tract symptoms (LUTS) grouped by 24-h urine output determined from a

bladder voiding diary. An online database was queried to identify men who completed a 24-hour bladder diary (24HBD), and the Lower Urinary Tract Symptom Score (LUTSS) questionnaire from 2015 to 2019 using a mobile app. Data from the bladder diary and questionnaire were contemporaneously matched within a 2-week period. Additional data, including maximum uroflow (Qmax) and postvoid residual urine (PVR), were obtained from the electronic medical record (EMR). The cohort was divided into three groups: normal, oliguria, and polyuria based on their 24-hour voided volume (24HVV). The LUTSS, 24HVV, maximum voided volume (MVV), maximum flow rate (Qmax), and PVR were compared between those with oliguria and polyuria. These observations suggest that men with oliguria or polyuria and LUTS constitute easily distinguished phenotypes that might require different diagnostic and therapeutic algorithms. Those with oliguria were older, and had lower MVVs and much lower uroflows, suggesting that they are more likely to have underlying disorders such as bladder outlet obstruction and detrusor underactivity or may be patients with overactive bladder who reduced fluid intake to improve symptoms.

Treatment for Urinary Incontinence in Women Older Than 65 Years

Giulia I Lane, Elisabeth Erekson, Andrea Austin, Donald Carmichael, Vatche A Minassian, **Francine Grodstein**, Julie Pw Bynum

Urinary incontinence (UI) is common among women older than 65 years and negatively affects quality of life. However, the prevalence of UI treatment and determinants of treatment are largely unknown. We estimate that only approximately 1 in 9 older women with self-reported UI underwent treatment within the year before reporting symptoms, of which pharmacotherapy was the most common UI intervention, and women with more severe and longer duration of symptoms were most often treated.

[Why Are Some People with Lower Urinary Tract Symptoms \(LUTS\) Depressed? New Evidence That Peripheral Inflammation in the Bladder Causes Central Inflammation and Mood Disorders](#)

Francis M Hughes Jr, Michael R Odom, Anissa Cervantes, Austin J Livingston, J Todd Purves

Anecdotal evidence has long suggested that patients with lower urinary tract symptoms (LUTS) develop mood disorders, such as depression and anxiety, at a higher rate than the general population and recent prospective studies have confirmed this link. Breakthroughs in our understanding of the diseases underlying LUTS have shown that many have a substantial inflammatory component and great strides have been made recently in our understanding of how this inflammation is triggered. Meanwhile, studies on mood disorders have found that many are associated with central neuroinflammation, most notably in the hippocampus. Excitingly, work on other diseases characterized by peripheral inflammation has shown that they can trigger central neuroinflammation and mood disorders. In this review, we discuss the current evidence tying LUTS to mood disorders, its possible bidirectionality, and inflammation as a common mechanism. We also review modern theories of inflammation and depression. Finally, we discuss exciting new animal studies that directly tie two bladder conditions characterized by extensive bladder inflammation (cyclophosphamide-induced hemorrhagic cystitis and bladder outlet obstruction) to neuroinflammation and depression. We conclude with a discussion of possible mechanisms by which peripheral inflammation is translated into central neuroinflammation with the resulting psychiatric concerns.

KIDNEY

[Clinical and Genetic Characteristics of CKD Patients with High-risk APOL1 Genotypes](#)

Elliott MD, Marasa M, Cocchi E, Vena N, Zhang JY, Khan A, Murthy SK, Bheda S, Rasouly HM, Povysil G, Kiryluk K, Gharavi AG

APOL1 genotype has significant effects on kidney disease development and progression that vary among specific causes of kidney disease, suggesting the presence of effect modifiers. We assessed the risk of kidney failure and eGFR decline rate in patients with chronic kidney disease (CKD) carrying high-risk (N=239) and genetically matched low-risk (N=1187) APOL1 genotypes. Exome sequencing revealed monogenic kidney diseases. Exome-wide association studies and gene-based and gene-set based collapsing analyses evaluated genetic modifiers of the effect of APOL1 genotype on CKD. In this genetically matched cohort, high-risk APOL1 genotypes were associated with an increased risk of kidney failure and eGFR decline rate, with a graded risk between specific high-risk genotypes and a lower rate of monogenic kidney disease. Rare missense variants in the inflammasome pathway may act as genetic modifiers of APOL1 effect on kidney disease.

[Genetics of Kidney Disease: The Unexpected Role of Rare Disorders](#)

Elliott MD, Rasouly HM, Gharavi AG

Hundreds of different genetic causes of chronic kidney disease are now recognized, and while individually rare, taken together they are significant contributors to both adult and pediatric diseases. Traditional genetics approaches relied heavily on the identification of large families with multiple affected members and have been fundamental to the identification of genetic kidney diseases. With the increased utilization of massively parallel sequencing and improvements to genotype imputation, we can analyze rare variants in large cohorts of unrelated individuals, leading to personalized care for patients and significant research advancements. This review evaluates the contribution of rare

disorders to patient care and the study of genetic kidney diseases and highlights key advancements that utilize new techniques to improve our ability to identify new gene-disease associations.

[The impact of genetic education on referral of patients to genetic evaluation: Findings from a national survey of nephrologists](#)

Milo Rasouly H, Balderes O, Marasa M, Fernandez H, Lipton M, Lin F, Gharavi AG, Sabatello M

The success of genomic medicine hinges on implementation of genetic knowledge in clinical settings. In novel subspecialties, it requires that clinicians refer patients to genetic evaluation or testing, but referral is likely to be impacted by genetic knowledge. 201 nephrologists completed the survey. All reported treating patients with genetic forms of kidney disease, but 37% have referred less than 5 patients to genetic evaluation. A third had limited basic genetic knowledge. Most nephrologists (85%) reported concerns regarding future health insurance eligibility as a barrier to referral to genetic testing. Most adult nephrologists reported insufficient genetic education during residency (65%) and fellowship training (52%). Lower rating of genetic education and lower knowledge in recognizing signs of genetic kidney diseases were significantly associated with lower number of patients referred to genetic evaluation (p-value<0.001). Most nephrologists reported that improving their genetic knowledge is important for them (>55%). The conclusion showed that there is a need to enhance nephrologists' genetic education to increase genetic testing utilization in nephrology.

[Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-CTrial](#)

Michael M, Groothoff JW, Shasha-Lavsky H, Lieske JC, Frishberg Y, Simkova E, Sellier-Leclerc AL, Devresse A, Guebre-Egziabher F, Bakaloglu SA, Mourani C, Saqan R, Singer R, Willey R, Habtemariam B, Gansner JM, Bhan I, McGregor T, Magen D

Primary hyperoxaluria type 1 (PH1) is a rare genetic disease characterized by excessive hepatic oxalate production that frequently causes kidney failure.

Lumasiran is an RNA interference therapeutic that is administered subcutaneously for the treatment of PH1. Lumasiran has been shown to reduce oxalate levels in the urine and plasma of patients with PH1 who have relatively preserved kidney function. In the ILLUMINATE-C study, the efficacy and safety of lumasiran were evaluated in patients with PH1 and advanced kidney disease, including a cohort of patients undergoing hemodialysis. During the 6-month primary analysis period, lumasiran resulted in substantial reductions in plasma oxalate with acceptable safety in patients with PH1 complicated by advanced kidney disease. Lumasiran resulted in substantial reductions in POx with acceptable safety in patients with PH1 who have advanced kidney disease, supporting its efficacy and safety in this patient population.

[Primary Hyperoxaluria Type 3](#)

Milliner DS, Harris PC, Sas DJ, Lieske JC

Primary hyperoxaluria type 3 (PH3) is characterized by recurring calcium oxalate stones beginning in childhood or adolescence and, on occasion, nephrocalcinosis or reduced kidney function. PH3 most often presents in childhood (median age 2 to 3 years) with signs or symptoms related to stones including hematuria, frequent urination, dysuria, blood visible in the urine, or stone-associated pain. Some individuals with PH3 do not present until adulthood, usually with stone-related symptoms or findings. Over time, frequent stones and/or nephrocalcinosis may compromise kidney function, resulting in chronic kidney disease. To date, systemic oxalosis has not been reported in PH3.

PROSTATE

[Impact of the bladder detrusor muscular ring on lower urinary tract symptoms due to benign prostatic hyperplasia: A quantitative MRI analysis](#)

Nandalur KR, Walker D, Ye H, Al-Katib S, Seifman B, Gangwish D, Dhaliwal A, Connor E, Dobies K, Sesoko C, Dejoie W, Zwaans B, Nandalur S, Nguyen J, Hafron J

The etiology of lower urinary tract symptoms secondary to benign prostatic

hyperplasia (LUTS/BPH) remains uncertain. The purpose of our study was to quantitatively analyze anatomic characteristics on magnetic resonance imaging (MRI) to assess novel independent factors for symptoms. This retrospective single-institution study evaluated treatment-naïve men who underwent prostate MRI within 3 months of international prostate symptom score (IPSS) scoring from June 2021 to February 2022. Factors measured on MRI included: size of the detrusor muscular ring (DMR) surrounding the bladder outlet, central gland (CG) mean apparent diffusion coefficient (ADC), levator hiatus (LH) volume, intrapelvic volume, intravesicular prostate protrusion (IPP) volume, CG volume, peripheral zone (PZ) volume, prostate urethra angle (PUA), and PZ background ordinal score. Multivariable logistic regression and receiver operating characteristic analysis were used to analyze factors for moderate/severe (IPSS ≥ 8) and severe LUTS/BPH (IPSS ≥ 20). Expansion of the DMR surrounding the bladder outlet is a novel anatomic factor independently associated with moderate and severe LUTS/BPH, taking into account prostate volumes, including quantified IPP volume, which were unrelated. Detrusor ring diameter, easily and reliably measured on routine prostate MRI, may relate to detrusor dysfunction from chronic stretching of this histologically distinct smooth muscle around the bladder neck.

[Steroid hormone imbalance drives macrophage infiltration and Spp1/osteopontin+ foam cell differentiation in the prostate](#)

Popovics P, Skaltitzky KO, Schroeder E, Jain A, Silver SV, Van Fritz F, Uchtmann KS, Vezina CM, Ricke WA
Benign Prostatic Hyperplasia (BPH) occurs progressively with aging in men and drives deteriorating symptoms collectively known as Lower Urinary Tract Symptoms (LUTS). Age associated changes in circulating steroid hormones, and prostate inflammation have been postulated in the etiology of BPH/LUTS. The link between hormones and inflammation in the development of BPH/LUTS is conflicting because they

may occur independently or as sequential steps in disease pathogenesis. This study aimed to decipher the prostatic immune landscape in a mouse model of lower urinary tract dysfunction (LUTD). Steroid hormone imbalance was generated by the surgical implantation of testosterone (T) and estradiol (E2) pellets into male C57BL/6J mice and gene expression analysis was performed on ventral prostates (VP). These experiments identified an increase in the expression of macrophage markers and Spp1/osteopontin (OPN). Localization studies of OPN pinpointed that OPN+ macrophages travel to the prostate lumen and transition into lipid accumulating foam cells. We also observed a significantly increase in number of tissue macrophages in the VP which was prevented in OPN knockout (OPN-KO) mice. In contrast, mast cells, but not macrophages, were significantly elevated in the dorsal prostate of T+E2 treated mice which was diminished in OPN-KO mice. Steroid hormone implantation progressively increased urinary frequency, which was ameliorated in OPN-KO mice. Our study underscores the role of age associated steroid hormone imbalances as a mechanism of expanding the prostatic macrophage population, their luminal translocation and foam cell differentiation. This article is protected by copyright. All rights reserved.

[Toxicoproteomics of Mono\(2-ethylhexyl\) phthalate and Perfluorooctanesulfonic Acid in Models of Prostatic Diseases](#)

Thomas S, Ricke WA, Li L

Benign and malignant prostatic diseases are common, costly, and burdensome; moreover, they share fundamental underlying molecular processes. Several ubiquitous contaminants may perturb these processes, possibly via peroxisome proliferator-activated receptor (PPAR) signaling, but the role of environmental exposures—particularly mixtures—in prostatic diseases is undefined. In the present study, nontumorigenic prostate stromal cells and metastatic prostate epithelial cells were exposed to

ubiquitous exogenous PPAR ligands under different dosing paradigms, including a mixture, and effects were assessed via mass spectrometry-based global proteomics. In prostate stromal cells, environmentally relevant levels of mono(2-ethylhexyl) phthalate (MEHP), alone and in combination with perfluorooctanesulfonic acid, led to significant changes in proteins involved in key processes underlying prostatic diseases: oxidative stress defense, proteostasis, damage-associated molecular pattern signaling, and innate immune response signaling. A follow-up experiment in metastatic prostate epithelial cells showed that the occupationally relevant levels of MEHP perturbed similar processes, including lipid, cholesterol, steroid, and alcohol metabolism; apoptosis and coagulation regulation; wound response; and aging. This work shows that environmental exposures may contribute to prostatic diseases by perturbing key processes of a proposed adverse outcome pathway, including lipid metabolism, oxidative stress, and inflammation. Future in vivo research will investigate the role of contaminants in prostatic diseases and in preventative agents.

STONES

Development of a Surgical Decision Aid for Patients with Nephrolithiasis: Shockwave Lithotripsy vs Ureteroscopy

John Michael DiBianco, Bronson Conrado, Stephanie Daighault-Newton, Sarah T Hawley, **Giulia Lane**, David Wenzler, Brian Seifman, Jessica R Phelps, Michael Cotant, Khurshid R Ghani, Casey A Dauw

Shared decision making is recommended to guide medical/surgical treatment strategies. We aimed at developing a surgical decision aid (SDA) facilitating decision making between ureteroscopy (URS) or shockwave lithotripsy (SWL) in patients with symptomatic nephrolithiasis. We developed an SDA facilitating treatment choice between SWL and URS with promising content and face validity. Agreement and contradiction between anesthesia type and recovery validation results indicate the importance of shared decision

making and the need for a validated SDA. Future work should focus on the SDAs value and opportunities for refinement in practice.

Pediatric Nephrolithiasis

Cao B, Daniel R, McGregor R, **Tasian GE**

The prevalence of pediatric nephrolithiasis has increased dramatically in the past two decades for reasons that have yet to be fully elucidated. Workup of pediatric kidney stones should include metabolic assessment to identify and address any risk factors predisposing patients to recurrent stone formation, and treatment should aim to facilitate stone clearance while minimizing complications, radiation and anesthetic exposure, and other risks. Treatment methods include observation and supportive therapy, medical expulsive therapy, and surgical intervention, with choice of treatment method determined by clinicians' assessments of stone size, location, anatomic factors, comorbidities, other risk factors, and preferences and goals of patients and their families. Much of the current research into nephrolithiasis is restricted to adult populations, and more data are needed to better understand many aspects of the epidemiology and treatment of pediatric kidney stones.

Underinsurance And Multiple Surgical Treatments for Kidney Stones

David Bayne, Cameron R Hicks, Sudarshan Srirangapatanam, Manuel Armas-Phan, Johsias Maru, Efstathios Gennatas, Isabel Elaine Allen, Hilary Seligman, Marshall Stoller, **Anne Suskind**, **Thomas L Chi**

To further elucidate the relationship between low socioeconomic status (SES) and larger, more complex stones requiring staged surgical interventions. Specifically, we aimed to determine if underinsurance (Medicaid, Medicare, and self-pay insurance types) is associated with multiple surgeries within 1 year. In a statewide, California database from 2009 to 2018, underinsured adults had higher odds of undergoing a second procedure for kidney stones within 1 year of initial surgical treatment. This study adds to the

expanding body of literature linking suboptimal healthcare access and disparate outcomes for kidney stone patients.

Ureteral Stent Placement Prior to Definitive Stone Treatment is Associated with Higher Post-Operative Emergency Department Visits and Opioid Prescriptions for Youth Having Ureteroscopy or Shockwave Lithotripsy

Tasian GE, Maltenfort MG, Rove K, Ching CB, Ramachandra P, DeFoor B, Fernandez N, Forrest CB, **Ellison JS**

Little is known about the impact of ureteral stents on youth having stone surgery. We evaluated the association of ureteral stent placement before or concurrent with ureteroscopy (URS) and shockwave lithotripsy (SWL) with emergency department (ED) visits and opioid prescriptions among pediatric patients. We conducted a retrospective cohort study of individuals aged 0-24 years who underwent URS or SWL from 2009-2021 at 6 hospitals in PEDSnet, a research network that aggregates electronic health record data from children's health systems in the United States. The exposure, primary ureteral stent placement, was defined as a stent placed concurrent with or within 60 days before URS or SWL. Associations between primary stent placement and stone-related ED visits and opioid prescriptions within 120 days of the index procedure were evaluated with mixed-effects Poisson regression. The conclusion showed that primary ureteral stent placement was associated with more frequent ED visits and opioid prescriptions, driven by pre-stenting. These results support elucidating situations where stents are not necessary for youth with nephrolithiasis.

- *Jennifer Allmaras MPH, Muen Wang, 2/28/2023*

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

BLADDER

[Bladder Mucosal Cystitis Cystica Lesions are Tertiary Lymphoid Tissues that Correlate with Recurrent UTI Frequency in Postmenopausal Women](#)

Ligon MM, Liang B, Lenger SM, Parameswaran P, Sutcliffe S, Lowder JL, Mysorekar IU

A retrospective, observational cohort of women with rUTIs that underwent cystoscopy (n=138) from 2015 to 2018 were identified using electronic medical records. CC status was abstracted from cystoscopy reports and correlations were identified by logistic regression. UTI-free survival time associated with CC was evaluated by Cox proportional hazards regression. Exact logistic regression was used to identify factors associated with changes to CC lesions on repeat cystoscopy. Biopsies of CC lesions were examined by routine histology and immunofluorescence. 53 patients (38%) had CC on cystoscopy. CC was associated with postmenopausal status (odds ratio [OR] [95% confidence interval [CI]]: 5.53 [1.39-37.21]), pelvic floor myofascial pain (PFMP; 6.82 [1.78-45.04]), having ≥ 4 UTIs in the past year (2.28 [1.04-5.09]), and a shorter time to next UTI (hazard ratio: 1.54 [1.01-2.35]). 42 patients (82%) demonstrated improvement or resolution of lesions. 10/11 (91%) biopsied CC lesions were tertiary lymphoid tissue with germinal centers and resembled follicular cystitis (FC). The conclusion showed CC lesions were associated with postmenopausal status, PFMP, and number of UTIs in the prior year and predicted worse rUTI outcomes. CC lesions are tertiary lymphoid tissue/FC that may improve or resolve over time with treatment. Identifying CC in rUTI patients may be useful in informing future UTI risk and tailoring appropriate treatment strategies.

[Collaborating for the advancement of interdisciplinary research in benign urology \(CAIRIBU\): outcomes, effectiveness, and future directions of annual CAIRIBU meetings](#)

Penniston KL, Allmaras JM

The 5th annual CAIRIBU Meeting (CAIRIBU = Collaborating for the Advancement of Interdisciplinary Research in Benign Urology) was held November 29-December 2, 2022 in Bethesda, MD and organized by the CAIRIBU (U24) Interactions Core. Altogether, nearly 100 individuals participated, representing U54 Urology OBrien Centers, P20 Urology Centers, and K12 Urology Career Development Programs currently and previously funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Several NIDDK Program Officers participated in the meeting, including those representing the NIDDK Central Repository and several urologic research consortia. The science presented during scientific and poster sessions represented the various areas of research among CAIRIBU and CAIRIBU-affiliated investigators. They included non-malignant prostate and lower urinary tract dysfunction; urinary tract microbes and infection; bladder function and physiology; neurourology in the lower urinary tract; and obstructions and calculi in the urinary tract. A primary objective of the CAIRIBU Interactions Core is to develop metrics for evaluating collaborative research initiatives. This requires understanding engagement within the CAIRIBU Community and whether it leads to cross-disciplinary interactions and collaborative research products and resources. The annual CAIRIBU meeting is one window through which the outcomes and direction of the CAIRIBU Community may be observed.

[Compound 48/80 increases murine bladder wall compliance independent of mast cells](#)

Saxena P, Broemer E, Herrera GM, Mingin GC, Roccabianca S, Tykocki NR

A balance between stiffness and compliance is essential to normal bladder function, and changes in the mechanical properties of the bladder wall occur in many bladder pathologies. These changes are often associated with the release of basic secretagogues that in turn drive the release of inflammatory mediators from mast cells. Mast cell

degranulation by basic secretagogues is thought to occur by activating an orphan receptor, Mas-related G protein-coupled receptor B2 (Mrgprb2). We explored the effects of the putative mast cell degranulator and Mrgprb2 agonist Compound 48/80 on urinary bladder wall mechanical compliance, smooth muscle contractility, and urodynamics, and if these effects were mast cell dependent. In wild-type mice, Mrgprb2 receptor mRNA was expressed in both the urothelium and smooth muscle layers. Intravesical instillation of Compound 48/80 decreased intermicturition interval and void volume, indicative of bladder overactivity. Compound 48/80 also increased bladder compliance while simultaneously increasing the amplitude and leading slope of transient pressure events during ex vivo filling and these effects were inhibited by the Mrgprb2 antagonist QWF. Surprisingly, all effects of Compound 48/80 persisted in mast cell-deficient mice, suggesting these effects were independent of mast cells. These findings suggest that Compound 48/80 degrades extracellular matrix and increases urinary bladder smooth muscle excitability through activation of Mrgprb2 receptors located outside of mast cells. Thus, the pharmacology and physiology of Mrgprb2 in the urinary bladder is of potential interest and importance in terms of treating lower urinary tract dysfunction.

[Current research and future directions in non-malignant urologic research - proceedings of the annual CAIRIBU meeting](#)

Popovics P, Penniston KL

The Annual Collaborating for the Advancement of Interdisciplinary Research (CAIRIBU) Meeting in 2022 highlighted basic, translational, and clinical non-malignant urology research within five main areas affecting the urinary tract: urinary dysfunction due to prostate disease, microbes and infection, bladder function and physiology, neurology and neuromuscular influences and calculi and obstruction. In this paper, we summarize main findings and future

directions outlined by CAIRIBU-affiliated scientists who presented as part of the scientific sessions.

[Mendelian Disorders in an Interstitial Cystitis/Bladder Pain Syndrome Cohort](#)

Elicia Estrella, Shira Rockowitz, Marielle Thorne, Pressley Smith, Jeanette Petit, Veronica Zehnder, Richard N Yu, Stuart Bauer, Charles Berde, Pankaj B Agrawal, Alan H Beggs, **Ali G Gharavi**, Louis Kunkel, **Catherine A Brownstein**

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder causing symptoms of urinary frequency, urgency, and bladder discomfort or pain. Although this condition affects a large population, little is known about its etiology. Genetic analyses of whole exome sequencing are performed on 109 individuals with IC/BPS. One family has a previously reported SIX5 variant (ENST00000317578.6:c.472G>A, p.Ala158Thr), consistent with Branchiootorenal syndrome 2 (BOR2). A likely pathogenic heterozygous variant in ATP2A2 (ENST00000539276.2:c.235G>A, p.Glu79Lys) is identified in two unrelated probands, indicating possible Darier-White disease. Two private heterozygous variants are identified in ATP2C1 (ENST00000393221.4:c.2358A>T, p.Glu786Asp (VUS/Likely Pathogenic) and ENST00000393221.4:c.989C>G, p.Thr330Ser (likely pathogenic)), indicative of Hailey-Hailey Disease. Sequence kernel association test analysis finds an increased burden of rare ATP2C1 variants in the IC/BPS cases versus a control cohort ($p = 0.03$, OR = 6.76), though does not survive Bonferroni correction. The data suggest that some individuals with IC/BPS may have unrecognized Mendelian syndromes. Comprehensive phenotyping and genotyping aid in understanding the range of diagnoses in the population-based IC/BPS cohort. Conversely, ATP2C1, ATP2A2, and SIX5 may be candidate genes for IC/BPS. Further evaluation with larger numbers is needed. Genetically screening individuals with IC/BPS may help diagnose and treat this painful disorder due to its heterogeneous nature.

[Optimizing reflex urine cultures: Using a population-specific approach to diagnostic stewardship](#)

Sonali D Advani, Nicholas A Turner, Kenneth E Schmader, Rebekah H Wrenn, Rebekah W Moehring, Christopher R Polage, Valerie M Vaughn, Deverick J Anderson

Clinicians and laboratories routinely use urinalysis (UA) parameters to determine whether antimicrobial treatment and/or urine cultures are needed. Yet the performance of individual UA parameters and common thresholds for action are not well defined and may vary across different patient populations. When used as a part of a diagnostic workup, UA parameters should be leveraged for their NPV instead of sensitivity. Because many laboratories and hospitals use reflex urine culture algorithms, their workflow should include clinical decision support and/or education to target symptomatic patients and focus on populations where absence of pyuria has high NPV.

[Strategies for Difficult Fluoroscopic Landmarking During Sacral Neuromodulation Lead Placement](#)

Luchristt D, **Amundsen C**

Fluoroscopic guidance is a key tool used in combination with sensory and motor testing to ensure optimal sacral neuromodulation lead placement. The objectives of this video are to briefly review bony landmarks for fluoroscopic imaging and provide strategies to overcome common obstacles during fluoroscopic mapping for sacral neuromodulation lead placement. We provide an overview of normal fluoroscopic landmarks for both AP and lateral fluoroscopic imaging during sacral neuromodulation lead placement, along with a series of 6 non-ideal examples. Strategies for overcoming barriers to identification of bony anatomy on fluoroscopy are provided in the context of these examples. While appropriate patient preparation and positioning are important to optimize fluoroscopic guidance during sacral neuromodulation lead placement, patient anatomy and other factors often obscure or distort expected anatomic landmarks. We demonstrate our approach to overcoming common fluoroscopic

obstacles and provide strategies for improvement of operative efficiency. These strategies can be combined with other intraoperative information such as tactile feedback, additional fluoroscopic views, and intraoperative complex nerve mapping to help optimize sacral neuromodulation lead placement and improve operative efficiency.

KIDNEY

[Serum myo-inositol and valine improve metabolomic-based estimated glomerular filtration rate among kidney transplant recipients](#)

Meeusen JW, Stämmeler F, Dasari S, Schiffer E, **Lieske JC**

Close monitoring of glomerular filtration rate (GFR) is essential for the management of patients post kidney transplantation. Measured GFR (mGFR), the gold standard, is not readily accessible in most centers. Furthermore, the performance of new estimated GFR (eGFR) equations based upon creatinine and/or cystatin C have not been validated in kidney transplant patients. Here we evaluate a recently published eGFR equation using cystatin C, creatinine, myo-inositol and valine as measured by nuclear magnetic resonance (eGFRNMR). Residual sera was obtained from a cohort of patients with clinically ordered iothalamate renal clearance mGFR ($n = 602$). Kidney transplant recipients accounted for 220 (37%) of participants. The 2021 CKD-EPI eGFRcr and eGFRcr-cys have similar bias, P15, and agreement while eGFRNMR more closely matched mGFR with the strongest improvement among kidney transplant recipients.

PROSTATE

[White's operation: the history of 19th century attempts to treat prostate disease with castration](#)

Nicholson TM, Best SL, **Ricke EA**, Timms BG, **Ricke WA**

To understand the roots of 19th century hormonal treatments for BPH in the career of J. William White, a prominent surgeon scientist at the University of Pennsylvania. We reviewed primary and secondary literature available in

PUBMED, the University of Pennsylvania Archives, and internet resources. In 1893, Dr. White presented a series of experiments demonstrating atrophy of the canine prostate following castration and advocated for this procedure in men suffering from prostatic hypertrophy. This approach was adopted by many of White's contemporaries. In 1895, White presented findings from 111 patients and reported improvement of urinary symptoms in three quarters of these patients. Improvements in surgical techniques for prostatectomy have predominantly eliminated castration as a clinical procedure for BPH treatment. These early experiments demonstrated the critical dependence of the prostate on testicular androgens and were the basis for subsequent hormonal therapies for BPH. In conclusion, the bold experiments of late 19th century surgeons paved the way for our contemporary understanding of the important role of sex steroid hormones in BPH.

STONES

[Application of multivariate joint modeling of longitudinal biomarkers and time-to-event data to a rare kidney stone cohort](#)

Lisa E Vaughan, **John C Lieske**, Dawn S Milliner, Phillip J Schulte

Time-dependent Cox proportional hazards regression is a popular statistical method used in kidney disease research to evaluate associations between biomarkers collected serially over time with progression to kidney failure. Typically, biomarkers of interest are considered time-dependent covariates being updated at each new measurement using last observation carried forward (LOCF). Recently, joint modeling has emerged as a flexible alternative for multivariate longitudinal and time-to-event data. This study describes and demonstrates multivariate joint modeling using as an example the association of serial biomarkers (plasma oxalate [POX] and urinary oxalate [UOX]) and kidney function among patients with primary hyperoxaluria in the Rare Kidney Stone Consortium Registry. Multivariate joint modeling is more flexible than LOCF

and may better reflect biological plausibility since biomarkers are not steady-state values between measurements. While LOCF is preferred to naïve methods not accounting for changes in biomarkers over time, results may not accurately reflect flexible relationships that can be captured with multivariate joint modeling.

[Dietary Assessment of Lithogenic Factors in Plant-Based Meat Products](#)

Christine W Liaw, Aaron M Potretzke, Jared S Winoker, Brian R Matlaga, **John C Lieske**, Kevin Koo

Patients who form kidney stones are typically advised to limit intake of nondairy animal protein. Plant-based meat products may be a processed substitute protein source for these patients and have recently gained popularity because of health concerns, increased retail availability, decreased environmental impact, and meat supply shortages during the COVID-19 pandemic. Despite these perceived benefits and tangential association with whole food plant-based diets, the potential lithogenic risks associated with these products are not well characterized. Most plant-based meat products consist of protein sources that are, relative to animal protein sources, higher in oxalate, sodium, and calcium. Stone-forming patients should be counseled about the potential lithogenic risk of these processed products.

[Maternal family history of urolithiasis is associated with earlier age of onset of stone disease](#)

Rei Unno, Kazumi Taguchi, Gregory Hosier, Manint Usawachintachit, Wilson Sui, Heiko Yang, Fadl Hamouche, **David Bayne**, Marshall Stoller, **Thomas Chi**

To evaluate the impact of detailed family history on the severity of disease and age of onset in patients with urolithiasis. Any family history of kidney stone disease imparts an increased risk of recurrent stone event and an earlier age of onset for urolithiasis. The presence of both first- and second-degree relatives or a maternal-side relative with kidney stones may be a predictor for an earlier age of onset for urolithiasis.

[Pulse-modulated Holmium:YAG Laser vs the Thulium Fiber Laser for Renal and Ureteral Stones: A Single-center Prospective Randomized Clinical Trial](#)

Haas CR, Knoedler MA, Li S, Gralnek DR, Best SL, **Penniston KL**, Nakada SY

We sought to compare the clinical effectiveness of the pulse-modulated Ho:YAG (holmium:yttrium-aluminum-garnet) laser and the thulium laser fiber for ureteroscopic stone management in a randomized clinical trial. The primary outcome was the ureteroscope time required to adequately fragment stones to 1 mm or less. Secondary outcomes were stone-free rate, complications, subjective surgeon measurement of laser performance, patient related stone quality of life outcomes, and measurements of laser efficiency. An Institutional Review Board-approved randomized clinical trial was conducted to randomize patients to outpatient treatment with either the Moses 2.0 or thulium laser fiber in a 1:1 manner after stratification into groups based on the maximal diameter of treated stone (3-9.9 mm or 10-20 mm). Patient, stone, and operative parameters were compared using the appropriate categorical/continuous and parametric/nonparametric statistical tests (SPSS 25). This randomized clinical trial suggests no significant clinical advantage of one laser technology over the other. Surgeon and institutional preference are the best approach when selecting one or the other.

[PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2](#)

Michelle A Baum, Craig Langman, Pierre Cochat, **John C Lieske**, Shabbir H Moochhala, Shuzo Hamamoto, Hiroyuki Satoh, Chebl Mourani, Gema Ariceta, Armando Torres, Martin Wolley, Vladimir Belostotsky, Thomas A Forbes, Jaap Grothoff, Wesley Hayes, Burkhard Tönshoff, Tatsuya Takayama, Ralf Rosskamp, Kerry Russell, Jing Zhou, Aniruddha Amrite, Bernd Hoppe; PHYOX2 study investigators

Nedosiran is an investigational RNA interference agent designed to inhibit expression of hepatic lactate dehydrogenase, the enzyme thought responsible for the terminal step of oxalate synthesis. Oxalate

overproduction is the hallmark of all genetic subtypes of primary hyperoxaluria (PH). In this double-blind, placebo-controlled study, we randomly assigned (2:1) 35 participants with PH1 (n = 29) or PH2 (n = 6) with eGFR \geq 30 mL/min/1.73 m² to subcutaneous nedosiran or placebo once monthly for 6 months. The area under the curve (AUC) of percent reduction from baseline in 24-hour urinary oxalate (Uox) excretion (primary endpoint), between day 90-180, was significantly greater with nedosiran vs placebo (least squares mean [SE], +3507 [788] vs -1664 [1190], respectively; difference, 5172; 95% CI 2929-7414; P < 0.001). A greater proportion of participants receiving nedosiran vs placebo achieved normal or near-normal (<0.60 mmol/24 hours; <1.3 \times ULN) Uox excretion on \geq 2 consecutive visits starting at day 90 (50% vs 0; P = 0.002); this effect was mirrored in the nedosiran-treated PH1 subgroup (64.7% vs 0; P < 0.001). The PH1 subgroup maintained a sustained Uox reduction while on nedosiran, whereas no consistent effect was seen in the PH2 subgroup. Nedosiran-treated participants with PH1 also showed a significant reduction in plasma oxalate versus placebo (P = 0.017). Nedosiran was generally safe and well tolerated. In the nedosiran arm, the incidence of injection-site reactions was 9% (all mild and self-limiting). In conclusion, participants with PH1 receiving nedosiran had clinically meaningful reductions in Uox, the mediator of kidney damage in PH.

Risk Factors for Increased Stent-Associated Symptoms Following Ureteroscopy for Urinary Stones: Results from STENTS

Harper JD, Desai AC, Maalouf NM, Yang H, Antonelli JA, Tasian GE, Lai HH, Reese PP, Curatolo M, Kirkali Z, Al-Khalidi HR, Wessells H, Scales CD
The STudy to Enhance uNderstanding of sTent-associated Symptoms (STENTS) sought to identify risk factors for pain and urinary symptoms, as well as how these symptoms interfere with daily activities after ureteroscopy for stone treatment. This prospective observational cohort study enrolled patients aged \geq 12 years undergoing

ureteroscopy with ureteral stent for stone treatment at 4 clinical centers. Participants reported symptoms at baseline; on postoperative days (POD) 1, 3, 5; at stent removal; and day 30 post-stent removal. Outcomes of pain intensity, pain interference, urinary symptoms, and bother were captured with multiple instruments. Multivariable analyses using mixed-effects linear regression models were identified characteristics associated with increased stent-associated symptoms (SAS). In this multicenter cohort, interference persisted even as pain intensity decreased. Patient factors (e.g., age, depression) rather than surgical factors were associated with symptom intensity. These findings provide a foundation for patient-centered care and highlight potential targets for efforts to mitigate the burden of SAS.

PATIENT-CENTERED RESEARCH

Associations Between Urological Chronic Pelvic Pain Syndrome Symptom Flares, Illness Impact, and Health Care Seeking Activity: Findings From the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Symptom Patterns Study

Sutcliffe S, Newcomb C, Bradley CS, Clemens JQ, Erickson B, Gupta P, Lai HH, Naliboff B, Strachan E, Stephens-Shields A

Most studies on interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome use typical or average levels of pelvic pain or urological symptom intensity as their outcome, as both are associated with reduced quality of life. Symptom exacerbations or "flares" have also been found to be associated with reduced quality of life, but no studies, to our knowledge, have investigated whether these associations are independent of typical pelvic pain levels and thus might be useful additional outcome measures (or stated differently, whether reducing flare frequency even without reducing mean pain intensity may be important to patients). We used screening visit and weekly run-in period data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Symptom Patterns Study to investigate

associations between flare frequency and multiple measures of illness impact and health care seeking activity, independent of typical nonflare and overall pelvic pain levels. Our findings suggest that flare frequency and possibly other flare characteristics may be worth considering as additional outcome measures in urological chronic pelvic pain syndrome research to support the development of new preventive and therapeutic flare strategies.

- Jennifer Allmaras MPH, Muen Wang,
1/30/2023

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