

**BLADDER**[In utero and lactational PCB exposure drives anatomic changes in the juvenile mouse bladder](#)

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Bladder dysfunction risk factors are not completely understood, and the influence of exposure to environmental chemicals, especially during development, on the formation and function of the bladder is understudied. Environmental contaminants such as polychlorinated biphenyls (PCBs) are known to pose a risk to the developing brain; however, their influence on the development of peripheral target organs, such as bladder, are unknown. To address this data gap, C57Bl/6J mouse dams were exposed to an environmentally-relevant PCB mixture at 0, 0.1, 1 or 6 mg/kg daily beginning two weeks prior to mating and continuing through gestation and lactation. Bladders were collected from offspring at postnatal days (P) 28-31. PCB concentrations were detected in bladders in a dose-dependent manner. PCB effects on the bladder were sex- and dose-dependent. Overall, PCB effects were observed in male, but not female, bladders. PCBs increased bladder volume and suburothelial  $\beta$ III-tubulin-positive nerve density compared to vehicle control. A subset of these nerves were sensory peptidergic axons indicated by increased calcitonin gene-related protein (CGRP) positive nerve fibers in mice exposed to the highest PCB dose compared to the lowest PCB dose. PCB-induced increased nerve density was also positively correlated with the number of mast cells in the bladder, suggesting inflammation may be involved. There were no detectable changes in epithelial composition or apoptosis as indicated by expression of cleaved caspase 3, suggesting PCBs do not cause overt toxicity. Bladder volume changes were not accompanied by changes in bladder mass or epithelial thickness, indicating that obstruction was not likely involved.

[Predictive accuracy of prenatal ultrasound findings for lower urinary tract obstruction: A systematic review and Bayesian meta-analysis](#)

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The objective of this systematic review and meta-analysis was to identify the diagnostic accuracy of ultrasound markers for LUTO. We performed a systematic literature review of studies reporting on fetuses with hydronephrosis or a prenatally suspected and/or postnatally confirmed diagnosis of LUTO. A total of 36,189 studies were identified; 636 studies were available for full text review and a total of 42 studies were included in the Bayesian meta-analysis. Among the ultrasound signs assessed, megacystis (DOR 49.15, [15.28, 177.44]), bilateral hydronephrosis (DOR 41.33, [13.36, 164.83]), bladder thickening (DOR 13.73, [1.23, 115.20]), bilateral hydronephrosis (DOR 8.36 [3.17, 21.91]), male sex (DOR 8.08 [3.05, 22.82]), oligo- or anhydramnios (DOR 7.75 [4.23, 14.46]), and urinoma (DOR 7.47 [1.14, 33.18]) were found to be predictive of LUTO (Table 1). The predictive sensitivities and specificities however are low and wide study heterogeneity existed. Classically, LUTO is suspected in the presence of prenatally detected megacystis with a dilated posterior urethra (i.e., the keyhole sign), and bilateral hydronephrosis. However, keyhole sign has been found to have modest diagnostic performance in predicting the presence of LUTO in the literature which we confirmed in our analysis. The surprisingly low specificity may be influenced by several factors, including the degree of obstruction, and the diligence of the sonographer at searching for and documenting it during the scan. As a result, providers should consider this when establishing the differential for a fetus with hydronephrosis as the presence or absence of keyhole sign does not reliably rule in or rule out LUTO.

[A NEW approach for characterizing mouse urinary pathophysiologies](#)

**Hannah M Ruetten**, Gervaise H Henry, **Teresa T Liu**, Heidi M Spratt, **William A Ricke**, **Douglas W Strand**, **Chad M Vezina**

The void spot assay (VSA) is a cost-effective method for evaluating and quantifying mouse urinary voiding phenotypes. The VSA has been used to differentiate voiding behaviors between experimental groups, but not as a diagnostic assay. To build toward this goal, we used the VSA to define voiding patterns of male mice with diabetic diuresis (BTBR.Cg-Lepob/WiscJ mice), irritative urinary dysfunction (E. coli UTI89 urinary tract infection), and obstructive urinary dysfunction (testosterone and estradiol slow-release implants) compared to their respective controls. Many studies compare individual VSA endpoints (urine spot size, quantity, or distribution) between experimental groups. Here, we consider all endpoints collectively to establish VSA phenomes of mice with three different etiologies of voiding dysfunction. We created an approach called normalized endpoint work through (NEW) to normalize VSA outputs to control mice, and then applied principal components analysis and hierarchical clustering to 12 equally weighted, normalized, scaled, and zero-centered VSA outcomes collected from each mouse (the VSA phenome). This approach accurately classifies mice based on voiding dysfunction etiology. We used principal components analysis and hierarchical clustering to show that some aged mice (>24 months old) develop an obstructive or a diabetic diuresis VSA phenotype while others develop a unique phenotype that does not cluster with that of diabetic, infected, or obstructed mice. These findings support use of the VSA to identify specific urinary phenotypes in mice and the continued use of aged mice as they develop urinary dysfunction representative of the various etiologies of LUTS in men.

## [Hip and Pelvic Floor Muscle Strength in Women with and without Urgency and Frequency Predominant Lower Urinary Tract Symptoms](#)

Stefanie N Foster, Theresa M Spitznagle, Lori J Tuttle, Siobhan Sutcliffe, Karen Steger-May, **Jerry L Lowder**, Melanie R Meister, Chiara Ghetti, Jinli Wang, Michael J Mueller, Marcie Harris-Hayes

Urgency and frequency are common lower urinary tract symptoms (UF-LUTS) in women. There is limited evidence to guide physical therapist-led treatment. The study compared hip and pelvic floor muscle strength between women with and without UF-LUTS. We hypothesized women with UF-LUTS would demonstrate 1) diminished hip external rotator and abductor strength and 2) equivalent pelvic floor strength and diminished endurance compared to controls. Women with UF-LUTS (cases) and controls were matched on age, body mass index (BMI), vaginal parity. Examiner measured participants' 1) hip external rotator and abductor strength via dynamometry (maximum voluntary effort against fixed resistance) and 2) pelvic floor muscle strength (peak squeeze pressure) and endurance (squeeze pressure over a 10 second hold) via vaginal manometry. Values compared between cases and controls with paired-sample t-tests (hip) or Wilcoxon signed rank tests (pelvic floor). 21 pairs (42 women): Hip external rotation ( $67.0 \pm 19.0$  N vs  $83.6 \pm 21.5$  N;  $P=0.005$ ) and hip abduction strength ( $163.1 \pm 48.1$  N vs  $190.1 \pm 53.1$  N;  $P=0.04$ ) were significantly lower in cases than controls. There was no significant difference in pelvic floor strength ( $36.8 \pm 19.9$  cmH<sub>2</sub>O vs  $41.8 \pm 21.0$  cmH<sub>2</sub>O;  $P=0.40$ ) or endurance ( $234.0 \pm 149.6$  cmH<sub>2</sub>O\*seconds vs  $273.4 \pm 149.1$  cmH<sub>2</sub>O\*seconds;  $P=0.24$ ). Women with UF-LUTS had weaker hip external rotator and abductor muscles, but similar pelvic floor strength and endurance compared to controls. Hip strength may be important to assess in patients with UF-LUTS, further research is needed.

## STONES

### [Effect of stone composition on surgical stone recurrence: single center longitudinal analysis](#)

Shuang Li, Viacheslav Iremashvili, Simone L Vernez, **Kristina L Penniston**, R Allan Jhagroo, Sara L Best, Sean P Hedican, Stephen Y Nakada

The objective of this study was to explore the association between urinary stone composition and surgical recurrence. Patients who underwent kidney stone surgeries (between 2009-2017), were followed for > 1 year, and had  $\geq 1$  stone composition analyses were included in our analysis. Surgical stone recurrence (repeat surgery) was defined as the second surgery on the same kidney unit. Recurrence-free survival analysis was used. A total number of 1051 patients were included (52.7% men, average age  $59.1 \pm 15.1$  years). Over 4.7 +/- 2.5 years follow up, 26.7% of patients required repeat surgery. Patients' stone compositions were calcium oxalate (66.0%), uric acid (12.2%), struvite (10.0%), brushite (5.7%), apatite (5.1%) and cystine (1.0%). Results suggested that patients with cystine stones had the highest surgical recurrence risk; brushite had the second-highest surgical recurrence risk. Struvite, uric acid, and apatite stones were at higher risk compared with calcium oxalate stones (lowest risk in our cohort). When pre and postoperative stone size was controlled, patients with a history of uric acid, brushite, and cystine stones were at higher surgical risk. After controlling clinical and demographic factors, only brushite and cystine stones were associated with higher surgical recurrence.

### [Disparities in Kidney Stone Disease: A Scoping Review](#)

Joseph J Crivelli, Naim M Maalouf, Henry J Paiste, Kyle D Wood, Amy E Hughes, Gabriela R Oates, Dean G Assimos

This study reviewed the available evidence regarding health disparities in kidney stone disease to identify knowledge gaps in this area. A literature search was conducted using PubMed®, Embase® and Scopus® limited to articles published in English from 1971 to 2020. Articles were selected based on their relevance to disparities in kidney stone disease among adults in the United States. Several large epidemiological

studies suggest disproportionate increases in incidence and prevalence of kidney stone disease among women as well as Black and Hispanic individuals in the United States, whereas other studies of comparable size do not report racial and ethnic demographics. Numerous articles describe disparities in imaging utilization, metabolic workup completion, analgesia, surgical intervention, stone burden at presentation, surgical complications, followup, and quality of life based on race, ethnicity, socioeconomic status and place of residence. Differences in urinary parameters based on race, ethnicity and socioeconomic status may be explained by both dietary and physiological factors. All articles assessed had substantial risk of selection bias and confounding. Health disparities are present in many aspects of kidney stone disease. Further research should focus not only on characterization of these disparities but also on interventions to reduce or eliminate them.

### [Meta-analysis of Clinical Microbiome Studies in Urolithiasis Reveal Age, Stone Composition, and Study Location as the Predominant Factors in Urolithiasis-Associated Microbiome Composition](#)

Naveen Kachroo, Dirk Lange, **Kristina L Penniston**, Joshua Stern, **Gregory Tasian**, Petar Bajic, Alan J Wolfe, Mangesh Suryavanshi, Andrea Ticinesi, Tiziana Meschi, Manoj Monga, Aaron W Miller

To determine whether functionally relevant questions associated with the urinary or gut microbiome and urinary stone disease (USD) can be answered from metagenome-wide association studies (MWAS), we performed the most comprehensive meta-analysis of published clinical MWAS in USD to date, using publicly available data published prior to April 2021. Six relevant studies met inclusion criteria. For alpha-diversity, significant differences were noted between USD status, stone composition, sample type, study location, age, diet, and sex. For beta-diversity, significant differences were noted by USD status, stone composition, sample type, study location, antibiotic use (30 days and 12 months before sampling), sex, hypertension, water intake, body habitus, and age. *Prevotella* and *Lactobacillus* in the gut and urinary

tract, respectively, were associated with healthy individuals, while Enterobacteriaceae was associated with USD in the urine and stones. Paradoxically, other Prevotella strains were also strongly associated with USD in the gut microbiome. When data were analyzed together, USD status, stone composition, age group, and study location were the predominant factors associated with microbiome composition. Meta-analysis showed significant microbiome differences based on USD status, stone composition, age group or study location. However, analyses were limited by a lack of public data from published studies, metadata collected, and differing study protocols. Results highlight the need for field-specific standardization of experimental protocols in terms of sample collection procedures and the anatomical niches to assess, as well as in defining clinically relevant metadata and subphenotypes such as stone composition.

### [Prevention of Urinary Stones With Hydration \(PUSH\): Design and Rationale of a Clinical Trial](#)

Charles D Scales Jr, Alana C Desai, Jonathan D Harper, H Henry Lai, **Naim M Maalouf**, Peter P Reese, **Gregory E Tasian**, Hussein R Al-Khalidi, Ziya Kirkali, Hunter Wessells, Urinary Stone Disease Research Network

Although maintaining high fluid intake is an effective low-risk intervention for the secondary prevention of urinary stone disease, many patients with stones do not increase their fluid intake. We describe the rationale and design of the Prevention of Urinary Stones With Hydration (PUSH) Study, a randomized trial of a multicomponent behavioral intervention program to increase and maintain high fluid intake. Participants are randomly assigned (1:1 ratio) to the

intervention or control arm. The target sample size is 1,642 participants. Adults and adolescents 12 years and older with a symptomatic stone history and low urine volume are eligible. Exclusion criteria include infectious or monogenic causes of urinary stone disease and comorbid conditions precluding increased fluid intake. All participants receive usual care and a smart water bottle with smartphone application. Participants in the intervention arm receive a fluid intake prescription and an adaptive program of behavioral interventions, including financial incentives, structured problem solving, and other automated adherence interventions. Control arm participants receive guideline-based fluid instructions. The primary end point is recurrence of a symptomatic stone during 24 months of follow-up. Secondary end points include changes in radiographic stone burden, 24-hour urine output, and urinary symptoms.

### ERECTILE DYSFUNCTION

#### [Topically delivered nitric oxide acts synergistically with an orally administered PDE5 inhibitor in eliciting an erectile response in a rat model of radical prostatectomy](#)

**Moses T Tar**, **Joel M Friedman**, Andrew Draganski, **Kelvin P Davies**

Patients undergoing radical prostatectomy (RP) have a high incidence of postoperative erectile dysfunction (ED) refractory to treatment by oral phosphodiesterase-5 inhibitors (PDE5i). In the present studies, we investigated if a topically applied, nitric oxide microparticle delivery system (NO-MP) might act synergistically with an oral PDE5i (sildenafil) to improve erectile function outcomes in a rat model of RP.

Thirty-five Sprague-Dawley rats underwent bilateral transection of the cavernous nerve (CN) for 1 week. After 1 week, animals were orally administered 0, 0.05, or 0.005 mg sildenafil/kg and the erectile response following topical application to the penile shaft of 250 or 100 mg NO-MP, or blank-MP, was monitored over a 2-h timeframe by recording the intracorporal pressure normalized to systemic blood pressure (ICP/BP, N=5 animals/treatment group). Oral treatment with sildenafil by itself resulted in no observable erectile response. However, a combination of orally administered 0.05 sildenafil/kg with topical application of 250 mg NO-MP, compared to 250 mg NO-MP by itself, resulted in significantly more spontaneous erections (4.6 compared to 2 erections per hour, t-test; p value = 0.043), with a significantly faster onset for the first erectile response (11 compared to 22 min; t-test, p value = 0.041). Our results demonstrate a synergistic effect between orally administered PDE5i and topically applied NO-MP in eliciting an erectile response. Furthermore, they suggest a potential novel therapeutic approach to treat men with ED resulting from RP, through combination therapy of a topically applied NO-MP and an orally administered PDE5i.

- Jennifer Allmaras, MPH, 8/25/2021

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