

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization focused on interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
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RESEARCH UPDATE - SEPTEMBER 2022

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS, BLADDER PAIN SYNDROME, HUNNER LESION, HYPERSENSITIVE BLADDER, CHRONIC (PELVIC) PAIN, KETAMINE CYSTITIS, URINARY TRACT INFECTION AND ASSOCIATED DISORDERS

Most of these have a direct link to the PubMed abstract if you click on the title. An increasing number of scientific articles "In Press" or "Early View" are being published early online (on the Journal website) as "Epub ahead of print" sometimes long before they are published in the journals. While abstracts are usually available on PubMed, the pre-publication articles can only be read online if you have online access to that specific journal. However, in some cases there may be [free access](#) to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of free access.

Terminology: different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, (primary) bladder pain syndrome, hypersensitive bladder, chronic pelvic pain (syndrome) or combinations of these. Hunner's ulcer, Hunner lesion, Hunner IC and Classic IC are synonymous. When reviewing the article, we use the terminology used by the authors.

IC/BPS AND COVID 19

[500 EFFECTS OF COVID-19 PANDEMICS ON SYMPTOMS AND QUALITY OF LIFE IN PATIENTS AFFECTED BY INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME \(IC/PBS\) AND IRRITABLE BOWEL SYNDROME \(IBS\)](#)

M Marturano, G Campagna, E Gaetani, F Natale, S Mastrovito, L Vacca, G Panico, D Caramazza, P Troisi, A Lombisani, G Scambia, A Ercoli. *Continence (Amst)*. 2022 Jun;2:1-2. doi: 10.1016/j.cont.2022.100451. Epub 2022 Jul 8. PMID: 35822129 PMCID: PMC9263121 DOI: 10.1016/j.cont.2022.100451

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Interstitial Cystitis (IC), also known as Painful Bladder Syndrome (BPS), is a chronic painful bladder condition characterized by persistent unpleasant sensations attributable to the bladder, of which the most consistent feature is an increase in discomfort with bladder filling and a relief with voiding. IC/PBS often coexists with other chronic pain syndromes such as irritable bowel syndrome (IBS). IBS is a chronic functional disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits. Both IC/BPS and IBS do not have a certain aetiology and are characterized by chronic relapsing course. There is a positive correlation between the incidence of this association and increased healthcare seeking, reduction in quality of life, and higher levels of mood disorders, which suggests a common underlying pathophysiology. Furthermore, exacerbations of IBS and IC/BPS symptoms have been associated to acute stressful life events. Those determine a high prevalence of anxiety, depression and stress, chronic reduction in coping capacity and endurance of pain and fatigue. The COVID-19 pandemic has led to unprecedented disruptions in healthcare. During the first months of the pandemic, mental health was influenced by various vulnerability factors and stressors, led alone in patients affected by chronic diseases such as IC/BPS and IBS. One of the most evident psychological consequences of Coronavirus was the deterioration of quality of life of those patients, as their daily life is dominated by management of sphincter functions and pain. The aim of this study from Italy was to observe the changes that the Covid19 lockdown brought in terms of symptoms and quality of life.

STATPEARLS [INTERNET].

[INTERSTITIAL CYSTITIS](#)

Yizhe Lim, Seanan O'Rourke. In: *StatPearls [Internet]. Free Books & Documents. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2022 Apr 14. PMID: 34033350 Bookshelf ID: NBK570588*

Interstitial cystitis is a condition that affects the urinary bladder, characterized by chronic inflammation. It is not secondary to an infection. In many cases, because it remains a diagnosis of exclusion, the condition is often diagnosed late in the patient's journey. Patients often describe pain in the bladder region (suprapubic), with a strong sensation to want to urinate (urgency). This sensation is worsened by filling the bladder and is often relieved by passing urine more often (frequency). This may be during the daytime and/or during the night (nocturia). There may also be other symptoms such as pain or discomfort on passing urine (dysuria) and pain or discomfort during sexual intercourse, known as dyspareunia. Due to these symptoms, there is a profound impact on the emotional, psychological and social well-being of the patient.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: BASIC SCIENCE, DIAGNOSIS AND TREATMENT

IS PELVIC FLOOR MUSCLE TENDERNESS A DISTINCT UROLOGIC CHRONIC PELVIC PAIN SYNDROME PHENOTYPE? FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK SYMPTOM PATTERN STUDY

Priyanka Gupta, Robert Gallop, Theresa Spitznagle, Henry Lai, Frank Tu, John N Krieger, J Quentin Clemens, Catherine S Bradley, Claire Yang, Siobhan Sutcliffe, Robert Moldwin, Karl Kreder, Jason Kutch, Larissa V Rodriguez. J Urol. 2022 Aug;208(2):341-349. doi: 10.1097/JU.0000000000002679. Epub 2022 Mar 28. PMID: 35344391 DOI: 10.1097/JU.0000000000002679

Of women with interstitial cystitis/bladder pain syndrome and men with chronic prostatitis/chronic pelvic pain syndrome 85% have concomitant pelvic floor muscle tenderness (PFT). The significance of this finding is incompletely understood. This USA study examines PFT among participants in the MAPP (Multidisciplinary Approach to the Study of Chronic Pelvic Pain) Research Network and its relationship with urologic chronic pelvic pain syndrome (UCPPS) symptom severity in order to determine whether this is a phenotypic predictor in UCPPS. Participants in the MAPP Network Symptom Patterns Study underwent a standardized pelvic examination (PEX). Trained examiners palpated 6 locations evaluating the pelvic musculature for PFT. Participants were assigned a 0 to 6 PEX score based on the number of areas with tenderness on PEX. Using regression tree models, PEX scores were divided into low (0, 1), mid (2, 3, 4, 5) and high (6). The relationship between PFT and UCPPS symptoms was examined using several validated questionnaires. The study cohort consisted of 562 UCCPS participants (375 females and 187 males) and 69 controls. Diagnoses included interstitial cystitis/bladder pain syndrome (397), chronic prostatitis/chronic pelvic pain syndrome (122), both (34) or no diagnosis (9). Of UCCPS participants 81% had PFT on PEX compared to 9% of controls: 107 (19%) low, 312 (56%) mid and 143 (25%) high. Participants with higher PFT scores had more severe disease burden (worse pelvic pain and urinary symptoms), worse quality of life and more widespread distribution of nonpelvic pain. It was concluded that UCCPS patients with more widespread PFT have severe pain and urinary symptoms, worse quality of life and a more centralized pain phenotype.

SAFETY OF HUMAN EMBRYONIC STEM CELL-DERIVED MESENCHYMAL STEM CELLS FOR TREATING INTERSTITIAL CYSTITIS: A PHASE I STUDY

Jung Hyun Shin, Chae-Min Ryu, Hwan Yeul Yu, Juhyun Park, Ah Reum Kang, Jeong Min Shin, Ki-Sung Hong, Eun Young Kim, Hyung-Min Chung, Dong-Myung Shin, Myung-Soo Choo. Stem Cells Transl Med. 2022 Sep 7;szac065. doi: 10.1093/stcltm/szac065. Online ahead of print. PMID: 36069837.

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There are still no definite treatment modalities for interstitial cystitis (IC). Meanwhile, stem cell therapy is rising as potential alternative for various chronic diseases. This study from Korea aimed to investigate the safety of the clinical-grade mesenchymal stem cells (MSCs) derived from human embryonic stem cells (hESCs), code name MR-MC-01 (SNU42-MMSCs), in IC patients. Three female IC patients with (1) symptom duration >6 months, (2) visual pain analog scale (VAS) ≥ 4 , and (3) one or two Hunner lesions <2 cm in-office cystoscopy within 1 month were included. Under general anesthesia, participants received cystoscopic submucosal injection of SNU42-MMSCs (2.0 \times 10⁷/5 mL) at the center or margin of Hunner lesions and other parts of the bladder wall except trigone with each injection volume of 1 mL. Follow-up was 1, 3, 6, 9, and 12 months postoperatively. Patients underwent scheduled follow-ups, and symptoms were evaluated with validated questionnaires at each visit. No SNU42-MMSCs-related adverse events including immune reaction and abnormalities on laboratory tests and image examinations were reported up to 12-month follow-up. VAS pain was temporarily improved in all subjects. No de novo Hunner lesions were observed and one lesion of the first subject was not identifiable on 12-month cystoscopy. This study reports the first clinical application of transurethral hESC-derived MSC injection in three patients with IC. hESC-based therapeutics was safe and

proved to have potential therapeutic efficacy in IC patients. Stem cell therapy could be a potential therapeutic option for treating IC.

[BRUTON TYROSINE KINASE \(BTK\) MAY BE A POTENTIAL THERAPEUTIC TARGET FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Guang Wang, Tong-Xin Yang, Jiong-Ming Li, Zi-Ye Huang, Wen-Bo Yang, Pei Li, Da-Lin He. *Aging (Albany NY)*. 2022 Sep 5;14(undefiend). doi: 10.18632/aging.204271. Online ahead of print. PMID: 36069808

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The aim of this study from China was to determine the potential diagnostic and therapeutic targets of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). The authors selected the GSE11783, GSE57560 and GSE621 datasets from the GEO database and merged them. R software was used to screen differentially expressed genes (DEGs) between IC/BPS and normal bladder tissues. The "String" online tool is used to analyze DEGs interaction and functional protein enrichment. CIBERSORT online tool was used to analyze the infiltration of immune cells. In addition, they verified the function of BTK in IC/BPS at the clinical samples and cells level. Bioinformatics analysis revealed that 5 genes were significantly overexpressed in IC/BPS, and the protein-protein interaction diagram showed that BTK was a critical link between these five proteins. At the same time, functional enrichment showed that they were significantly related to innate immunity. Immunoinfiltration showed that mast cell resting in IC/BPS was significantly higher. IHC staining of clinical samples showed that the mast cell markers Tryptase and BTK were highly expressed in IC/BPS tissues. At the cell level, knockdown of BTK inhibited proliferation, migration, invasion, and degranulation of mast cells. This study provides a new perspective for understanding the molecular mechanisms involved in IC/BPS and suggests that BTK may be a target for treating IC/BPS.

[THE DOUBLE INSULT OF NEONATAL CYSTITIS PLUS ADULT SOMATIC INFLAMMATION RESULTS IN CORTICOTROPIN RELEASING FACTOR TYPE 2 RECEPTOR-DEPENDENT BLADDER HYPERSENSITIVITY IN FEMALE RATS](#)

Timothy J Ness, Cary DeWitte, Alan Randich. *J Pain*. 2022 Sep 8;S1526-5900(22)00388-1. doi: 10.1016/j.jpain.2022.08.005. Online ahead of print. PMID: 36089237.

The spinal mechanisms of visceral hypersensitivity are poorly understood, particularly when there is an interaction with somatic systems. Recently the authors from the USA demonstrated that rats which were pretreated with neonatal bladder inflammation (NBI) and subsequently pretreated as adults with bladder re-inflammation had augmented reflex and neuronal responses to urinary bladder distension via a corticotropin-releasing factor receptor type 2 (CRFR2) mechanism. Another insult producing similar augmented responses is somatic inflammation induced by Complete Freund's Adjuvant (CFA) in the hindlimb. Using neurochemical measures and both reflex and neuronal responses to urinary bladder distension as endpoints, the present study probed the role of CRFR2-related mechanisms in bladder hyperalgesia secondary to NBI and CFA-induced hindlimb inflammation. ELISA measures of the lumbosacral spinal cord demonstrated increased CRFR2 protein following pretreatment with NBI+CFA. Intrathecal CRFR2 antagonists blocked the augmentation of visceromotor responses to distension following pretreatment with both NBI+CFA. Lumbosacral dorsal horn neuronal responses to bladder distension in rats pretreated with NBI+CFA were attenuated by the spinal topical administration of a CRFR2 antagonist. These findings are the first demonstration of a somatovisceral interaction working via CRFR2 receptors and support the therapeutic value of these agents in the treatment of painful bladder disorders, particularly when triggered by somatic events. Bladder hypersensitivity occurs following neonatal cystitis and an adult insult such as somatic inflammation. This paper demonstrates that CRFR2-related mechanisms are associated with this hypersensitivity. This supports the therapeutic value of these agents in the treatment of painful bladder disorders, particularly when triggered by somatic events.

[CULTURED VERSUS FRESHLY ISOLATED ADIPOSE-DERIVED STEM CELLS IN IMPROVEMENT OF THE HISTOPATHOLOGICAL OUTCOMES IN HCL-INDUCED CYSTITIS IN A RAT MODEL](#)

Hanan Hendawy, Elsayed Metwally, Ahmed Elfadadny, Tomohiko Yoshida, Danfu Ma, Kazumi Shimada, Lina Hamabe, Kenta Sasaki, Ryou Tanaka. *Biomed Pharmacother*. 2022 Sep;153:113422. doi: 10.1016/j.biopha.2022.113422. Epub 2022 Jul 19. PMID: 36076544

Interstitial cystitis (IC) is an incurable chronic disease. The etiology of IC is unclear, and no effective therapies have been established. In this study from Egypt and Japan, using a hydrogen chloride (HCL)-induced IC in a rat model, the therapeutic potency of stromal vascular fraction (SVF) and Adipose-derived stem cells (ADSCs) was studied. Thirty-six female Sprague Dawley rats were divided into four groups: the sham, HCL, (HCL+SVF) group, and (HCL+ADSCs) group (9 for each). Cystitis was induced by transurethral instillation of HCL, while PBS was

used for the sham group. A single dose of SVF or ADSCs was injected into the submucosa of the rat bladder in HCL-induced IC groups. The bladder tissues were analyzed for Toluidine Blue, Masson Trichrome, CD3, and CD34 to evaluate mast cell activation, fibrosis, inflammatory cells, and bladder regeneration, respectively. Compared to HCL-induced IC, SVF or ADSCs injection into IC bladder dramatically decreased mast cell infiltration, T-cell activation, and fibrosis. Taken together, administration of SVF cells or cultured ADSCs improves the histopathological outcomes of HCL-induced bladder injury in a time-dependent manner. Of note, SVF injection into the bladder submucosa was estimated to have the most potent therapeutic efficacy and may represent an essential component in future clinical applications.

[URINARY EXTRACELLULAR VESICLE MICRORNA PROFILING FOR DETECTION IN PATIENTS WITH INTERSTITIAL CYSTITIS](#)

Fumihiko Urabe, Akira Furuta, Taro Igarashi, Yasuyuki Suzuki, Shin Egawa, Takahiro Kimura. Transl Androl Urol. 2022 Jul;11(7):1063-1066. doi: 10.21037/tau-22-240. PMID: 35958900.

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Interstitial cystitis (IC) is characterized by pelvic pain, pressure, or discomfort related to the urinary bladder, often accompanied by urinary urgency or frequency and relieved by voiding. However, diagnosis varies widely depending on the urologist's experience. The identification of a novel objective biomarker for IC could greatly improve diagnostic consistency and expedite timely intervention where needed. Recently, liquid biopsy using microRNA (miRNA) in biofluids shows promise for early cancer detection. miRNAs are small noncoding RNAs consisting of about 20 nucleotides. They can be stably present in extracellular vesicles (EVs), and the profiles of miRNA expression in EVs make them good candidates for improving the diagnosis of a variety of diseases. This paper from Japan describes the authors' comprehensive analysis of the urinary EV miRNA expression profile and evaluates its potential as a novel biomarker in IC/BPS patients.

[URODYNAMIC AND HISTOLOGICAL EVALUATION OF CYCLOPHOSPHAMIDE-INDUCED BLADDER PAIN SYNDROME IN SD RATS](#) [Article in Chinese]

L Zhu, W Y Zhang, K X Xu. Beijing Da Xue Xue Bao Yi Xue Ban. 2022 Aug 18;54(4):735-740. doi: 10.19723/j.issn.1671-167X.2022.04.024. PMID: 35950400.

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The purpose of this study from China was to establish a model of bladder pain syndrome in SD rats by cyclophosphamide intraperitoneal injection, to evaluate the effectiveness of the model from the urodynamic and histological levels, to lay a zoological foundation for the clinical study of bladder pain syndrome, and to further guide clinical treatment. Thirty-two 8-week-old SD rats were randomly divided into 4 groups, including acute test group, acute control group, chronic test group, and chronic control group, with 8 rats in each group. The acute test group received intraperitoneal injection of cyclophosphamide 150 mg/kg immediately after the measurement of urodynamic data on the first day, and urodynamic examination was performed again 2 days later. After that, the rats were sacrificed to obtain bladder tissue. In the chronic test group, after measuring the baseline data of urodynamics on the first day, cyclophosphamide 75 mg/kg was intraperitoneally injected on the first, fourth, and seventh days, and the rats were sacrificed after measuring the urodynamic data again on the eighth day to obtain bladder tissue. The acute control group and the chronic control group were injected with the same amount of normal saline during intraperitoneal injection, and the urodynamic testing time point were consistent with the corresponding test groups. Histopathological changes of the bladder were assessed by HE staining. In each acute and chronic group, there were no intragroup differences in baseline urodynamic levels between the test and control groups. The urodynamic maximum bladder volume was significantly reduced in the acute test group after administration, histologically, severe interstitial edema, obvious inflammatory cell infiltration, mucosal edema and submucosal hemorrhage, and partial urothelium were absent could be seen, which were consistent with acute cystitis performance. The urodynamic maximum bladder capacity was significantly reduced in the chronic test group after administration, and the bladder compliance was lower than that in the control group, but not significant, the histological manifestations were urothelial exfoliation, interstitial edema, submucosal hemorrhage, infiltration of inflammatory cells such as lymphocytes, and dense vascular distribution. In the acute test group, a single intraperitoneal injection of cyclophosphamide could induce acute bladder inflammation in the rats. In the chronic test group, repeated injections of cyclophosphamide could induce histological changes in chronic inflammation of chronic bladder pain syndrome in the rats. But the bladder function was not significantly impaired.

COMPREHENSIVE TRANSCRIPTOME PROFILING OF UROTHELIAL CELLS FOLLOWING TNFA STIMULATION IN AN IN VITRO INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME MODEL

Tadeja Kuret, Dominika Peskar, Mateja Erdani Kreft, Andreja Erman, Peter Veranič. Front Immunol. 2022 Aug 15;13:960667. doi: 10.3389/fimmu.2022.960667. eCollection 2022. Front Immunol. 2022 Aug 15;13:960667. doi: 10.3389/fimmu.2022.960667. eCollection 2022. PMID: 36045687

Urothelial cells of the urinary bladder play a critical role in the development and progression of interstitial cystitis/bladder pain syndrome (IC/BPS), a chronic and debilitating inflammatory disease. Given the lack of data on the exact phenotype and function of urothelial cells in an inflammatory setting (as in IC/BPS), the authors performed the first in-depth characterization of these cells using RNA sequencing, qPCR, ELISA, Western blot, and immunofluorescence. After TNF α stimulation, urothelial cells in the in vitro model of IC/BPS showed marked upregulation of several proinflammatory mediators, such as SAA, C3, IFNGR1, IL1 α , IL1 β , IL8, IL23A, IL32, CXCL1, CXCL5, CXCL10, CXCL11, TNFAIPR, TNFRSF1B, and BIRC3, involved in processes and pathways of innate immunity, including granulocyte migration and chemotaxis, inflammatory response, and complement activation, as well as TLR-, NOD-like receptor- and NF κ B-signaling pathways, suggesting their active role in shaping the local immune response of the bladder. This study from Slovenia demonstrates that the TNF α -stimulated urothelial cells recapitulate key observations found in the bladders of patients with IC/BPS, underpinning their utility as a suitable in vitro model for understanding IC/BPS mechanisms and confirming the role of TNF α signaling as an important component of the associated pathology. The present study also identifies novel upregulated gene targets of TNF α in urothelial cells, including genes encoding the acute phase protein SAA, complement component C3, and the cytokine receptor IFNGR1, which could be exploited as therapeutic targets of IC/BPS. Altogether, the study provides a reference database of the phenotype of urothelial cells in an inflammatory environment that will not only increase our knowledge of their role in IC/BPS, but also advance our understanding of how urothelial cells shape tissue immunity in the bladder.

TGR5 AGONISTS INDUCE PERIPHERAL AND CENTRAL HYPERSENSITIVITY TO BLADDER DISTENSION

Ashlee Caldwell, Luke Grundy, Andrea M Harrington, Sonia Garcia-Caraballo, Joel Castro, Nigel W Bunnett, Stuart M Brierley. Sci Rep. 2022 Jun 15;12(1):9920. doi: 10.1038/s41598-022-14195-w. PMID: 35705684 PMCID: PMC9200837.

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The mechanisms underlying chronic bladder conditions such as interstitial cystitis/bladder pain syndrome (IC/BPS) and overactive bladder syndrome (OAB) are incompletely understood. However, targeting specific receptors mediating neuronal sensitivity to specific stimuli is an emerging treatment strategy. Recently, irritant-sensing receptors including the bile acid receptor TGR5, have been identified within the viscera and are thought to play a key role in neuronal hypersensitivity. Here, in mice, the authors from Australia and the USA identify mRNA expression of TGR5 (Gpbar1) in all layers of the bladder as well as in the lumbosacral dorsal root ganglia (DRG) and in isolated bladder-innervating DRG neurons. In bladder-innervating DRG neurons Gpbar1 mRNA was 100% co-expressed with Trpv1 and 30% co-expressed with Trpa1. In vitro live-cell calcium imaging of bladder-innervating DRG neurons showed direct activation of a sub-population of bladder-innervating DRG neurons with the synthetic TGR5 agonist CCDC, which was diminished in Trpv1 $^{-/-}$ but not Trpa1 $^{-/-}$ DRG neurons. CCDC also activated a small percentage of non-neuronal cells. Using an ex vivo mouse bladder afferent recording preparation the authors show intravesical application of endogenous (5 α -pregnan-3 β -ol-20-one sulphate, Pg5 α) and synthetic (CCDC) TGR5 agonists enhanced afferent mechanosensitivity to bladder distension. Correspondingly, in vivo intravesical administration of CCDC increased the number of spinal dorsal horn neurons that were activated by bladder distension. The enhanced mechanosensitivity induced by CCDC ex vivo and in vivo was absent using Gpbar1 $^{-/-}$ mice. Together, these results indicate a role for the TGR5 receptor in mediating bladder afferent hypersensitivity to distension and thus may be important to the symptoms associated with IC/BPS and OAB.

ECHINACOSIDE AMELIORATES CYCLOPHOSPHAMIDE-INDUCED BLADDER DAMAGE IN MICE

Yunpeng Shao, Yu Liu, Baixin Shen, Qiao Zhou, Zhongqing Wei. J Med Food. 2022 Jun 27. doi: 10.1089/jmf.2021.K.0194. Online ahead of print. PMID: 35758826 DOI: 10.1089/jmf.2021.K.0194

Interstitial cystitis (IC) is featured by apoptosis and chronic inflammation in bladder tissue. The authors from Nanjing, China aimed to evaluate the effect of echinacoside (ECH), which is known to modulate inflammation and apoptosis on IC using relevant models. They established a mouse model of cystitis using cyclophosphamide (CYP) and treated human urothelium cells (SV-HUC-1) with lipopolysaccharide (LPS) + ATP as in vitro model. The bladder function was tested by urodynamics. Apoptosis of bladder cells was assessed by

terminal deoxynucleotidyl transferase dUTP nick-end labeling assay. Expressions of apoptosis-associated and inflammation-related proteins were assessed using western blotting. Treatment with ECH significantly improved bladder function, reduced inflammatory damage, and decreased apoptosis in the models. Furthermore, ECH decreased the phosphorylation levels of I κ B and NF- κ B(p65) and upregulated the expression of peroxisome proliferator-activated receptor gamma (PPAR γ), which are related to apoptosis and inflammation in CYP-induced mouse cystitis. Moreover, ECH did not reduce apoptosis of urothelial cells after treatment with PPAR γ antagonist GW9662. These findings suggest that ECH might have protective effect against IC in bladder and be mediated through modulation of the PPAR γ /NF- κ B pathway.

[THE NLRP3 INFLAMMASOME INHIBITOR DAPANSUTRILE ATTENUATES CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS](#)

Sonia Kiran, Ahmed Rakib, Udai P Singh. *Front Immunol.* 2022 Jun 3;13:903834. doi: 10.3389/fimmu.2022.903834. eCollection 2022. PMID: 35720309 PMCID: PMC9205468.

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Interstitial cystitis (IC)/bladder pain syndrome (BPS), hereafter referred together as IC, is a clinical syndrome characterized by sterile inflammation in the bladder. While the etiology and pathophysiology of IC remain unclear, it may involve autoimmunity in light of the significant role played by the NLRP3 inflammasome. However, the effect of NLRP3 inhibitors including dapansutril (Dap) on IC had not been explored previously. Here, the authors from the USA investigated the effect of Dap in the cyclophosphamide (CYP)-induced experimental mouse model of IC, which results in functional and histological alterations confined to the urinary bladder (UB) comparable to that of clinical IC. CYP-induced mice treated with Dap exhibited improved UB pathology and reductions in inflammation scores and the frequency and the number of mast cells and neutrophils, relative to mice that received CYP alone. Dap- and CYP-treated mice also exhibited infiltration of T cells in the spleen and iliac lymph nodes (ILNs) and a concurrent significant decrease ($p < 0.01$) in CXCR3+CD8+ T cells in the UB, induction of systemic and mucosal dendritic cells (DCs), and reduced levels of systemic proinflammatory cytokines, as compared to CYP alone. They also observed decreases in the expression of several signaling pathways regulators, including interleukin-1 beta (IL-1 β), NLRP3, caspase-1, nuclear factor kappa B (NF- κ B), and inducible nitric oxide synthase (iNOS) in the UB of CYP- and Dap-treated mice, relative to those receiving CYP alone. Taken together, these results suggest that Dap suppresses IC through the reduction of CXCR3+T cells, mast cells, and neutrophils in the UB and induces DCs as a protective measure. The present study identifies the mechanisms underlying the amelioration of IC by the NLRP3 inhibitor Dap and may provide an avenue for a potential therapeutic agent for the treatment of IC.

[EFFECTS OF BLADDER PERFUSION OF PENTOSAN POLYSULFATE SODIUM AND HYALURONIC ACID ON MUCOSAL MAST CELLS OF RATS WITH INTERSTITIAL CYSTITIS](#)

Yong Yu, Ying Zhu, Dongqi Li. *Minerva Surg.* 2022 Jun 16. doi: 10.23736/S2724-5691.22.09557-0. Online ahead of print. PMID: 35708444 DOI: 10.23736/S2724-5691.22.09557-0

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Research article from Heilongjiang Province, China.

[DECREASED AUTOPHAGIC ACTIVITY OF DETRUSOR CELLS IS INVOLVED IN THE INFLAMMATORY RESPONSE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Jiang Zhao, Qudong Lu, Zhengxin Yang, Bishao Sun, Jingzheng Zhu, Hengshuai Zhang, Chengfei Yang, Shanghong Yi, Xinyou Dong. *Int Urogynecol J.* 2022 Jun 11. doi: 10.1007/s00192-022-05224-3. Online ahead of print. PMID: 35689690.

Genome-wide association studies suggest that autophagy plays an important regulatory role in inflammatory and autoimmune diseases. Inflammation and immune regulation disorders are involved in the occurrence and development of interstitial cystitis/bladder pain syndrome (IC/BPS). However, the changes and roles of autophagy in IC/BPS have not been reported. Therefore, this study from Chongqing in China aimed to investigate bladder autophagy and inflammation changes in patients with IC/BPS. Bladder specimens ($n = 5$) from patients with cystectomy due to end-stage IC/BPS were collected. The bladder samples of the control group ($n = 5$) were derived from the normal area bladder tissue after radical cystectomy. H&E and toluidine blue staining were used for histological evaluation. The co-location of LC3, alpha-smooth muscle actin (α -SMA), and autophagosome was investigated with double-labeled immunofluorescence and transmission electron microscopy (TEM). The expression of IL-6, TNF- α , Bax, caspase-3, and BCL-2 in the detrusor layer was analyzed using immunohistochemistry (IHC) and Western blot (WB). Compared with the control group, bladder tissue from IC/BPS patients revealed thinner and edematous epithelium with many mast cells ($P < 0.05$)

infiltrating into the muscle layer. By using TEM ($P < 0.05$), double-labeled immunofluorescence ($P < 0.05$), and Western blot ($P < 0.05$) in IC/BPS patients, autophagy was also found and was significantly increased in detrusor myocytes. IHC and WB indicate the expression of BCL-2 ($P < 0.05$) was decreased, while IL-6, TNF- α , Bax, and caspase-3 expression was elevated ($P < 0.05$). The number of autophagosomes in detrusor cells was increased in IC/BPS. However, autophagy of detrusor muscle cells may not have sufficient phagocytic activity to effectively remove damaged proteins and mitochondria, which may lead to the continued deterioration of IC/BPS inflammation and apoptosis.

ACYLOXYACYL HYDROLASE REGULATES MICROGLIA-MEDIATED PELVIC PAIN

Afrida Rahman-Enyart, Ryan E Yaggie, Justin L Bollinger, Constadina Arvanitis, Deborah R Winter, Anthony J Schaeffer, David J Klumpp. PLoS One. 2022 Aug 18;17(8):e0269140. doi: 10.1371/journal.pone.0269140. eCollection 2022. PMID: 35980963

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Chronic pelvic pain conditions such as interstitial cystitis/bladder pain syndrome (IC/BPS) remain clinical and mechanistic enigmas. Microglia are resident immune cells of the central nervous system (CNS) that respond to changes in the gut microbiome, and studies have linked microglial activation to acute and chronic pain in a variety of models, including pelvic pain. The authors from the USA have previously reported that mice deficient for the lipase acyloxyacyl hydrolase (AOAH) develop pelvic allodynia and exhibit symptoms, comorbidities, and gut dysbiosis mimicking IC/BPS. Here, they assessed the role of AOAH in microglial activation and pelvic pain. RNAseq analyses using the ARCHS4 database and confocal microscopy revealed that AOAH is highly expressed in wild type microglia but at low levels in astrocytes, suggesting a functional role for AOAH in microglia. Pharmacologic ablation of CNS microglia with PLX5622 resulted in decreased pelvic allodynia in AOAH-deficient mice and resurgence of pelvic pain upon drug washout. Skeletal analyses revealed that AOAH-deficient mice have an activated microglia morphology in the medial prefrontal cortex and paraventricular nucleus, brain regions associated with pain modulation. Because microglia express Toll-like receptors and respond to microbial components, the authors also examine the potential role of dysbiosis in microglial activation. Consistent with their hypothesis of microglia activation by leakage of gut microbes, they observed increased serum endotoxins in AOAH-deficient mice and increased activation of cultured BV2 microglial cells by stool of AOAH-deficient mice. Together, these findings demonstrate a role for AOAH in microglial modulation of pelvic pain and thus identify a novel therapeutic target for IC/BPS.

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Ashlee Caldwell, Luke Grundy, Andrea M Harrington, Sonia Garcia-Caraballo, Joel Castro, Nigel W Bunnett, Stuart M Brierley. Sci Rep. 2022 Jun 15;12(1):9920. doi: 10.1038/s41598-022-14195-w.PMID: 35705684

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The mechanisms underlying chronic bladder conditions such as interstitial cystitis/bladder pain syndrome (IC/BPS) and overactive bladder syndrome (OAB) are incompletely understood. However, targeting specific receptors mediating neuronal sensitivity to specific stimuli is an emerging treatment strategy. Recently, irritant-sensing receptors including the bile acid receptor TGR5, have been identified within the viscera and are thought to play a key role in neuronal hypersensitivity. Here, in mice, the authors from Australia and New York identify mRNA expression of TGR5 (Gpbar1) in all layers of the bladder as well as in the lumbosacral dorsal root ganglia (DRG) and in isolated bladder-innervating DRG neurons. In bladder-innervating DRG neurons Gpbar1 mRNA was 100% co-expressed with Trpv1 and 30% co-expressed with Trpa1. In vitro live-cell calcium imaging of bladder-innervating DRG neurons showed direct activation of a sub-population of bladder-innervating DRG neurons with the synthetic TGR5 agonist CCDC, which was diminished in Trpv1 $^{-/-}$ but not Trpa1 $^{-/-}$ DRG neurons. CCDC also activated a small percentage of non-neuronal cells. Using an ex vivo mouse bladder afferent recording preparation they show intravesical application of endogenous (5 α -pregnan-3 β -ol-20-one sulphate, Pg5 α) and synthetic (CCDC) TGR5 agonists enhanced afferent mechanosensitivity to bladder distension. Correspondingly, in vivo intravesical administration of CCDC increased the number of spinal dorsal horn neurons that were activated by bladder distension. The enhanced mechanosensitivity induced by CCDC ex vivo and in vivo was absent using Gpbar1 $^{-/-}$ mice. Together, these results indicate a role for the TGR5 receptor in mediating bladder afferent hypersensitivity to distension and thus may be important to the symptoms associated with IC/BPS and OAB.

SUPERIOR THERAPEUTIC ACTIVITY OF TGF- β -INDUCED EXTRACELLULAR VESICLES AGAINST INTERSTITIAL CYSTITIS

Kwonwoo Song, Ahmed Abdal Dayem, Soobin Lee, Yujin Choi, Kyung Min Lim, Sehee Kim, Jongyub An, Yeokyung Shin, Hyojin Park, Tak-Il Jeon, Soo Bin Jang, Hanbit Bong, Jeong Ik Lee, Geun-Ho Kang, Sejong Kim, Aram Kim, Ssang-Goo Cho. *J Control Release*. 2022 Jun 27;S0168-3659(22)00387-X. doi: 10.1016/j.jconrel.2022.06.045. Online ahead of print. PMID: 35772569.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disease characterized by incapacitating pelvic pain. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) are considered key mediators of the paracrine action of MSCs and show better biological activities than the parent MSCs, especially in the bladder tissue, which may be unfavorable for MSC survival. In this study from Korea, the authors produced MSC-EVs using advanced three-dimensional (a3D) culture with exogenous transforming growth factor- β 3 (TGF- β 3) (T-a3D-EVs). Treatment with T-a3D-EVs led to significantly enhanced wound healing and anti-inflammatory capacities. Moreover, submucosal layer injection of T-a3D-EVs in chronic IC/BPS animal model resulted in restoration of bladder function, superior anti-inflammatory activity, and recovery of damaged urothelium compared to MSCs. Interestingly, they detected increased TGF- β 1 level in T-a3D-EVs, which might be involved in the anti-inflammatory activity of these EVs. Taken together, they demonstrate the excellent immunomodulatory and regenerative abilities of T-a3D-EVs as observed by recovery from urothelial denudation and dysfunction, which could be a promising therapeutic strategy for IC/BPS.

PERIOSTIN ATTENUATES CYCLOPHOSPHAMIDE-INDUCED BLADDER INJURY BY PROMOTING UROTHELIAL STEM CELL PROLIFERATION AND MACROPHAGE POLARIZATION

Zhihong Chen, Liyong Liu, Yunhua Chen, Minjie Liu, Andy Peng Xiang, Chunhua Deng, Mei Hua Jiang. *Stem Cells Transl Med*. 2022 Jun 22;11(6):659-673. doi: 10.1093/stcltm/szac025.

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Interstitial cystitis (IC) is a bladder syndrome of unclear etiology with no generally accepted treatment. Growing evidence suggest that periostin (POSTN) is an important homeostatic component in the tissue repair and regeneration in adulthood, but its function in urinary bladder regeneration is still unknown. In this study from Guangdong, China, the authors investigated whether POSTN is involved in bladder tissue repair in a cyclophosphamide (CYP)-induced interstitial cystitis model. POSTN is primarily expressed in bladder stroma (detrusor smooth muscle and lamina propria) and upregulated in response to CYP-induced injury. POSTN deficiency resulted in more severe hematuria, aggravated edema of the bladder, and delayed umbrella cell recovery. Furthermore, less proliferative urothelial cells (labelled by pHH3, Ki67, and EdU) and lower expression of Krt14 (a urothelial stem cell marker) were detected in POSTN-/- mice post CYP exposure, indicating a limited urothelial regeneration. Further investigations revealed that POSTN could induce Wnt4 upregulation and activate AKT signalling, which together activates β -catenin signalling to drive urothelial stem cell proliferation. In addition, POSTN can promote resident macrophage proliferation and polarization to a pro-regenerative (M2) phenotype, which favors urothelial regeneration. Furthermore, the authors generated injectable P-GelMA granular hydrogel as a biomaterial carrier to deliver recombinant POSTN into the bladder, which could increase urothelial stem cells number, decrease umbrella cells exfoliation, and hence alleviate hematuria in a CYP-induced interstitial cystitis model. In summary, their findings identify a pivotal role of POSTN in bladder urothelial regeneration and suggest that intravesical biomaterials-assisted POSTN delivery may be an efficacious treatment for interstitial cystitis.

FUNCTIONAL BRAIN IMAGING AND CENTRAL CONTROL OF THE BLADDER IN HEALTH AND DISEASE

Dongqing Pang, Yi Gao, Limin Liao. *Front Physiol*. 2022 Aug 12;13:914963. doi: 10.3389/fphys.2022.914963. eCollection 2022. PMID: 36035497

Central control of the bladder is a complex process. With the development of functional imaging technology and analysis methods, research on brain-bladder control has become more in-depth. In this study from China, the authors review previous functional imaging studies and combine their latest findings to discuss brain regions related to bladder control, interactions between these regions, and brain networks, as well as changes in brain function in diseases such as urgency urinary incontinence, idiopathic overactive bladder, interstitial cystitis/bladder pain syndrome, urologic chronic pain syndrome, neurogenic overactive bladder, and nocturnal enuresis. Implicated brain regions include the pons, periaqueductal grey, thalamus, insula, prefrontal cortex, cingulate cortex, supplementary motor area, cerebellum, hypothalamus, basal ganglia, amygdala, and hippocampus. Because the brain is a complex information transmission and processing system, these regions do not work in isolation but through functional connections to form a number of subnetworks to achieve bladder control. In summarizing previous studies, they found changes in the brain functional connectivity

networks related to bladder control in healthy subjects and patients involving the attentional network, central executive network or frontoparietal network, salience network, interoceptive network, default mode network, sensorimotor network, visual network, basal ganglia network, subcortical network, cerebella, and brainstem. The authors extend the working model proposed by Griffiths et al. from the brain network level, providing insights for current and future bladder-control research.

INHIBITION OF U-II/UT SIGNALING AMELIORATES CYSTITIS-ASSOCIATED BLADDER HYPERACTIVITY BY TARGETING THE RHOA/RHO-KINASE PATHWAY

Qian Liu, Qu-Dong Lu, Bi-Shao Sun, Jiang Zhao, Fan He, Jing-Zhen Zhu. Kaohsiung J Med Sci. 2022 Jun 29. doi: 10.1002/kjm2.12569. Online ahead of print. PMID: 35766129.

Urotensin II (U-II) and its receptor (UT) are involved in the pathogenesis of various diseases; however, their association with the development of cystitis has not been elucidated. This study from Chongqing and Chengdu in China was designed to investigate the functional role of U-II/UT signalling in cyclophosphamide (CYP)-induced cystitis. A total of 60 female rats were randomly divided into the control and CYP-treated groups. Intraperitoneal injection of CYP successfully induced cystitis in rats of the CYP-treated group. The protein and mRNA expression levels of U-II and UT were significantly enhanced in rat bladder tissues of the CYP-treated group. Furthermore, the results of the immunofluorescence staining analysis demonstrated that CYP treatment apparently increased the expression levels of UT in the urothelium layer, detrusor smooth muscle, and bladder interstitial Cajal-like cells. The selective antagonist of UT, SB657510 (10 µm), significantly suppressed the CYP-induced increase in the spontaneous contractions of muscle strips and ameliorated the bladder hyperactivity of CYP-treated rats. Moreover, CYP treatment significantly increased the protein expression levels of Ras homolog family member (Rho) A and Rho-associated protein kinase 2 in rat bladder tissues. Following pretreatment with the Rho-kinase inhibitor Y-27632 (10 µm), the inhibitory effects of SB657510 (10 µm) on the spontaneous contractions of muscle strips were eliminated. In conclusion, the results of this study suggested that activation of U-II/UT signalling promoted the development of cystitis-associated-bladder hyperactivity by targeting the RhoA/Rho-kinase pathway, indicating that the U-II/UT signalling could serve as a novel target for the treatment of IC/BPS.

CLINICAL PRESENTATION, VIDEOURODYNAMIC CHARACTERISTICS, AND TREATMENT OUTCOME IN MEN WITH INTERSTITIAL CYSTITIS-LIKE LOWER URINARY TRACT SYMPTOMS

Wan-Ru Yu, Wei-Chuan Chang, Hann-Chorng Kuo. Int Urol Nephrol. 2022 Jul 8. doi: 10.1007/s11255-022-03294-2. Online ahead of print. PMID: 35804206.

Purpose: In men, lower urinary tract symptoms (LUTS) similar to interstitial cystitis/bladder pain syndrome (IC/BPS) are difficult to diagnose, and treatment outcomes are poor. This study from Hualien, Taiwan investigated clinical characteristics and videourodynamic study (VUDS) parameters, pathophysiology, and treatment outcomes in men with IC-like LUTS. Men with frequency, urgency, dysuria, and bladder pain initially diagnosed as IC/BPS by ESSIC criteria were assessed to rule out other lower urinary tract diseases (LUTD) by voiding diary, digitorectal examination, urinalysis, VUDS, and cystoscopic hydrodistention. Subsequent treatments for LUTD and specific treatment for IC/BPS were based on VUDS and cystoscopic findings. Clinical VUDS characteristics and treatment outcomes were compared with those of women with IC/BPS. Seventy consecutive men (median age 54.5 years) were enrolled. The median maximum bladder capacity under cystoscopic hydrodistention was 650 mL (IQR 495-763) and glomerulation grade was 2 (1.0-2.0). The patients had moderate anxiety and depression severity; 49% had improved treatment outcomes. On VUDS, 42 (60%) patients had variable LUTD, including detrusor overactivity (n = 14), bladder neck dysfunction (n = 15), dysfunctional voiding (n = 3), and poor relaxation of the external sphincter (n = 24); also, 22 (31.4%) had a previous bladder outlet procedure. The self-reported treatment outcome was significantly better for patients with vs. without LUTD (p = 0.014). The authors concluded that men with IC-like LUTS diagnosed as IC/BPS may have bladder outlet dysfunction as well as bladder dysfunction, causing a hypersensitive and painful bladder. The IC-like symptoms in the patients with LUTD might, in part, originated from bladder outlet dysfunction rather than the bladder alone.

GENE EXPRESSION-BASED FUNCTIONAL DIFFERENCES BETWEEN THE BLADDER BODY AND TRIGONAL UROTHELIUM IN ADOLESCENT FEMALE PATIENTS WITH MICTURITION DYSFUNCTION

Natalia Zeber-Lubecka, Maria Kulecka, Katarzyna Załęska-Oracka, Michalina Dąbrowska, Aneta Bałabas, Ewa E Hennig, Magdalena Szymanek-Szwed, Michał Mikula, Beata Jurkiewicz, Jerzy Ostrowski. Biomedicines. 2022 Jun 17;10(6):1435. doi: 10.3390/biomedicines10061435. PMID: 35740457.

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The aim of this study from Poland was to determine the molecular differences between the urothelial transcriptomes of the bladder body and trigone. The transcriptomes of the bladder body and trigonal epithelia were analyzed by massive sequencing of total epithelial RNA. The profiles of urothelial and urinal microbiomes were assessed by amplicon sequencing of bacterial 16S rRNA genes in 17 adolescent females with pain and micturition dysfunction and control female subjects. The RNA sequencing identified 10,261 differentially expressed genes (DEGs) in the urothelia of the bladder body and trigone, with the top 1000 DEGs at these locations annotated to 36 and 77 of the Reactome-related pathways in the bladder body and trigone, respectively. These pathways represented 11 categories enriched in the bladder body urothelium, including extracellular matrix organization, the neuronal system, and 15 categories enriched in the trigonal epithelium, including RHO GTPase effectors, cornified envelope formation, and neutrophil degranulation. Five bacterial taxa in urine differed significantly in patients and healthy adolescent controls. The evaluation of their transcriptomes indicated that the bladder body and trigonal urothelia were functionally different tissues. The molecular differences between the body and trigonal urothelia responsible for clinical symptoms in adolescents with bladder pain syndrome/interstitial cystitis remain unclear.

EXPERIMENTAL IN VIVO MODEL TO EVALUATE THE IMPACT OF CERNITIN™ ON PAIN RESPONSE ON INDUCED CHRONIC BLADDER INFLAMMATION

Céline Augé, Nishtman Dizeyi, Lena Ramnemark, Philippe Lluel, Magnus Grabe. Scand J Urol. 2022 Jun 29;1-9. doi: 10.1080/21681805.2022.2090602. Online ahead of print. PMID: 35766197 DOI: 10.1080/21681805.2022.2090602

Inflammation of the urinary bladder may cause burdensome pain also called bladder pain syndrome (BPS). A limitation in understanding BPS pathophysiology is the lack of appropriate preclinical model. Previously published clinical and preclinical studies revealed positive impact of Cernitin™ on pain relief in chronic prostatitis. The objective of this study from Sweden and France was to evaluate the effects of Cernitin™ on induced inflammation of the urinary bladder in rats. The authors also sought to identify biomarkers which might play a role in the management of BPS. Cystitis was induced by injection of cyclophosphamide (CYP) in female rats. Thereafter, animals were randomly divided into four treatment groups and two control groups. Evaluation of pain scores was assessed by von Frey assay. Expression of pain- and pro-inflammatory biomarkers was determined by enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry. Treatments with Cernitin™ displayed significant anti-nociceptive effects on CYP-induced visceral pain ($p < .01$). In contrast, vehicle-treated animals showed high pain score even at the lowest force. Furthermore, results of ELISA showed that Cernitin™-treated animals had significantly reduced levels of COX-2 (T60, $p < .01$; GBX, $p < .05$) in bladder tissue homogenate. Immunohistochemical (IHC) staining of bladder tissues showed that Cernitin™-treated animals exhibited less CD45-positive cells, while massive CD45-positive cells infiltration was detected in vehicle-treated animals. IHC also revealed lower SP and PGD2 expression levels in Cernitin™-treated tissues. It was concluded that Cernitin™ components reduced pain score and inflammatory marker COX-2 and suggested a potential therapeutic role for Cernitin™ in the management of BPS.

NIRS: PAST, PRESENT, AND FUTURE IN FUNCTIONAL UROLOGY

Alexander Koven, Sender Herschorn. Curr Bladder Dysfunct Rep. 2022 Aug 11;1-9. doi: 10.1007/s11884-022-00665-4. Online ahead of print. PMID: 35971538 PMCID: PMC9366124 DOI: 10.1007/s11884-022-00665-4

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Near infrared spectroscopy (NIRS) is a non-invasive optical technique that uses near infrared light to detect the oxygenation status and hemodynamics of various organs. This article from Canada reviews the use of NIRS for the non-invasive assessment of lower urinary tract dysfunction (LUTD). Applications include assessment of bladder outlet obstruction, overactive and underactive bladder, neurogenic LUTD, pediatric LUTD, interstitial cystitis/bladder pain syndrome, and pelvic floor dysfunction. In addition, the article describes how NIRS is elucidating more about the brain-bladder connection. Technological advancements enabling these applications are also discussed. While evidence exists for the application of NIRS throughout a wide range of LUTD, most of these studies are limited by small sample sizes without matched controls. Investigators have experienced problems with reproducibility and motion artifacts contaminating the data. The literature is also becoming dated with use of older technology. NIRS holds potential for the non-invasive acquisition of urodynamic information over time scales and activities not previously accessible, but it is not yet ready for use in routine clinical practice. Advances in wearable technology will address some of the current limitations of NIRS, but to realize its full potential, larger scale validation studies will be required. Moreover, multidisciplinary collaboration between clinicians, scientists, engineers, and patient advocates will be critical to further optimize these systems.

IS THERE A ROLE FOR BLADDER BIOPSY IN THE DIAGNOSIS OF NON-HUNNER LESIONS INTERSTITIAL CYSTITIS?

Franca Natale, Giuseppe Campagna, Monia Marturano, Daniela Caramazza, Giovanni Panico, Lorenzo Vacca, Eleonora Torcia, Mauro Cervigni, Giovanni Scambia, Alfredo Ercoli. Urol Int. 2022 Jul 27;1-6. doi: 10.1159/000525849. Online ahead of print. PMID: 35896088

Bladder pain syndrome/interstitial cystitis (BPS/IC) is either Hunner lesion interstitial cystitis (HL IC) or non-Hunner lesion interstitial cystitis (N-HL IC), differing in the presence of HLs on cystoscopy. Cystoscopy is essential in diagnosing HL but are bladder biopsies useful in N-HL IC patients? The objective of this single-centre retrospective study from Italy was to assess bladder biopsy in patients with N-HL IC, evaluating whether the count of mast cells (MCs) and percentage of activated MCs could measure severity. Inclusion criteria comprised diagnosis of BPS/IC by ESSIC definition; absence of HLs. Each patient had three bladder biopsies. The authors separated 48 women into Group 1 with <50% of MCs activated and Group 2 with >50%. They compared the results of the O'Leary-Sant questionnaire between the two groups and did not find any correlation between the severity of the pathology and either the MC count in the detrusor or the percentage of activated MCs in the lamina propria or detrusor. The authors concluded that their findings cast doubt on the usefulness of bladder biopsy for the evaluation of severity in N-HL IC.

CYSTECTOMY FOR BENIGN INDICATIONS

Owen P Aftreth, Christopher F Tenggardjaja, Polina Reyblat. Curr Urol Rep. 2022 Sep 3. doi: 10.1007/s11934-022-01100-1. Online ahead of print. PMID: 36057019.

This article from the USA evaluates the historical influences, current use, surgical techniques, and recent evidence on outcomes for cystectomy performed for benign indications. At the population level, cystectomy for benign indications has similar perioperative morbidity to radical cystectomy for cancer. Postoperative patient satisfaction is high and functional outcomes appear good, including sexual function. Patient regret about diversion choice is low provided decisions are well informed. Cystectomy is important both as a primary procedure for benign disease and as an adjunct to primary urinary diversion. Early morbidity remains high but long-term results are encouraging. Further studies are needed to guide patient decision-making, to help inform diversion choice, and to understand the long-term impact of surgery and diversion choice on quality of life.

INTRAVESICAL SUSTAINED RELEASE SYSTEM OF LIDOCAINE AND OXYBUTYNIN RESULTS FROM IN VITRO AND ANIMAL STUDY

David Dothan, Galiya Raisin, Nadav Malchi, Avi Gordon, Dan Touitou, Boris Chertin. Int Urol Nephrol. 2022 Jul 3. doi: 10.1007/s11255-022-03280-8. Online ahead of print. PMID: 35780464

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic debilitating condition of unknown etiology. Intravesical lidocaine demonstrated pain relief in patients with IC/BPS. Intravesical oxybutynin has shown therapeutic efficacy in patients with urinary bladder disorders. However, loss of drug with urination requiring multiple administrations and immediate dilution of drug concentration by residual urine in the bladder mitigated intravesical use of both drugs in clinical practice. The aim of this study from Jerusalem, Israel was to evaluate the efficacy and safety of fixed-dose combination of lidocaine and oxybutynin, forming in the urine a sustained delivery system named TRG-042. In-vitro, the authors quantitatively tested the concentration of lidocaine and oxybutynin released from TRG-042 in artificial urine. Following the successful in-vitro study weekly formulation of TRG-042 was instilled intravesically into six pigs. All pigs were followed with cystoscopy to assess the gradual degradation of the delivery system and to evaluate bladder response over 7 days. Daily blood samples were tested for drug quantization. In-vitro studies have demonstrated oxybutynin and lidocaine sustained release over 1-week period coupled with full degradation of the matrix. None of the animals demonstrated any side effects following instillation. Cystoscopy examination observed gradual disintegration of TRG-042 over 1-week with no adverse reaction to the mucosa. Plasma concentrations of oxybutynin and lidocaine were uniformly stable over the 1-week period [1.46 ± 0.176 ng/ml and 4.29 ± 2.48 ng/ml respectively (mean \pm SEM)] with almost undetectable concentration of N-desethyloxybutynin (NDO) [0.032 ± 0.068 ng/ml]. The authors concluded that the in-vitro and animal data demonstrated that TRG-042 can safely be used for intravesical sustained release of lidocaine and oxybutynin in the treatment of BPS/IC.

[PROTECTIVE PROPERTIES OF UROTHELIUM AND POSSIBILITIES OF TARGETED PATHOGENETIC THERAPY OF CHRONIC PELVIC PAIN: SODIUM PENTOSAN POLYSULFATE]

[Article in Russian]

G R Kasyan, A V Zaitsev, K A Baibarin, A E Karasev, D Yu Pushkar. *Urologiia*. 2022 Sep;(4):91-95. PMID: 36098600

This review article from Russia is devoted to the possibilities of using targeted therapy for urothelial diseases, namely bladder pain syndrome (BPS). The protective structural components of the bladder mucosa, as well as their chemical features, are described in detail. Pentosan polysulfate (PPS), being an oral heparinoid, can be used as part of pathogenetic therapy to restore the mucous membrane of the bladder. According to the authors, the efficacy and safety of this drug has been proven in this multicenter, randomized, double-blind, placebo-controlled trial.

[\[BLADDER PAIN SYNDROME: LONG-TERM RESULTS \(15 YEARS\) OF A SINGLE-CENTER EXPERIENCE\]](#)

[Article in French]

M De Cian, T Tricard, C Saussine. *Prog Urol*. 2022 Jun 10;S1166-7087(22)00075-6. doi: 10.1016/j.purol.2022.03.003. Online ahead of print. PMID: 35697555

The authors note that management of bladder pain syndrome (BPS) in their center is standardized although there is no real consensus and recommendations. The objectives of this French study were to assess the effectiveness of the treatment offered and to identify predictive factors of response to treatment. This was a single-center retrospective study including all patients with BPS. Patient and outcome measures included ICSI and ICPI scores, daytime voiding interval (DVI), nocturnal pollakiuria (NPK), and subjective satisfaction (SS). The complete care protocol (CCP) was based on a hydrodistension test followed by a cimetidine treatment then by 6 instillations of dimethyl sulfoxide followed by a maintenance treatment with pentosan polysulfate. The main objective of this study was the patient's SS at 3months and at medium term. One of the secondary objectives was to study the predictive factors of response to treatment. From 2002 to 2019, 211 patients (90.5% women) were treated for BPS. Sixty-nine patients (35%) underwent the CCP that provided significant improvement in ICSI, ICPI, DVI and NPK and SS of 52.2%). In the medium term, 149 patients were reassessed with a median follow-up of 99.6months (± 3.6): 71.8% were satisfied and 54.2% were no longer receiving treatment. Among the 49 patients who initially received PSC, 74% were satisfied at 89.8 months of median follow-up (± 2.9). In multivariate analysis, patients with a pain perception disorder or consuming anxiolytics had a statistically greater risk of not being satisfied. The authors concluded that in their study the CCP achieves subjective medium-term satisfaction in nearly 75% of patients with BPS. These data deserve to be confirmed on a larger scale in a prospective protocol.

[\[CLINICAL APPLICATION OF BOTULINUM NEUROTOXIN IN LOWER-URINARY-TRACT DISEASES AND DYSFUNCTIONS: WHERE ARE WE NOW AND WHAT MORE CAN WE DO?\]](#)

Hann-Chorng Kuo. *Toxins (Basel)*. 2022 Jul 18;14(7):498. doi: 10.3390/toxins14070498. PMID: 35878235 DOI: 10.3390/toxins14070498

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Botulinum toxin A (Botox) had been considered a promising drug that has an effect on functional disorders of the lower urinary tract. Because Botox exhibits anti-inflammatory and antispasmodic effects, Botox injection into the bladder can decrease detrusor contractility, reduce bladder hypersensitivity, and eliminate painful sensations. Injecting Botox into the bladder outlet can relax the hyperactivity of the bladder neck, and of the urethral smooth and striated muscles. Based on these therapeutic effects, Botox has been widely applied to treat lower-urinary-tract dysfunctions (LUTDs) such as overactive bladder and neurogenic detrusor overactivity. However, this treatment has not been licensed for use in other LUTDs such as interstitial cystitis, voiding dysfunction due to benign prostatic hyperplasia in men, and dysfunctional voiding in women. Botox has also not been approved for the treatment of children with overactive bladder and dysfunctional voiding; in patients with spinal cord injuries with detrusor sphincter dyssynergia and autonomic dysreflexia; or for poorly relaxed external sphincter in non-neurogenic patients. This article from Hualien, Taiwan reviews current knowledge regarding Botox treatment for LUTDs and discusses the potential clinical applications of Botox, as well as work that can be conducted in the future.

[\[CHANGES IN CYSTOSCOPIC FINDINGS AFTER INTRAVESICAL HYALURONIC ACID INSTILLATION THERAPY IN PATIENTS WITH INTERSTITIAL CYSTITIS\]](#)

Chia-Ju Lin, Chih-Ku Liu, Hsiao-Yun Hsieh, Ming-Jer Chen, Ching-Pei Tsai. *Diagnostics (Basel)*. 2022 Aug 19;12(8):2009. doi: 10.3390/diagnostics12082009. PMID: 36010358

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Limited data showed changes in glomerulation in the bladder mucosa of patients with interstitial cystitis (IC) after intravesical hyaluronic acid (HA) bladder infusion. The authors from Taiwan aimed to investigate the

above changes. Medical records of IC patients were reviewed retrospectively, from January 2010 to October 2019. Patients who had received repeated cystoscopy after intravesical HA treatment were enrolled. The associations of multiple parameters, including the ages, symptoms, initial glomerulation stage, HA doses, and the interval period of repeated cystoscopy between the glomerulation change in the repeated cystoscopy were analyzed. Among the 35 patients, 9 cases (25.7%) showed better glomerulation grades in the repeated cystoscopy (Group 1), 20 cases (57.1%) showed the same grades (Group 2), and 6 cases showed worse grades (Group 3). No difference was seen in the initial grades or treatment course among the three groups. The interval periods from the initial to the repeated cystoscopy of Group 1 were longer than Group 2 and Group 3 ($p = 0.031$). Group 3 presents an elder age trend than the other two groups. Intravesical HA repaired bladder glomerulation in a small group of patients with IC. Prolonged treatment has potential benefits, while older age is possibly a negative factor. However, no strong correlation was found between the initial glomerulation grades or changes in glomerulation grades with clinical symptoms.

ACUPUNCTURE FOR FEMALE BLADDER PAIN SYNDROME: A RANDOMIZED CONTROLLED TRIAL

Larissa Bresler, Lauren C Westbay, Lauren Hekman, Cara Joyce, Colleen M Fitzgerald. Can J Urol. 2022 Jun;29(3):11154-11161. PMID: 35691037

Growing evidence supports acupuncture for several pain conditions including chronic prostatitis. This study from the USA aimed to determine the safety, tolerability, and effectiveness of acupuncture in reducing pain in women with interstitial cystitis/bladder pain syndrome (IC/BPS). This prospective randomized single-blinded study compared electro-acupuncture (EA) to minimal acupuncture (MA) after 6 weekly treatments and again after 6 weeks of no treatment. Pain was assessed using the Brief Pain Inventory-Short Form (worst pain, average pain, pain severity, pain interference) and the Pain Catastrophizing Scale (PCS). Physical exams evaluated pelvic floor muscle tenderness. Mixed-effects models were used to estimate adjusted means over follow up. Patients were randomized to EA ($n = 11$) or MA ($n = 10$). There were no adverse events. Both groups' worst pain improved at 6 weeks, -2.91 ± 0.59 and -2.09 ± 0.68 for EA and MA respectively with no difference between groups ($p = 0.37$). Results were similar at 12 weeks. The EA group had greater improvement in pain interference at 6 weeks, -3.28 ± 0.51 versus -1.67 ± 0.58 ($p = 0.049$). The between group difference was not maintained at 12 weeks ($p = 0.13$). Average pain and pain severity showed no difference between groups ($p > 0.05$). The PCS improved overall at 6 weeks, -6.2 ± 2.5 ($p = 0.03$), with no difference between groups ($p = 0.39$). On physical exam, only the EA group showed a significant decrease in levator ani tenderness ($p = 0.031$) after treatment. Both EA and MA showed improvement in worst pain scores, however EA showed greater improvement in pain interference and pelvic floor muscle tenderness in women with IC/BPS.

ELECTRO-ACUPUNCTURE FOR BLADDER PAIN SYNDROME: A PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL AND STUDY FOR CENTRAL MECHANISM

Yunyun Xu, Yangyun Chen, Yan Shi, Jianhua Lu, Zonglin Wu, Zhe Liu, Yuerong Chen, Wenqin Ni, Qike Ding, Wei Dai, Xinyuan Wu, Jianqiao Fang, Yuanyuan Wu. J Pain Res. 2022 Jul 13;15:1959-1970. doi: 10.2147/JPR.S370751. eCollection 2022. PMID: 35860417 PMCID: PMC9289574

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The efficacy of conventional treatments for treating bladder pain syndrome (BPS) remains unsatisfactory. Electro-acupuncture (EA) is one of the complementary treatments with great analgesic effect and minimal side effect, but evidence of the efficacy of EA on BPS is limited. This study from China aims to investigate the efficacy and safety of EA for treating BPS and study on central mechanism of patients with BPS. The study is a randomized controlled and assessor-blinded design trial. A total of 84 participants will be randomly assigned to medication group ($n=21$), EA group ($n=42$) and sham electro-acupuncture (SA) group ($n=21$) in a 1:2:1 allocation ratio. This trial will include baseline period, 4-week treatment period and 4-week follow-up period. Participants in medication group will undergo treatment of amitriptyline for a period of 4 weeks. Participants in EA and SA groups will receive a 30 min EA or SA treatment for a total of 12 sessions over 4 weeks. The primary outcome is the Visual Analog Scale (VAS). The secondary outcomes include the O'Leary-Sant questionnaire, 24-hour voiding diary, Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) and functional magnetic resonance imaging (fMRI). The VAS will be collected at baseline, week 2, week 4, and week 8 after randomization. The O'Leary-Sant questionnaire, HAMA and HAMD will be assessed at baseline, week 4 and week 8 after randomization. The 24-hour voiding diary will be assessed every single day. The fMRI data will be collected at baseline and week 4. The results will provide evidence on the efficacy and safety of EA in the management of BPS and investigate the central mechanism of EA in treating patients with BPS.

ASSOCIATION OF PHYSICAL THERAPY TECHNIQUES CAN IMPROVE PAIN AND URINARY SYMPTOMS OUTCOMES IN WOMEN WITH BLADDER PAIN SYNDROME. A RANDOMIZED CONTROLLED TRIAL

Claudia Rosenblatt Hacad, Marcos Lucon, Suehellen Anne Rocha Milhomem, Homero Bruschini, Clarice Tanaka. Int Braz J Urol. 2022 Sep-Oct;48(5):807-816. doi: 10.1590/S1677-5538.IBJU.2022.0056. PMID: 35838507.

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The purpose of this study from São Paulo, Brazil was to verify the effects of biofeedback (BF) and manual therapy (MT) associated with transcutaneous electrical nerve stimulation (TENS) or postural exercises (PE) in the treatment of bladder pain syndrome (BPS) in women regarding pain and urinary symptoms. A parallel-randomized controlled trial was conducted in BPS patients diagnosed according to NIH clinical criteria. Two specialized physiotherapists applied demographic and validated questionnaires of perineal and suprapubic pain (VAS), urinary symptoms and problems (ICSI and ICPI) and sexual function (FSFI) and a physical assessment was made to identify myofascial trigger points. Thirty-one women, mean age 51.8 ± 10.9 were randomized in three groups of treatment consisting of ten weekly sessions of BF and MT (Conventional group); BF, MT, and TENS (TENS group); and BF, MT, and PE (Postural group). Postural group improved perineal and suprapubic pain after treatment, and the suprapubic pain improvement remained persistent at 3 months of follow up. Postural group improved urinary symptoms and problems after treatment and during follow up. Biofeedback and manual therapy associated with postural exercises showed a significant improvement in perineal and suprapubic pain and urinary symptoms after treatment and during follow-up. Both results suggest a possible role for the use of this physiotherapy technique to treat BPS patients. Longer follow-up and a larger number of patients are necessary to confirm these conclusions.

TRANSVAGINAL PHOTOBIO-MODULATION IMPROVES PAIN IN WOMEN WITH PELVIC MUSCLE TENDERNESS AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PRELIMINARY OBSERVATIONAL STUDY.

Charles W Butrick, Georgine Lamvu. Urology. In Press. September 14, 2022.

DOI:https://doi.org/10.1016/j.urology.2022.08.036

Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS) is characterized by pelvic/bladder pain, associated with pelvic muscle tenderness, urgency, frequency, and dysuria. Prior studies show that transvaginal photobiomodulation (TV-PBM) reduces pain in women with chronic pelvic pain (CPP). The objective of this study was to obtain preliminary data on treatment effect and adherence, in women with IC/BPS who selected TV-PBM therapy for management of pelvic pain. This was a before-and-after observational cohort study of women with IC/BPS who received TV-PBM in 17 US practices. Pain was measured using a 0-10 numeric rating scale (NRS). The primary outcome was a minimal clinical important difference (MCID); reduction of overall pelvic pain severity by ≥ 2 NRS points from baseline compared to after 8 treatments. Cohen d coefficient measured effect size (low effect size $d < 0.2$, medium $0.2 < d < 0.8$, and high $d > 0.8$). Of 140 patients with IC/BPS who self-selected to start TV-PBM therapy, 89.3% ($n=125$) completed 4 treatments and 59.3% ($n=83$) completed 8. Improvement ≥ 1 NRS point was reported by 73.5% ($n=61$) and meaningful improvement (≥ 2 points) was reported by 63.9% ($n=53$) after 8 treatments. In this group, patients with severe / moderate pain decreased from 83.1% ($n=44$) to 38.5% ($n=20$); $p < 0.001$. Pain levels decreased as follows: overall pelvic pain MCID=-2.7, $d=1.07$, pain with urination MCID=-2.6, $d=1.0$; pain with exercise MCID=-2.6, $d=0.91$, pain with intercourse MCID=-2.5, $d=0.82$. In real-world clinical settings, 2/3 women with IC/BPS who opted to undergo TV-PBM therapy reported significant decrease in pelvic pain and dysuria. These findings are promising; however, controlled studies are needed.

PULSED ELECTROMAGNETIC FIELD THERAPY FOR PAIN MANAGEMENT IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PROOF-OF-CONCEPT CASE SERIES

Dylan T Wolff, Christina Ross, Peyton Lee, Gopal Badlani, Catherine A Matthews, Robert J Evans, Stephen J Walker. Urology. 2022 May 27;S0090-4295(22)00435-6. doi: 10.1016/j.urology.2022.05.021. Online ahead of print. PMID: 35636637.

The purpose of this study from the USA was to evaluate the efficacy of pulsed electromagnetic field (PEMF) therapy for symptom and pain management in women with non-bladder centric interstitial cystitis/bladder pain syndrome (IC/BPS). Women with non-bladder centric IC/BPS and a numeric rating scale score for pelvic pain ≥ 6 underwent twice-daily 8-minute full body PEMF therapy sessions for 4 weeks. The primary outcome metric was a reduction in pelvic pain score ≥ 2 points. A 7-day voiding diary (collected at baseline and conclusion), three validated symptom scores, and the Short Form-36 Quality of Life questionnaire (completed at baseline, conclusion of treatment, and 8-week follow-up), were used to assess secondary outcomes. Treatment effects were analyzed via Wilcoxon-signed rank test; $p < 0.05$ was considered significant. The 4-week treatment protocol was completed by 8 of 10 enrolled patients, and 7/8 (87.5%) had a significant reduction in

pelvic pain after 4 weeks. There was also a significant decrease in scores on all validated IC/BPS questionnaires, daily number of voids, and nocturia symptom score. Significant increases in several quality-of-life questionnaire sub-scores were also identified at 4 weeks. At 8-week post-therapy, the positive effects were somewhat attenuated, yet 4/8 patients (50%) continued to have significant pain reduction. No adverse events or side effects were reported. Whole body pulsed electromagnetic field therapy is an alternative treatment option for women with chronic bladder pain syndrome that warrants investigation through comparative trials.

LONG-TERM SYMPTOM TRAJECTORIES IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME: A MAPP RESEARCH NETWORK STUDY

Catherine S Bradley 1, Robert Gallop 2, Siobhan Sutcliffe 3, Karl J Kreder 4, H Henry Lai 5, J Quentin Clemens 6, Bruce D Naliboff 7, Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. Urology. 2022 Aug 9;S0090-4295(22)00654-9. doi: 10.1016/j.urology.2022.07.045. Online ahead of print. PMID: 35961564

The purpose of this MAPP study from the USA was to characterize Urologic Chronic Pelvic Pain Syndrome (UCPPS) pain and urinary symptom trajectories with up to 9 years of follow-up and evaluate whether initial 1-year trajectories are associated with longer-term changes. Data were analyzed from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Network's prospective observational protocols including the Epidemiology and Phenotyping Study (EPS; baseline to Year 1), EPS Extension (EXT; Years 1-5), and Symptom Patterns Study (SPS: 3-year study; Years 3-9). Adults with Interstitial Cystitis/Bladder Pain Syndrome or Chronic Prostatitis/Chronic Pelvic Pain Syndrome provided patient-reported assessments biweekly (EPS), every 4 months (EXT), or quarterly (SPS). Primary outcomes were composite pain (0-28) and urinary (0-25) severity scores. Multi-phase mixed effects models estimated outcomes over time, adjusted for baseline severity and stratified by EPS symptom trajectory. 163 participants (52% women; mean \pm SD age 46.4 \pm 16.1 years) completed EPS and enrolled in EXT; 67 also enrolled in SPS. Median follow-up was 4.6 years (range 1.3-9.0). After 1 year: 27.6%, 44.8% and 27.6% and 27.0%, 38.0% and 35.0% were improved, stable or worse in pain and urinary symptom severity, respectively. On average, pain and urinary symptom scores did not change further during EXT and SPS periods. Women and men with UCPPS showed remarkable stability in pain and urinary symptom severity for up to 9 years, irrespective of their initial symptom trajectory, suggesting UCPPS is a chronic condition with stable symptoms over multiple years of follow-up.

BEARBERRY IN THE TREATMENT OF ACUTE UNCOMPLICATED CYSTITIS (BRUMI): PROTOCOL OF A MULTICENTRE, RANDOMISED DOUBLE-BLIND CLINICAL TRIAL

Barbara Tóth, András Jávornházy, Péter Nyirády, Boglárka Csupor-Löffler, Péter Birinyi, George Zhanel, Kurt Naber, Reinhard Länger, Nóra Vörhendi, Noémi Gede, Szilárd Váncsa, Péter Hegyi, Dezső Csupor. BMJ Open. 2022 Jun 24;12(6):e057982. doi: 10.1136/bmjopen-2021-057982. PMID: 35750460 DOI: 10.1136/bmjopen-2021-057982

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Bearberry (*Arctostaphylos uva-ursi*) leaf is available as a treatment of uncomplicated cystitis in several European countries. The antimicrobial activity of its extracts and some of its individual constituents has been observed in vitro. However, the efficacy of bearberry compared with standard antimicrobial therapy has not been assessed yet. The objective of this randomised controlled double-blinded multicentre trial study from Hungary is to assess the safety and non-inferiority of bearberry as an alternative therapy in the treatment of acute uncomplicated cystitis in comparison with standard antibiotic therapy (fosfomycin). Eligible patients will be premenopausal women with a sum score of ≥ 6 for the typical acute uncomplicated cystitis symptoms (frequency, urgency, painful urination, incomplete emptying, suprapubic pain and visible haematuria) reported on the Acute Cystitis Symptom Score (ACSS) typical domain and pyuria. Patients will be randomly assigned to receive 3 g single dose of fosfomycin powder and two placebo tablets three times a day for 7 days or B a single dose of placebo powder and two tablets containing a dry extract of *Uvae ursi folium*. At least 504 patients (allocated as 1:1) will need to be enrolled to access non-inferiority with a non-inferiority limit of 14% for the primary endpoint. Improvement of symptoms of uncomplicated cystitis (based on the ACSS score) at day 7 is defined as the primary endpoint, whereas several secondary endpoints such as the number and ratio of patients with bacteriuria at day 7, frequency and severity of side effects; recurrence of urinary tract infection, concurrent use of other over the counter (OTC) medications and food supplements will be determined to elucidate more detailed differences between the groups. The number of recurrences and medications taken for treatment will be monitored for a follow-up period of 90 days (80-100 days).

[ANALYSIS OF GINSENG IN THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME BASED ON NETWORK PHARMACOLOGY](#)

L Wang, L Yuan. *Eur Rev Med Pharmacol Sci*. 2022 Jul;26(13):4709-4720. doi: 10.26355/eurrev_202207_29196. PMID: 35856363

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The network pharmacology is adopted in this paper from Chongqing, China to elaborate the active components, targets, and pathways of ginseng in the treatment of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). The active components and potential targets of ginseng were obtained through the Traditional Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP). The OMIM, Disgenet, and Genecards databases for IC/BPS targets, and the STRING11.0 database were used for the protein-protein interaction (PPI) network. Meanwhile, the latter covers R language was used for the target of ginseng for IC/BPS, Bioconductor bioinformatics software for GO and KEGG functional enrichment analysis of key target genes, and the Cytoscape 3.8.2 software for constructing the "component-target" network and the "component-target-pathway" network map. The results are categorized into three camps: components, targets, and pathways. As for components, 22 active components of ginseng that perform biological activities in the cell membrane, cytoplasm, and nucleus were observed, among which kaempferol, girinimbim, suchilacton, arachidonate, and gomisin B are the main active ones. 650 targets were found, mainly represented by PTGS2, PTGS1, AR, SLC6A4, and CHRM2, 134 of which (especially AKT1, TNF, VEGFA, TP53, EGFR, STAT3, IL-1 β , ESR1, and JUN) contribute to the treatment of IC/BPS. Moreover, the pathways that serve as major contributors are the PI3K-Akt signaling pathway, the HIF-1 signaling pathway, the STAT3 signaling pathway, the MAPK signaling pathway, the NF- κ B signaling pathway, and the apoptosis-related pathway. It was concluded that Ginseng can exert anti-inflammatory, anti-oxidative stress and anti-apoptotic effects on IC/BPS thanks to its multi-component, multi-target and multi-way functions.

[ANTI-INFLAMMATORY DIET FOR WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: THE AID-IC PILOT STUDY](#)

Barbara Gordon, Cynthia Blanton, Rebekah Ramsey, Andrea Jeffery, Laura Richey, Rachel Hulse. *Methods Protoc*. 2022 May 18;5(3):40. doi: 10.3390/mps5030040. PMID: 35645348 PMCID: PMC9149882 DOI: 10.3390/mps5030040

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition characterized by pelvic pain coupled with urinary frequency and urgency. The underlying cause of IC/BPS is unknown; there is no cure. Dietary components exacerbate symptoms. The Anti-Inflammatory Diet for Interstitial Cystitis (AID-IC) employs a randomized, crossover design to evaluate the effect of a plant-based, low saturated fat diet on the quality of life of women with IC/BPS. Insights on the implementation of the protocol and reflections on the facilitators and barriers experienced during the pilot study follow. The logistics of the protocol proved time-consuming; however, the barriers were surmountable. Quantitative and qualitative findings suggest that the AID-IC therapeutic diet may have lessened symptoms and improved the quality of life for many of the women in the study.

[STUDY PROTOCOL AND METHODS FOR EASING PELVIC PAIN INTERVENTIONS CLINICAL RESEARCH PROGRAM \(EPPIC\): A RANDOMIZED CLINICAL TRIAL OF BRIEF, LOW-INTENSITY, TRANSDIAGNOSTIC COGNITIVE BEHAVIORAL THERAPY VS EDUCATION/SUPPORT FOR UROLOGIC CHRONIC PELVIC PAIN SYNDROME \(UCPPS\)](#)

Jeffrey M Lackner, James Jaccard, Brian M Quigley, Tova S Ablow, Teresa L Danforth, Rebecca S Firth, Gregory D Gudleski, Susan S Krasner, Christopher D Radziwon, Alison M Vargovich, J Quentin Clemens, Bruce D Naliboff. *Trials*. 2022 Aug 13;23(1):651. doi: 10.1186/s13063-022-06554-9. PMID: 35964133

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Urologic chronic pelvic pain syndrome (UCPPS) encompasses several common, costly, diagnoses including interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome that are poorly understood and inadequately treated with conventional medical therapies. Behavioral strategies, recommended as a first-line treatment for managing symptoms, are largely inaccessible, time and labor intensive, and technically complex. The Easing Pelvic Pain Interventions Clinical Research Program (EPPIC) is a clinical trial examining the efficacy of low-intensity cognitive behavioral therapy (Minimal Contact CBT or MC-CBT) for UCPPS and its durability 3 and 6 months post treatment. Additional aims include characterizing the operative processes (e.g., cognitive distancing, context sensitivity, coping flexibility, repetitive negative thought) that drive MC-CBT-induced symptom relief and pre-treatment patient variables that moderate differential response. UCPPS patients (240) ages 18-70 years, any gender, ethnicity, and race, will be

randomized to 4-session MC-CBT or a credible, non-specific education comparator (EDU) that controls for the generic effects from simply going to treatment. Efficacy assessments will be administered at pre-treatment, 2 weeks, and 3 and 6 months post treatment-week acute phase. A novel statistical approach applied to micro-analytic mediator assessment schedule will permit the specification of the most effective CBT component(s) that drive symptom relief. Empirical validation of a low-intensity self-management therapy transdiagnostic in scope has the potential to improve the health of chronic pelvic pain patients refractory to medical therapies, reduce social and economic costs, conserve health care resources, as well as inform evidence-based practice guidelines. Identification of change mechanisms and moderators of treatment effects can provide proactive patient-treatment matching fundamental to goals of personalized medicine.

RELATIONSHIP BETWEEN OPIOID PRESCRIPTIONS AND NUMBER OF CHRONIC PAIN CONDITIONS IN WOMEN WITH INTERSTITIAL CYSTITIS

Jordann-Mishael Duncan, Christopher X Hong, Heidi S Harvie, Lily A Brown, Lily A Arya, Edward K Kim. Female Pelvic Med Reconstr Surg. 2022 May 5. doi: 10.1097/SPV.0000000000001195. Online ahead of print. PMID: 35536666

The aim of this study from Philadelphia, USA was to determine the relationship between opioid prescriptions and number of chronic pain conditions in women with interstitial cystitis (IC). This was a cross-sectional study. Women diagnosed with IC based on International Classification of Diseases, Ninth Revision/Tenth Revision codes over an 11-year period (2010-2020) were identified from electronic medical records. Data on comorbidities and ambulatory opioid prescriptions were also extracted. Univariable and multivariable logistic regressions were used to assess the relationship between opioid prescriptions and the number and type of coexisting chronic pain conditions. Of the 1,219 women with IC, 207 (17%) had received at least 1 opioid prescription. The proportions of women with opioid prescriptions for no, 1, 2, and 3 or more coexisting chronic pain conditions were 13%, 20%, 28%, and 32%, respectively. On univariable analysis, factors significantly associated with opioid use were higher body mass index, depression, sleep disorder, endometriosis, chronic pelvic pain, fibromyalgia, joint pain, and number of coexisting chronic pain diagnoses. On multivariable analysis, opioid prescriptions remained significantly associated with the number of coexisting chronic pain diagnoses. It was concluded that the likelihood of opioid prescriptions in women with IC increases with the number and type of coexisting chronic pain conditions and sleep disorders.

URINE OXIDATIVE STRESS BIOMARKERS AS NOVEL BIOMARKERS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yuan-Hong Jiang, Jia-Fong Jhang, Han-Chen Ho, Dan-Yun Chiou, Hann-Chorng Kuo. Biomedicines. 2022 Jul 14;10(7):1701. doi: 10.3390/biomedicines10071701. PMID: 35885006.

Both hypoxia and chronic suburothelial inflammation are important pathophysiological findings in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). This study from Taiwan investigated the roles of urine oxidative stress biomarkers and inflammatory cytokines in patients with IC/BPS. Urine samples were collected from 159 IC/BPS patients and 28 controls. The targeted analytes included oxidative stress biomarkers (8-OHdG, 8-isoprostane, and total antioxidant capacity) and inflammatory cytokines (MCP-1, RANTES, CXCL10, Eotaxin, MIP-1 β , and IL-8). IC/BPS patients were classified into four clinical subgroups, based on the glomerulation grade and the maximal bladder capacity under anesthesia. Patients with IC/BPS had urine oxidative stress biomarkers and inflammatory cytokines profiles that were distinct from those of the controls and among each subgroup. Both 8-OHdG and 8-isoprostane showed a high diagnostic ability to distinguish type 2 IC/BPS patients (as classified by the European Society for the Study of Interstitial Cystitis) from controls. Additionally, they both showed positive and negative correlations with the glomerulation grade and the maximal bladder capacity under anesthesia, respectively. Limitations included intra-individual variation and sex influence. Urine oxidative stress biomarkers might have a role in diagnosing IC/BPS and differentiating its clinical subtypes. In addition to inflammatory cytokines, urine oxidative stress biomarkers have the potential to be novel biomarkers in patients with IC/BPS.

NEW STRATEGIES ACCELERATE THE PATH TO OVERCOME REFRACTORY INTERSTITIAL CYSTITIS

Yiu-Tai Li, Wen-Hsun Chang, Peng-Hui Wang. J Chin Med Assoc. 2022 Jun 1;85(6):665-666. doi: 10.1097/JCMA.0000000000000733. Epub 2022 Jun 10. PMID: 35687138.

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Editorial.

GENDER DIFFERENCES IN THE EXPERIENCE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Sula S Windgassen, Susanna Sutherland, Michael T M Finn, Kemberlee R Bonnet, David G Schlundt, W Stuart Reynolds, Roger R Dmochowski, Lindsey C McKernan. Front Pain Res (Lausanne). 2022 Aug 11;3:954967. doi: 10.3389/fpain.2022.954967. eCollection 2022. PMID: 36034752

This study from the USA assessed gender differences in a debilitating urologic pain condition, interstitial cystitis/bladder pain syndrome (IC/BPS). The authors aimed to (1) evaluate how pain, symptom, and distress profiles of IC/BPS may differ between genders and (2) obtain in-depth first-hand accounts from patients to provide additional insight into their experiences that may explain potential gender differences. A mixed methods approach combined validated patient-reported outcome measures with a single timepoint 90-min focus group. Tests of summary score group differences between men and women were assessed across questionnaires measuring urologic symptoms, pain, emotional functioning, and diagnostic timeline. Qualitative analysis applied an inductive-deductive approach to evaluate and compare experiences of living with IC/BPS. Group narratives were coded and evaluated thematically by gender using the biopsychosocial model, providing insight into the different context of biopsychosocial domains characterizing the male and female experience of IC/BPS. Thirty-seven participants [women (n = 27) and men (n = 10)] completed measures and structured focus group interviews across eight group cohorts conducted from 8/2017 to 3/2019. Women reported greater pain intensity (p = 0.043) and extent (p = 0.018), but not significantly greater impairment from pain (p = 0.160). Levels of psychological distress were significantly elevated across both genders. Further, the duration between time of pain symptom onset and time to diagnosis was significantly greater for women than men (p = 0.012). Qualitative findings demonstrated key distinctions in experiences between genders. Men appeared not to recognize or to deter emotional distress while women felt overwhelmed by it. Men emphasized needing more physiological treatment options whilst women emphasized needing more social and emotional support. Interactions with medical providers and the healthcare system differed substantially between genders. While men reported feeling supported and involved in treatment decisions, women reported feeling dismissed and disbelieved. The findings indicate different pain experiences and treatment needs between genders in persons experiencing urologic pain and urinary symptoms, with potential intervention implications. Results suggest gender health inequality in medical interactions in this urologic population needing further investigation.

SPECIAL ISSUE "BIOMARKERS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)"

See all articles: https://www.mdpi.com/journal/diagnostics/special_issues/Biomarkers_in_IC_BPS

Editorial: SPECIAL ISSUE "BIOMARKERS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)"

Jochen Neuhaus, Andreas Gonsior, Mandy Berndt-Paetz. Diagnostics (Basel). 2022 Jul 11;12(7):1689. doi: 10.3390/diagnostics12071689. PMID: 35885593 DOI: 10.3390/diagnostics12071689

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Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a disabling chronic disease of still unknown origin and complex pathophysiology. The disease affects mainly female patients, with a female to male ratio of about 9 to 1. Prevalence ranges from 52 to 500/100,000 in females and 8 to 41/100,000 in males. The diagnosis of IC/BPS is mainly hampered by the lack of appropriate biomarkers and, therefore, extensive clinical examinations are required to exclude "confusable" diseases. In consequence, most patients experience several years of ineffective treatments of various urinary tract symptoms often associated with, but by themselves not characteristic of, IC/BPS. Unequivocal diagnosis of IC/BPS is the prerequisite to find more effective therapeutic approaches. Therefore, more specific biomarkers are needed to facilitate IC/BPS diagnosis and to stratify patients for treatment at earlier stages of the disease. In this Special Issue, the authors from Germany gathered reviews and original work elucidating the current developments in IC/BPS biomarker research.

FOOD SENSITIVITIES IN A DIVERSE NATIONWIDE COHORT OF VETERANS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Aubrey Jarman, Jessica L Janes, Barbara Shorter, Robert Moldwin, Amanda M De Hoedt, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. J Urol. 2022 Aug 24;101097JU0000000000002938. doi: 10.1097/JU.0000000000002938. Online ahead of print. PMID: 36001744

A MULTISITE FOCUS GROUP STUDY OF US ADULT WOMEN'S BELIEFS AND ASSUMPTIONS ABOUT BLADDER HEALTH AND FUNCTION

Beverly Rosa Williams, Kathryn L Burgio, Jeni Hebert-Beirne, Aimee James, Kimberly Kenton, Daphne Yvette LaCoursiere, Leslie Rickey, Sonya S Brady, Lisa Kane Low, Diane K Newman, Prevention of Lower Urinary Tract

Symptoms (PLUS) Research Consortium. Neurourol Urodyn. 2022 Sep;41(7):1590-1600. doi: 10.1002/nau.25006. Epub 2022 Jul 12. PMID: 35819129

This analysis from the USA explored and characterized the ideas adult women have about how the bladder works, the assumptions guiding their bladder-related behaviors, and the beliefs they hold about how their behaviors affect bladder health. This was a directed content analysis of qualitative data from the Study of Habits, Attitudes, Realities, and Experiences, a focus group study conducted at seven United States research centers (July 2017 to April 2018). Participants were 316 adult women organized by four age categories (age range: 18-93 years). Analysis and interpretation focused on the "bladder assumptions and beliefs" code using a transdisciplinary lens and inductive approach. During their focus group discourse, participants exhibited a speculative mode of thinking about bladder health and function characterized by uncertainty about how the bladder works. They described the bladder as a mechanism for cleansing the body of impurities, viewing it as part of a larger interconnected bodily system to enable the body to stay healthy. They saw it as susceptible to anatomical changes, such as those related to pregnancy and aging. The women also postulated perceived relationships between bladder function and several health behaviors, including eating healthy foods, staying hydrated, engaging in physical activity and exercise, and adopting specific toileting and hygiene practices. The findings underscore the importance of guidance from healthcare professionals and systematic community based educational programs for promoting women's understanding about bladder health and empowering them to exert agency to engage in healthy bladder behaviors.

CENTERING GROUP TREATMENT FOR WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A QUALITATIVE ANALYSIS

Kate Vellenga Meriwether, Virginia Panter, Magdalena McWethy, Heidi Rishel Brakey, Yuko M Komesu. Female Pelvic Med Reconstr Surg. 2022 Jun 18. doi: 10.1097/SPV.0000000000001228. Online ahead of print. PMID: 35759784 DOI: 10.1097/SPV.0000000000001228

Women with interstitial cystitis/bladder pain syndrome (ICBPS) face challenging treatment and feelings of isolation. Centering models of group medical visits have been successful in other spheres but have not been explored in ICBPS therapy. The authors from the USA sought to describe opinions of women with ICBPS regarding Centering visits, including advantages, experience, and barriers to participation and efficacy. Patients who attended Centering visits participated in a focus group and/or filled out written commentary in evaluations, and control patients were individually interviewed. They coded transcripts using NVivo software for emergent themes. The authors conducted 4 control patient individual interviews, had one focus group of Centering patients, and collected comments from 34 post-Centering surveys. Emergent themes of interest included motivations and barriers to joining, cost, leadership, connecting with others, diversity, learning, alternative treatments, and areas for improvement. Regardless of participation in Centering, patients noted the importance of self-care and sharing with other women with ICBPS, and they emphasized feelings of isolation in their disease and discouraging health care experiences. Women in Centering noted that the biggest advantages of Centering were learning from other women with ICBPS, the creation of a welcoming and safe space, and the feeling that Centering was more of a support group than a medical visit. Women noted that barriers to Centering included cost and logistical issues, such as time and format. It was concluded that women with ICBPS treatment note that Centering group visits provide a sense of learning and community that opens them to a wider variety of options.

EXPERIENCES OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: WHAT CAN WE LEARN FROM WOMEN'S ONLINE DISCUSSIONS?

Gabriela Gonzalez, Kristina Vaculik, Carine Khalil, Yuliya Zektser, Corey W Arnold, Christopher V Almario, Brennan M R Spiegel, Jennifer T Anger. J Urol. 2022 Sep 8;101097JU0000000000002955. doi: 10.1097/JU.0000000000002955. Online ahead of print. PMID: 36075005.

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a debilitating chronic condition that disproportionately affects women at a ratio 5:1. The authors from the USA sought to capture women's experiences with IC/BPS by conducting a large-scale digital ethnographic analysis of anonymous posts on internet forums. Online posts were identified using condition-specific keywords and data mining extraction services. Once posts were identified, a random sample of 200 online posts were coded and analyzed by hand using qualitative methods. A Latent Dirichlet Allocation (LDA) probabilistic topic model was applied to the complete dataset to substantiate the qualitative analysis and allow for further thematic discovery. A total of 6,842 posts written by 3,902 unique users from 224 websites were identified. There was a significant overlap between the hand coding and LDA themes. The analysis yielded the following themes: online community engagement, triggers and disease etiologies, medical co-morbidities, quality of life impact, patient experience with medical care, and

alternative therapies and self-management strategies. Additionally, their population appeared to have a high burden of non-urolological associated syndromes (NUAS). The authors identified barriers to patient-centered care and found that online peer support was important for women. They concluded that their digital ethnographic analysis is a novel application of qualitative methods using online sources. Social media analytics appears to capture a broader patient population than that typically included in clinic-based qualitative studies, such as patient interviews and focus groups. Understanding patient behaviors and concerns are important to guide strategies for improving care and the overall experience with this difficult-to-treat condition.

THE CUMULATIVE EFFECT OF UNMET SOCIAL NEEDS ON NONCANCEROUS GENITOURINARY CONDITIONS AND SEVERITY OF LOWER URINARY TRACT SYMPTOMS

T Anne Zwaschka, Elisabeth M Sebesta, Stephanie Gleicher, Melissa R Kaufman, Roger R Dmochowski, William Stuart Reynolds. Neurourol Urodyn. 2022 Sep 6. doi: 10.1002/nau.25038. Online ahead of print. PMID: 36066087.

There is growing awareness on how social determinants of health may significantly influence health outcomes. The purpose of this study from the USA was to investigate the relationship between unmet social needs and the incidence and severity of multiple noncancerous genitourinary conditions. A community-based sample of United States adults was recruited electronically to complete questionnaires on clinical and demographic information, urinary symptoms, and social needs. Logistic regression was used to assess the effect between the number of unmet social needs and various noncancerous genitourinary conditions and severity of lower urinary tract symptoms. Model was adjusted for age, gender, race, insurance, and type of living community. A total of 4,224 participants were included for final analysis. The incidence of all genitourinary conditions assessed was associated with an increasing number of unmet social needs. Additionally, having three or more unmet social needs, as compared to no needs, was associated with an increased risk of all conditions and worse symptoms-including a 23.7% increased risk of interstitial cystitis, 21.9% risk of urge urinary incontinence, and 20.6% risk of overactive bladder. Unmet social needs are associated with an increased incidence of noncancerous genitourinary conditions as well as worse symptom severity, with multiple unmet social needs displaying a cumulative effect. These findings suggest that there is utility in screening patients for unmet social needs, and that the healthcare system should develop a more integrated approach to manage patients with urinary conditions.

NATIONAL PREVALENCE OF IC/BPS IN WOMEN AND MEN UTILIZING VETERANS HEALTH ADMINISTRATION DATA

Jennifer T Anger, Kai B Dallas, Catherine Bresee, Amanda M De Hoedt, Kamil E Barbour, Katherine J Hoggatt, Marc T Goodman, Jayoung Kim, Stephen J Freedland. Front Pain Res (Lausanne). 2022 Aug 24;3:925834. doi: 10.3389/fpain.2022.925834. eCollection 2022. PMID: 36093391

Interstitial cystitis/bladder pain syndrome (IC/BPS) is an immense burden to both patients and the American healthcare system; it is notoriously difficult to diagnose. Prevalence estimates vary widely (150-fold range in women and >500-fold range in men). The authors from the USA aimed to create accurate national IC/BPS prevalence estimates by employing a novel methodology combining a national population-based dataset with individual chart abstraction. In this epidemiological survey, all living patients, with ≥ 2 clinic visits from 2016 to 2018 in the Veterans Health Administration, with an ICD-9/10 code for IC/BPS ($n = 9,503$) or similar conditions that may represent undiagnosed IC/BPS ($n = 124,331$), were identified (other were controls $n = 5,069,695$). A detailed chart review of random gender-balanced samples confirmed the true presence of IC/PBS, which were then age- and gender-matched to the general US population. Of the 5,203,529 patients identified, IC/BPS was confirmed in 541 of 1,647 sampled charts with an IC/BPS ICD code, 10 of 382 charts with an ICD-like code, and 3 of 916 controls. After age- and gender-matching to the general US population, this translated to national prevalence estimates of 0.87% (95% CI: 0.32, 1.42), with female and male prevalence of 1.08% (95% CI: 0.03, 2.13) and 0.66% (95% CI: 0.44, 0.87), respectively. The authors estimate the prevalence of IC/BPS to be 0.87%, which is lower than prior estimates based on survey data, but higher than prior estimates based on administrative data. These potentially represent the most accurate estimates to date, given the broader and more heterogeneous population studied and their novel methodology of combining in-depth chart abstraction with administrative data.

A BIBLIOMETRIC ANALYSIS OF TOP-CITED JOURNAL ARTICLES IN INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME

Xing-Peng Di, Liao Peng, Li-Yuan Xiang, Meng-Hua Wang, Jie Zhang, De-Yi Luo. Int Urogynecol J. 2022 Sep;33(9):2557-2563. doi: 10.1007/s00192-022-05298-z. Epub 2022 Jul 26. PMID: 35881178

The purpose of this study from China was to identify and compare the top-cited articles from all indexed journals and urology-nephrology and obstetrics-gynecology journals in the Institute for Scientific Information Web of Science's Citation Index Expanded on interstitial cystitis and bladder pain syndrome (IC/BPS). Cross-sectional bibliometric analysis of top-cited articles in Web of Science™ (WoS) from 1900-2022. The articles were retrieved by the MeSH terms from NCBI. The characteristics of top 100 cited articles from all indexed journals and specialized journals were evaluated. A total of 5547 articles were collected from 1115 journals, in which 3225 articles were from 141 urological and gynecological specialized journals. The USA and the UK were the top two origins for articles on interstitial cystitis. The articles from non-specialized journals were more frequently cited than those from specialized journals. The citation number per year showed similar results. There were many more open-access articles in non-specialized than specialized journals ($P = 0.0018$). The current study initially queried the articles published on WoS on IC/BPS by the number of citations to identify the differences between two journal categories. The characteristics and trends of research were analyzed by citations to provide insights into the current research status and future direction.

HUNNER LESION

[A PILOT STUDY ON ORAL CYCLOSPORINE A IN ASSOCIATION WITH FULGURATION FOR THE TREATMENT OF INTERSTITIAL CYSTITIS WITH HUNNER'S LESIONS](#)

Raphaëlle Brière, Frédérique Bouchard, Salima Ismail, Annie-Kim Gareau Labelle, Le Mai Tu. Neurourol Urodyn. 2022 Jun 22. doi: 10.1002/nau.24997. Online ahead of print. PMID: 35731015 DOI: 10.1002/nau.24997

The purpose of this study from Canada was to evaluate the efficacy and safety of lesion fulguration in combination with cyclosporine A (CyA) as a maintenance therapy in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) with Hunner's lesion (HL). Retrospective observational study of refractory patients with HL treated with daily 1.5 mg/kg or less of oral CyA following lesion fulguration. Pain severity, subjective improvement, urinary symptoms, and adverse events were used to assess long-term treatment efficiency and safety. Among the 22 patients, median follow-up under CyA was 27 months. Patients reported sustained significant reduction compared to pretreatment in pain, urinary frequency per 24 h, and nocturia. Subjective improvement rate (SIR) and patient global impression of improvement were of 90% and 1 ("very much better"), respectively, including four patients who considered themselves cured (SIR: 100%). Three patients needed an additional procedure due to pain relapse. Minor increase in creatinine was observed and three patients developed or worsened their arterial hypertension. CyA dosage was decreased to 1.2 mg/kg or less for long-term relief ($n = 8$), creatinine increase ($n = 5$), and neutropenia ($n = 1$) with subsequent improvement in renal function without symptom deterioration. Oral CyA seems to allow a sustained long-term relief following HL fulguration by alleviating pain, decreasing urinary symptoms, and procuring great subjective improvement. The daily low dose of 1.5 mg/kg or less appears to have limited adverse events while preventing repeated procedures. Larger trials are warranted.

[PROSPECTIVE RANDOMIZED CONTROLLED TRIAL COMPARING FULGURATION VERSUS FULGURATION AND HYDRODISTENSION FOR HUNNER-TYPE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Hee Seo Son, Hana Yoon, Hye Sun Lee, Jang Hwan Kim. World J Urol. 2022 Jun 15. doi: 10.1007/s00345-022-04062-8. Online ahead of print. PMID: 35704106.

In Hunner-type interstitial cystitis/bladder pain syndrome (IC/BPS), it is unclear whether suburothelial afferents underlying normal-appearing background areas contribute to symptom development. The authors from Korea examined whether adding hydrodistension (HD) to transurethral fulguration (TUF) of Hunner lesions, for the purpose of treating the background areas, is superior to TUF alone. This randomized controlled trial included 52 patients with Hunner-type IC/BPS allocated at a 1:1 (TUF:TUF+HD) ratio. HD was performed at 80 cmH₂O for 8 min before TUF in the TUF+HD group. Thirty-three patients remained until the end of the 6-month observational period. The primary endpoint was the visual analogue scale (VAS) pain score at 1 month. Major secondary endpoints were the treatment-failure rate, VAS pain scores at ≥ 2 months, and frequency-volume chart parameters. Both TUF and TUF+HD showed significant improvement in VAS pain score at 1 month. VAS pain scores were significantly lower in TUF+HD than TUF at 2, 4, and 6 months. Treatment-failure rate was higher in TUF (36.4%) than TUF+HD (17.4%), without significance. Functional capacity and urgency were not significantly different between groups. The addition of HD to TUF tended to be superior to TUF monotherapy for controlling pain in Hunner-type IC/BPS. This indicates that not only Hunner lesions but also normal-appearing background areas may have a role in the pain of IC/BPS.

PENTOSAN POLYSULFATE IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS WITH HUNNER'S LESIONS OR GLOMERULATIONS: SYSTEMATIC REVIEW AND META-ANALYSIS

Bagrat Grigoryan, George Kasyan, Laura Pivazyan, Dmitry Pushkar. Ther Adv Urol. 2022 Jun 2;14:17562872221102809. doi: 10.1177/17562872221102809. eCollection Jan-Dec 2022. PMID: 35677571 PMID: PMC9168945 DOI: 10.1177/17562872221102809

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Bladder pain syndrome/interstitial cystitis (BPS/IC) is a persistent pain perceived in the urinary bladder region, accompanied by at least one symptom, such as pain worsening with bladder filling and daytime or nighttime urinary frequency without any proven infection or obvious pathology. The aim of this study from Russia is to evaluate the efficacy and safety of pentosan polysulfate (PPS) in patients with BPS/IC. A systematic search was performed by PRISMA checklist. Electronic databases, including PubMed and Cochrane library, were checked until 2021 using keywords: 'pentosan polysulfate', 'pain syndrome', 'interstitial cystitis', and bibliography of relevant papers was checked. Inclusion criteria: Patients with confirmed diagnosis of BPS/IC and cystoscopy criteria - Hunner's lesions. Exclusion criteria included hypersensitivity, pregnancy, lactation, and oral therapy for BPS/IC in the period of 1 month before the study and abstracts or unpublished papers. In total, 13 clinical trials were included in systematic review and 7 were included in meta-analysis. Studies evaluated the effectiveness and safety of oral PPS versus placebo or other treatment options. In the first meta-analysis, three studies compared oral PPS with placebo. The second meta-analysis of two studies compared oral PPS with another treatment options (intravesical liposome and CyA). The third meta-analysis of two studies included intravesical regimen of PPS compared with intravesical placebo. The majority of studies do not report any particular serious side effects. PPS treatment has a statistically significant effect over placebo on the subjective improvement of patients with BPS/IC. There was no difference between PPS and other treatment options. Intravesical regimen of PPS had no significant impact on response rates. None of included studies reported severe side effects after intervention.

THE IMPACT OF HUNNER LESION-TYPE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME ON HEALTH-RELATED QUALITY OF LIFE AND THE EFFECTS OF TRANSURETHRAL ABLATION

Kwang Jin Ko, Jihyun Lim, Jiwoong Yu, Danbee Kang, Juhee Cho, Kyu-Sung Lee. Qual Life Res. 2022 Jul 23. doi: 10.1007/s11136-022-03183-2. Online ahead of print. PMID: 35870044 DOI: 10.1007/s11136-022-03183-2

Interstitial cystitis/bladder pain syndrome (IC/BPS) has a negative impact on quality of life. Kwang Jin Ko and colleagues from Korea compared health-related quality of life (HRQoL) of patients with IC/BPS with patients having other diseases using the EuroQol five-dimension (EQ-5D) and evaluated whether the HRQoL is improved after surgery. They compared EQ-5D of patients with Hunner lesion type IC/BPS with patients who had other diseases that cause chronic and severe pain including arthritis and cancer from a cross-sectional analysis of responses to the 2012-2016 Korea National Health and Nutrition Examination Survey. Changes in EQ-5D after transurethral coagulation (TUC) or resection (TUR) were measured in the IC/BPS participants. Compared to the EQ-5D index of normal population, patients with arthritis, cancer and IC/BPS had - 0.07 (95% CI - 0.07, - 0.06), - 0.01 (95% CI - 0.02, - 0.01), and - 0.21 (95% CI - 0.23, - 0.20) lower scores, respectively. Patients with IC/BPS were 35.9, 9.24, and 9.05 times more likely to have an "extreme problem" in pain/discomfort, anxiety/depression, and usual activities EQ-5D domains, respectively, than patients without arthritis/cancer. After TUC or TUR, EQ-5D index was 0.90 in the TUC group and 0.92 in the TUR group. It was concluded that IC/BPS patients have worse HRQoL than healthy individuals. However, after surgical treatment, HRQoL is restored to a level close to normal.

THE JAPANESE HERBAL MEDICINE YOKUKANSAN EXERTED ANTIOXIDANT AND ANALGESIC EFFECTS IN AN EXPERIMENTAL RAT MODEL OF HUNNER-TYPE INTERSTITIAL CYSTITIS

Tatsuki Inoue, Mana Tsukada, Yoshiki Tsunokawa, Yoshiko Maeda, Seiya Fukuoka, Takashi Fukagai, Yoshio Ogawa, Masataka Sunagawa. Medicina (Kaunas). 2022 Jun 15;58(6):810. doi: 10.3390/medicina58060810. PMID: 35744072 PMID: PMC9230041 DOI: 10.3390/medicina58060810

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The Japanese herbal medicine Yokukansan (YKS) has analgesic properties and is used for various pain disorders. The purpose of this study was to investigate the effects of YKS in Hunner-type interstitial cystitis (HIC) using an experimental rat model of HIC and to explore its antioxidant activity and role as the underlying mechanism of action. The antioxidant capacity of YKS was evaluated by determining its hydroxyl radical (-OH) scavenging capacity using electron spin resonance (ESR). Next, the effects of YKS administration were explored using a toll-like receptor-7 agonist-induced rat model of HIC. The von Frey test was performed to assess bladder pain. Three days after HIC induction, the bladder was removed, and the expression of oxidative stress

parameters in the bladder wall was investigated (reactive oxygen metabolites (ROMs), $\cdot\text{OH}$, and 8-hydroxy-2'-deoxyguanosine (8-OHdG)). YKS had a $\cdot\text{OH}$ scavenging capacity according to the ESR study. In the von Frey test, a significant decrease in the withdrawal threshold was observed in the HIC group compared with the control group; however, the decrease was ameliorated by the administration of YKS. Oxidative stress parameters showed increasing tendencies (ROMs test and 8-OHdG) or a significant increase ($\cdot\text{OH}$) in the HIC group compared with the control group; however, the increase was significantly suppressed by the administration of YKS. These findings suggest that YKS is effective against HIC and that its antioxidant activity is involved in the mechanism of action.

CO-EXISTING CONDITIONS (COMORBIDITIES)

SMALL-FIBER POLYNEUROPATHY IS PREVALENT IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Wolff Dylan T, Xu Raymond, Overholt Tyler, Bassett E Hadley, Ahn Christine, Simon Trang, Lee Peyton, Badlani Gopal, Matthews Catherine A, Evans Robert J, Walker Stephen J. *Female Pelvic Medicine & Reconstructive Surgery*: August 31, 2022 - Volume - Issue - 10.1097/SPV.0000000000001240. doi: 10.1097/SPV.0000000000001240.

The pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) is imperfectly understood. Recent studies reported that small-fiber polyneuropathy (SFPN) is common in fibromyalgia, a condition commonly comorbid with IC/BPS. The objective of this USA study was to determine the prevalence of SFPN in a large cohort of IC/BPS patients. Adults diagnosed with IC/BPS scheduled to undergo either therapeutic hydrodistention (n = 97) or cystectomy with urinary diversion (n = 3) were prospectively recruited to this study. A skin biopsy obtained from the lower leg was used for intraepidermal nerve fiber density measurement. Small-fiber polyneuropathy (+/-) status was determined by comparing linear intraepidermal nerve fiber density (fibers/mm²) with normative reference values. Demographic information, medical history, and diagnoses for 14 conditions (both urologic and nonurologic) known to co-occur with IC/BPS were documented from self-report and electronic medical record. In this large cohort of patients with IC/BPS, 31% (31/100) were positive for SFPN. Intraepidermal nerve fiber density was below the median for age and sex in 81% (81/100) of patients. Approximately one-third (31%) of SFPN+ patients reported co-occurring chronic fatigue syndrome, compared with 10.6% of the SFPN- group (P = 0.034). Small-fiber polyneuropathy-positive patients reported significantly fewer allergies than SFPN- patients (37.9% vs 60.6%; P = 0.047). There were no significant differences in bladder capacity or Hunner lesion status between the SFPN+ and SFPN- subgroups. Small-fiber polyneuropathy is a common finding in patients with IC/BPS, and SFPN status is significantly correlated with co-occurring chronic fatigue syndrome and negatively correlated with the presence of allergies in this population.

EXAMINING VAGINAL AND VULVAR HEALTH AND SEXUAL DYSFUNCTION IN PATIENTS WITH INTERSTITIAL CYSTITIS (UNICORN-1 STUDY)

Nobuo Okui, Machiko Okui, Marco Gambacciani. *Int Urogynecol J*. 2022 Sep;33(9):2493-2499. doi: 10.1007/s00192-022-05220-7. Epub 2022 May 11. PMID: 35543734.

The Vaginal Health Index Score (VHIS) and vulvodynia swab tests are used to assess vaginal health and vulvodynia. However, few studies have used these tests in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). IC/BPS is a chronic, debilitating disorder, characterised by urinary frequency, urinary urgency and pelvic pain. It adversely affects organs adjacent to the urinary system, leading to complications of sexual dysfunction. This study from Japan and Italy was aimed at understanding sexual dysfunction in patients with IC/BPS, as well as deterioration of vaginal health and vulvodynia. This study compared the vaginal health of IC/BPS patients with that of asymptomatic control individuals. The Pain Urgency Frequency (PUF) score, Female Sexual Function Index (FSFI), VHIS, and vulvodynia swab tests, were used as tools. The PUF and FSFI are questionnaire-based surveys of bladder symptoms and sexual function respectively. VHIS evaluation and vulvodynia swab tests are performed by physicians. The PUF was used to assess baseline IC/BPS symptoms to validate the patient population, and FSFI, vulvodynia swab tests and VHIS were used to determine between-group differences. Thirty-seven patients were recruited in each group. The IC/BPS group had a higher PUF score, worse total FSFI, and worse vulvodynia swab test and total VHIS scores than those of the control group. Asian women with IC/BPS experienced greater sexual dysfunction, worsened vaginal health and increased vulvodynia compared with control individuals. Information on vaginal and vulva health is very useful in evaluating IC/BPS patients.

[COMORBIDITIES OF BLADDER PAIN SYNDROME IN THE CONTEXT OF THE HITOP DISTRESS CATEGORY: A SYSTEMATIC REVIEW AND META-ANALYSIS](#)

Linda Fischer-Grote, Vera Fössing, Martin Aigner, Markus Boeckle, Elisabeth Fehrmann. *Int Urogynecol J.* 2022 Sep;33(9):2335-2356. doi: 10.1007/s00192-022-05129-1. Epub 2022 Mar 9. PMID: 35262767

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The aim of this systematic review and meta-analysis from Austria is, looking at different care settings, to examine prevalence rates of psychological distress-level comorbidities in female interstitial cystitis/bladder pain syndrome (IC/BPS) patients, their impact on Quality of Life (QoL), and the correlation between such comorbidities and symptom severity. A systematic literature search according to PRISMA guidelines was conducted in PubMed, PsycInfo, Web of Science, Science Direct, and Google Scholar. Twenty-nine studies were found that met inclusion criteria. Prevalence rates of depression and anxiety are higher in IC/BPS patients compared to the general population; however, due to a wide array of measurements, statistical comparisons between care settings were only possible in two cases showing mixed results. No studies meeting inclusion criteria exist that examine PTSD and borderline personality disorder, though rates of past traumatic experiences seem to be higher in patients than in healthy controls. Psychological comorbidities of the distress category, especially depression, are found in most studies to be related to symptom severity, also yielding statistically significant associations. While there is still a need for studies focused on some of the comorbidities as well as on different care settings, the data already show that psychological comorbidities of the distress category play an important role in IC/BPS patients regarding suffering, QoL, and symptom severity, thus emphasizing the need for highly specialized interdisciplinary treatment.

DIFFERENT TYPES OF INFLAMMATORY BLADDER

[MOLECULAR MECHANISMS AND KEY PROCESSES IN INTERSTITIAL, HEMORRHAGIC AND RADIATION CYSTITIS](#)

Clément Brossard, Anne-Charlotte Lefranc, Anne-Laure Pouliet, Jean-Marc Simon, Marc Benderitter, Fabien Milliat, Alain Chapel. *Biology (Basel).* 2022 Jun 28;11(7):972. doi: 10.3390/biology11070972. PMID: 36101353.

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Cystitis is a bladder disease with a high rate of prevalence in the world population. This report focuses on Interstitial Cystitis (IC), Hemorrhagic Cystitis (HC) and Chronic Radiation Cystitis. These pathologies have different etiologies, but they share common symptoms, for instance, pain, bleeding, and a contracted bladder. Overall, treatments are quite similar for abacterial cystitis, and include bladder epithelium protective or anti-inflammatory agents, alleviating pain and reducing bleeding. This review from France summarizes the mechanisms that the pathologies have in common, for instance, bladder dysfunction and inflammation. Conversely, some mechanisms have been described as present in only one pathology, such as neural regulation. Based on these specificities, the authors propose identifying a mechanism that could be common to all the above-mentioned pathologies.

Simple Summary

Pathologies of the bladder are called cystitis. They cause discomfort for the patient. Due to persistent pain, bleeding, urinary incontinence, and uncontrolled urination, the chronic forms cause considerable degradation to patient quality of life. Currently, there is no curative treatment for the most severe forms. This is both an economic and a societal problem. Although the different forms of cystitis have different causes, they share common mechanisms. The authors from France propose to describe in detail the key processes and the associated mechanisms involved in abacterial cystitis.

PERSISTENT NEED TO URINATE (PNU)

[PERSISTENT NEED TO URINATE: A COMMON SENSORY SYMPTOM LEADING TO URINARY DISCOMFORT. A STUDY OF 79 CASES](#)

Claire Hentzen, Jalesh N. Panicker, Martina Pericolini, Enrico Finazzi Agrò, Camille Chesnel, Emilie Blouet, Frederique Le Breton, Samer Sheikh Ismaël, Rebecca Haddad, Gerard Amarenco. *Continence Reports, Volume 2, June 2022, 100007*

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An unpleasant, inappropriate, and persistent need to urinate (PNU) is a sensory symptom reported by some patients with lower urinary tract symptoms (LUTS). However, no detailed definition of this symptom exists. This study from France, Italy and the UK aimed to describe the characteristics of patients reporting PNU and to discuss the pathophysiology and therapeutic approach. The clinical and urodynamic findings of patients presenting with PNU without chronic bladder pain syndrome or neurological or urological conditions between

October 2019 and December 2020 were retrospectively reviewed. The treatment efficacy was self-reported at follow-up as “total cure”, “significant improvement” or “no modification”. Seventy-nine patients were included (51 women (65%), mean age 49 years (Standard Deviation (SD)18)). The mean duration of symptoms was 7 years (SD 11). Frequency was commonly associated with PNU (mean interval between voids 103 min (SD 69)) and 50 patients (63%) reported nocturia. Voiding difficulties were described in 33 cases (40%). The mean first desire to void was 112mL (SD 93) with normal maximum cystometric capacity of 397mL (SD 135), and 5 patients had detrusor overactivity. Proposed treatments were tibial nerve stimulation (n=25) with a total cure or significant improvement in 17 cases, alpha-blockers (n=8) with an improvement in 4 patients, antimuscarinics (n=29) with an improvement in only 3 patients, and antidepressant or antiepileptic (n=8) with an improvement in 5 patients. It was concluded that PNU is poorly described but could be responsible for LUTS. Further studies to understand the underlying mechanisms and to assess the therapeutic efficacy of the different options are required.

GUIDELINES

MYOFASCIAL PELVIC PAIN: BEST ORIENTATION AND CLINICAL PRACTICE. POSITION OF THE EUROPEAN ASSOCIATION OF UROLOGY GUIDELINES PANEL ON CHRONIC PELVIC PAIN

Pedro Abreu-Mendes, Andrew P Baranowski, Bary Berghmans, Jan Borovicka, Angela M Cottrell, Paulo Dinis-Oliveira, Sohier Elneil, John Hughes, Bert E J Messelink, Victoria Tidman, Rui Pinto, Jure Tornic, Ida Flink, Brian A Parsons, Valentin Zumstein, Daniel S Engeler. Eur Urol Focus. 2022 Aug 6;S2405-4569(22)00168-7. doi: 10.1016/j.euf.2022.07.007. Online ahead of print. PMID: 35945131 DOI: 10.1016/j.euf.2022.07.007

Despite the high prevalence of a myofascial pain component in chronic pelvic pain (CPP) syndromes, awareness and management of this component are lacking among health care providers. The purpose of this article was to summarize the current state of the art for the management of myofascial pain in chronic primary pelvic pain syndromes (CPPPS) according to scientific research and input from experts from the European Association of Urology (EAU) guidelines panel on CPP. A narrative review was undertaken using three sources: (1) information in the EAU guidelines on CPP; (2) information retrieved from the literature on research published in the past 3 yr on myofascial pelvic pain; and (3) expert opinion from panel members. Studies confirm a high prevalence of a myofascial pain component in CPPPS. Examination of the pelvic floor muscles should follow published recommendations to standardize findings and disseminate the procedure. Treatment of pelvic floor muscle dysfunction and pain in the context of CPP was found to contribute to CPP control and is feasible via different physiotherapy techniques. A multidisciplinary approach is the most effective. Despite its high prevalence, the myofascial component of CPP has been under-evaluated and under-treated to date. Myofascial pain must be assessed in all patients with CPPPS. Treatment of the myofascial pain component is relevant for global treatment success. Further studies are imperative to reinforce and better define the role of each physiotherapy technique in CPPPS.

Patient summary: Pain and inflammation of the body's muscle and soft tissues (myofascial pain) frequently occurs in pelvic pain syndromes. Its presence must be evaluated to optimize management for each patient. If diagnosed, myofascial pain should be treated.

URINARY TRACT INFECTION

GUIDELINE OF GUIDELINES: MANAGEMENT OF RECURRENT URINARY TRACT INFECTIONS IN WOMEN

Michael Kwok, Stephen McGeorge, Johanna Mayer-Coverdale, Bianca Graves, David L Paterson, Patrick N A Harris, Rachel Esler, Caroline Dowling, Sumudu Britton, Matthew J Roberts. BJU Int. 2022 May 17. doi: 10.1111/bju.15756. Online ahead of print. PMID: 35579121 DOI: 10.1111/bju.15756

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The purpose of this article from Australia was to compare recurrent urinary tract infection (rUTI) guidelines from major urological and non-urological organisations internationally and identify areas of consensus and discrepancy. PubMed, Google Scholar and the official webpages of major urological, gynaecological, infectious diseases and general practice organisations were searched for rUTI guidelines in March 2022. Nine guidelines were included for review: European Association of Urology, National Institute for Health and Care Excellence (NICE), Society of Obstetricians and Gynaecologists of Canada, American Academy of Family Physicians, Mexican College of Gynaecology and Obstetrics Specialists, Swiss Society of Gynaecology and Obstetrics, Spanish Society of Infectious Diseases and Clinical Microbiology, German Association of Scientific Medical Societies, and the combined American Urological Association/Canadian Urological Association/Society of

Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction. The definition and evaluation of rUTIs, and antibiotic prophylaxis strategies, were mostly consistent across guidelines, and emphasised the importance of obtaining urine cultures and limiting cystoscopy and upper tract imaging in women without risk factors. Variable recommendations were noted for symptomatic treatment, self-initiated antibiotics, and antibiotic-sparing preventative strategies such as cranberry, vaginal oestrogen, immunoactive prophylaxis with OM-89, intravesical glycosaminoglycan instillation, and phytotherapeutics. Recent randomised evidence supports the use of methenamine hippurate. Either continuous or post-coital prophylactic antibiotics were supported by all guidelines. None of the guidelines were tailored to the management of recurrent complicated UTI. In conclusion, multiple rUTI guidelines were identified and mostly limited their recommendations to otherwise healthy non-pregnant women with uncomplicated cystitis. Variation was noted, particularly in antibiotic-sparing preventative strategies. Some conflicting recommendations are due to more recent guidelines including updated evidence. Future guidelines should consider recommendations to assist management of complex patient groups, such as recurrent complicated UTI.

KETAMINE CYSTITIS

[ACQUIRED METHEMOGLOBINEMIA IN A KETAMINE-INDUCED ULCERATIVE CYSTITIS PATIENT: A CASE REPORT](#)

Spencer Kozik, Cali Kirkham, Gabriel Sudario. Clin Pract Cases Emerg Med. 2022 May;6(2):137-140. doi: 10.5811/cpcem.2022.1.55277. PMID: 35701344 DOI: 10.5811/cpcem.2022.1.55277

As ketamine gains traction as an alternative to opiates in the treatment of chronic pain, ketamine-induced ulcerative cystitis is now being recognized as a complication of its use. The first-line treatment is phenazopyridine, an over-the-counter medication for dysuria that historically has been known to cause methemoglobinemia. This report from the USA details the case of a patient presenting to the emergency department (ED) with methemoglobinemia. A 66-year-old woman with a complicated medical history presented to the ED with anemia and hypoxia after extended use of phenazopyridine for treatment of ketamine-induced ulcerative cystitis. She was found to have methemoglobinemia secondary to phenazopyridine used to treat her ketamine-induced ulcerative cystitis, a previously undocumented sequelae of chronic ketamine use. She was admitted to the hospital for three days and made a full recovery. This case highlights the need to suspect ketamine-induced ulcerative cystitis in patients who use ketamine chronically and be judicious in the use of phenazopyridine for symptom management to prevent life-threatening complications.

URINARY TRACT

[P2 PURINERGIC RECEPTOR DYSREGULATION IN UROLOGIC DISEASE](#)

Janielle P Maynard, Karen S Sfanos. Purinergic Signal. 2022 Jun 10;1-21. doi: 10.1007/s11302-022-09875-1. Online ahead of print. PMID: 35687210 PMCID: PMC9184359 DOI: 10.1007/s11302-022-09875-1

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P2 purinergic receptors are involved in the normal function of the kidney, bladder, and prostate via signaling that occurs in response to extracellular nucleotides. Dysregulation of these receptors is common in pathological states and often associated with disease initiation, progression, or aggressiveness. Indeed, P2 purinergic receptor expression is altered across multiple urologic disorders including chronic kidney disease, polycystic kidney disease, interstitial cystitis, urinary incontinence, overactive bladder syndrome, prostatitis, and benign prostatic hyperplasia. P2 purinergic receptors are likewise indirectly associated with these disorders via receptor-mediated inflammation and pain, a common characteristic across most urologic disorders. Furthermore, select P2 purinergic receptors are overexpressed in urologic cancer including renal cell carcinoma, urothelial carcinoma, and prostate adenocarcinoma, and pre-clinical studies depict P2 purinergic receptors as potential therapeutic targets. The authors from the USA highlight the compelling evidence for the exploration of P2 purinergic receptors as biomarkers and therapeutic targets in urologic cancers and other urologic disease. Likewise, there is currently optimism for P2 purinergic receptor-targeted therapeutics for the treatment of inflammation and pain associated with urologic diseases. Further exploration of the common pathways linking P2 purinergic receptor dysregulation to urologic disease might ultimately help in gaining new mechanistic insight into disease processes and therapeutic targeting.

[NANOTECHNOLOGY AS A TOOL TO ADVANCE RESEARCH AND TREATMENT OF NON-ONCOLOGIC UROGENITAL DISEASES](#)

Justin Loloi, Mustafa Babar, Kelvin P Davies, Sylvia O Suadicani. *Ther Adv Urol.* 2022 Jul 26;14:17562872221109023. doi: 10.1177/17562872221109023. eCollection 2022 Jan-Dec. PMID: 35924206

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Nanotechnology represents an expanding area of research and innovation in almost every field of science, including Medicine, where nanomaterial-based products have been developed for diagnostic and therapeutic applications. Because of their small, nanoscale size, these materials exhibit unique physical and chemical properties that differ from those of each component when considered in bulk. In Nanomedicine, there is an increasing interest in harnessing these unique properties to engineer nanocarriers for the delivery of therapeutic agents. Nano-based drug delivery platforms have many advantages over conventional drug administration routes as this technology allows for local and transdermal applications of therapeutics that can bypass the first-pass metabolism, improves drug efficacy through encapsulation of hydrophobic drugs, and allows for a sustained and controlled release of encapsulated agents. In Urology, nano-based drug delivery platforms have been extensively investigated and implemented for cancer treatment. However, there is also great potential for use of nanotechnology to treat non-oncologic urogenital diseases. The authors from the USA provide an update on research that is paving the way for clinical translation of nanotechnology in the areas of erectile dysfunction (ED), overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS), and catheter-associated urinary tract infections (CAUTIs). Overall, preclinical and clinical studies have proven the utility of nanomaterials both as vehicles for transdermal and intravesical delivery of therapeutic agents and for urinary catheter formulation with antimicrobial agents to treat non-oncologic urogenital diseases. Although clinical translation will be dependent on overcoming regulatory challenges, it is inevitable before there is universal adoption of this technology to treat non-oncologic urogenital diseases.

UROBIOME / MICROBIOME

[THE UROBIOMES OF ADULT WOMEN WITH VARIOUS LOWER URINARY TRACT SYMPTOMS STATUS DIFFER: A RE-ANALYSIS](#)

Cara Joyce, Thomas Halverson, Caroline Gonzalez, Linda Brubaker, Alan J Wolfe. *Front Cell Infect Microbiol.* 2022 Jun 9;12:860408. doi: 10.3389/fcimb.2022.860408. eCollection 2022. PMID: 35755842 PMCID: PMC9218574 DOI: 10.3389/fcimb.2022.860408

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The discovery of the urinary microbiome (urobiome) has created opportunities for urinary health researchers who study a wide variety of human health conditions. This manuscript from the USA describes an analysis of catheterized urine samples obtained from 1,004 urobiome study participants with the goal of identifying the most abundant and/or prevalent (common) taxa in five clinically relevant cohorts: unaffected adult women (n=346, 34.6%), urgency urinary incontinence (UUI) (n=255, 25.5%), stress urinary incontinence (SUI) (n=50, 5.0%), urinary tract infection (UTI) (n=304, 30.4%), and interstitial cystitis/painful bladder syndrome (IC/PBS) (n=49, 4.9%). Urine was collected via transurethral catheter and assessed for microbes with the Expanded Quantitative Urine Culture (EQUC) technique. For this combined analytic cohort, the mean age was 59 ± 16 ; most were Caucasian (n=704, 70.2%), Black (n=137, 13.7%), or Hispanic (n=130, 13.0%), and the mean BMI was 30.4 ± 7.7 . Whereas many control or IC/PBS cohort members were EQUC-negative (42.4% and 39.8%, respectively), members of the other 3 cohorts were extremely likely to have detectable microbes. The detected urobiomes of the controls and IC/PBS did not differ by alpha diversity or genus level composition and differed by only a few species. The other 3 cohorts differed significantly from the controls. As expected, *Escherichia* was both prevalent and highly abundant in the UTI cohort, but other taxa also were prevalent at more moderate abundances, including members of the genera *Lactobacillus*, *Streptococcus*, *Staphylococcus*, *Corynebacterium*, *Actinomyces*, and *Aerococcus*. Members of these genera were also prevalent and highly abundant in members of the UUI cohort, especially *Streptococcus anginosus*. Intriguingly, these taxa were also detected in controls but at vastly lower levels of both prevalence and abundance, suggesting the possibility that UUI-associated symptoms could be the result of an overabundance of typical urobiome constituents. Finally, prevalence and abundance of microbes in the SUI cohort were intermediate to those of the UUI and control cohorts. These observations can inform the next decade of urobiome research, with the goal of clarifying the mechanisms of urobiome community composition and function. There is tremendous potential to improve diagnosis, evaluation and treatment for individuals affected with a wide variety of urinary tract disorders.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

MACULOPATHY SECONDARY TO CHRONIC USE OF PENTOSAN POLYSULFATE SODIUM IN TREATMENT OF INTERSTITIAL CYSTITIS

Tara L Atanasoff, Michelle N Schleis, Jaclyn A Keller. *Clin Exp Optom.* 2022 Aug 28;1-3. doi: 10.1080/08164622.2022.2111200. Online ahead of print. PMID: 36031934

PENTOSAN POLYSULFATE SODIUM-ASSOCIATED MACULOPATHY: EARLY DETECTION USING OCT ANGIOGRAPHY AND CHORIOCAPILLARIS FLOW DEFICIT ANALYSIS

Meira Fogel Levin, Ahmad Santina, Giulia Corradetti, Adrian Au, Anthony Lu, Neda Abraham, Swathi Somisetty, Veronica Romero Morales, Alice Wong, Srinivas Sadda, David Sarraf. *Am J Ophthalmol.* 2022 Jul 25;S0002-9394(22)00284-7. doi: 10.1016/j.ajo.2022.07.015. Online ahead of print. PMID: 35901995

This retrospective clinical cohort study from the USA compares choriocapillaris flow deficit (CC FD) analysis using optical coherence angiography (OCT) angiography in eyes of patients treated with high cumulative dosages of pentosan polysulfate sodium (PPS) but no signs of retinal toxicity versus healthy age matched controls. Patients treated with PPS for interstitial cystitis with cumulative dose of more than 1000 grams underwent multimodal imaging screening to exclude evidence of PPS maculopathy or other retinal findings. All study patients and age-matched healthy controls completed a 3 × 3 mm macular volume scan OCT angiography (OCTA) using the SOLIX full range OCT. En face OCTA images at the level of the CC were exported and CC FDs were computed and compared between groups. Fifteen patients treated with PPS and fifteen age-matched controls were included. The mean PPS cumulative dose was 1974±666 grams over a mean of 17.6 ±6.8 treatment years. All patients registered a visual acuity of 20/25 or better and normal fundus autofluorescence (FAF), OCT, multicolor, near-infrared reflectance (NIR) and ultra-widefield fundus color and AF images. The CC FD was 32.7±3.6% in the PPS group compared to 28.6±4.3% in the control group (p=0.023). Patients treated with PPS long enough to accumulate dosages greater than 1000 grams showed significant CC flow impairment before the development of macular toxicity signs with OCT, NIR, and FAF, compared to age-matched normal controls. Thus, the choroid may be the earliest manifestation of ocular toxicity, predating the development of clinically evident retinal pigment epithelium (RPE) injury. The subsequent RPE disruption may be the result of choriocapillaris impairment or primary PPS toxicity. Assessment of the CC on OCTA may be a useful tool for early detection of toxicity, although further longitudinal studies are required.

CHRONIC PELVIC PAIN/DYSFUNCTION

EXPLORING CONCOMITANT PELVIC FLOOR SYMPTOMS IN COMMUNITY-DWELLING FEMALES AND MALES

Grietje E Knol-de Vries, G G Alec Malmberg, Françoise J M Notenboom-Nas, Danny B H Voortman, Anouk de Groot, Janny H Dekker, Gommert A van Koeveringe, Peter Leusink, Marlies Bosch, Marijke C Ph Sliker-Ten Hove, Debby G Keuken, Marco H Blanker. *Neurourol Urodyn.* 2022 Aug 21. doi: 10.1002/nau.25020. Online ahead of print. PMID: 35989534.

Researchers and clinicians tend to focus on one pelvic floor symptom (PFS) at a time. However, the pelvic floor acts as one functional unit, increasing the likelihood of concurrent PFS in patients with pelvic floor dysfunction. There is also a paucity of literature on the prevalence of concomitant PFS, especially in males. Therefore, the authors from the Netherlands explored the occurrence of concomitant PFS in community-dwelling males and females. This prospective observational population-based cohort study included males and females aged ≥16 years from a single Dutch municipality. Participants completed validated questionnaires on lower urinary tract symptoms (LUTS), defecation problems, sexual dysfunction, pelvic pain, and pelvic organ prolapse. Medical general practitioner records were examined. Furthermore, a randomly selected group of non-responders aged <80 years received a short questionnaire, to study response bias. The authors invited 11 724 people, among which 839 females and 566 males completed the questionnaires. Of the female participants, 286 (34.1%) reported no PFS, and 251 (29.9%) reported two or more PFS. The most prevalent PFS clusters in females were sexual dysfunction and pelvic pain, sexual dysfunction and defecation problems, LUTS and defecation problems, and LUTS, defecation problems, and pelvic pain. Of the male participants, 212 (37.5%) reported no PFS, and 191 (33.7%) reported two or more PFS. The most prevalent clusters in males were sexual dysfunction and LUTS, defecation problems and LUTS, and sexual dysfunction, LUTS, and defecation problems. A considerable overlap existed between PFS, with differences in PFS clusters between females and males. Of note, females reported pelvic pain more than males. The authors concluded that healthcare providers should address all PFS in males and females.

A SYSTEMATIC REVIEW OF DIAGNOSTIC TESTS TO DETECT PELVIC FLOOR MYOFASCIAL PAIN

Supuni C Kapurubandara, Basia Lowes, Ursula M Sansom-Daly, Rebecca Deans, Jason A Abbott. Int Urogynecol J. 2022 Jul 7. doi: 10.1007/s00192-022-05258-7. Online ahead of print. PMID: 35796787 DOI: 10.1007/s00192-022-05258-7

Myofascial pain arising from pelvic floor muscles occurs in women with vaginismus, interstitial cystitis and endometriosis but is often overlooked. The aim of this study from Australia was to examine alternative diagnostic tests to detect pelvic floor myofascial pain compared with standardized vaginal palpation of pelvic floor muscles as the reference test. A systematic review was prospectively conducted (PROSPERO-CRD42020183092) according to PRISMA guidelines. Databases searched included Ovid Medline 1946-, Embase 1957-, Scopus 1960-, Cochrane Combined, Clinical trials, Google Scholar (top 200 articles), Web of Science, TRIP, BIOSIS, DARE, CINHALL, EmCare, PEDro, ProQuest and EBSCOhost up to July 2020. Articles were independently screened by two authors and assessed for bias using QUASDAS-2 tool. A total of 26,778 articles were screened and 177 were selected for full text review, of which 5 were selected for final analysis. Five studies included 9694 participants of which 1628 had pelvic floor myofascial pain. Only one study reported data to calculate sensitivities and specificities of the index test, which utilized a score of > 40 on the Central Sensitization Inventory to detect women with pelvic floor myofascial pain and revealed a sensitivity of 34.8% and a specificity of 84.9% compared to the reference test. This systematic review did not reveal any diagnostic test superior to the pre-defined reference test. There is a lack of consensus on the definition of pelvic floor myofascial pain and a lack of a validated diagnostic criteria which must be addressed to progress with meaningful research in this field.

CENTRAL SENSITISATION IN PELVIC PAIN: A COHORT STUDY

Amelia Ryan, Martin Healey, Claudia Cheng, Uri Dior, Charlotte Reddington. Aust N Z J Obstet Gynaecol. 2022 Aug 11. doi: 10.1111/ajo.13596. Online ahead of print. PMID: 35950448 DOI: 10.1111/ajo.13596

Central sensitisation (CS) leads to pain amplification and impacts on the management of pelvic pain (PP). Identification of CS in patients with PP may provide additional treatment pathways and improve patient outcomes. The aims of this study from Australia, New Zealand and Israel were to quantify the prevalence of questionnaire-predicted CS (QPCS) in patients presenting with PP and investigate associations between QPCS and clinical variables. This was an observational, cross-sectional study. Subjects with PP completed a questionnaire comprising four validated tools: the Central Sensitisation Inventory (CSI) for QPCS, Pain Catastrophising Scale for Catastrophising Trait, Bladder Pain/Interstitial Cystitis Symptom Score for bladder pain syndrome (BPS) and the Rome IV criteria for irritable bowel syndrome (IBS). One hundred and eleven women were enrolled in the study; 74.8% (n = 83) had a CSI score of >40, indicating the presence of QPCS. Subjects with QPCS were more likely to screen positive for catastrophising trait. They were more likely to experience pain for more than two years and other pain symptoms involving bladder, bowel, back and vulva. They also had higher previous diagnoses of mental health disorder. The authors concluded that QPCS occurs frequently in patients with PP, and subjects with QPCS experience more prolonged and complex pain.

ROLE OF PELVIC ORGAN CROSSTALK IN DYSFUNCTION OF THE BOWEL AND BLADDER.

Sinha, S., Vasudeva, P., Bharadwaj, S. et al. Curr Bladder Dysfunct Rep 17, 91–103 (2022).

The distal large bowel and urinary bladder are contiguous pelvic organs that share a common embryological origin with potential interaction in health and disease. The authors from India report that literature on the subject remains disorganized and largely unrecognized by clinical guidelines. Understanding this interaction could potentially improve patient outcomes. The bladder and bowel interact by several mechanisms that can be broadly classified as peripheral neural, spinal central, supraspinal central, and non-neuronal. In vivo studies show that experimental insults in one organ induce changes in behavior of the other. Laboratory studies have better defined the pathways that underlie these interactions. Clinical data shows an association between bowel and bladder symptoms in a wide spectrum of patient populations. Management of these bowel symptoms could potentially improve lower urinary tract symptoms in the clinical setting. Current clinical guidelines, such as the American Urological Association Guidelines for Overactive Bladder, European Society of Pediatric Urology Guidelines for Pediatric Neurogenic Bladder, European Association of Urology Neuro-Urology Guidelines, or the UK National Institute for Health and Care Excellence Guidelines on Urinary Incontinence and Pelvic Organ Prolapse, need to take better cognizance of this relationship. Dysfunctions of the bowel and bladder commonly co-exist. While this interaction occurs at multiple levels, much work remains to be done to improve our understanding especially with regard to management of bowel dysfunction to specifically improve lower urinary tract symptoms.

PHYSICAL EXAM EVALUATION OF PELVIC FLOOR DYSFUNCTION

Jaclyn H. Bonder, Tanya DiFrancesco. T. Physical Exam Evaluation of Pelvic Floor Dysfunction. Curr Bladder Dysfunct Rep 17, 69–75 (2022). <https://doi.org/10.1007/s11884-022-00651-w>

The complex etiologies of pelvic floor muscle dysfunction have led to a multidisciplinary and collaborative approach to the evaluation of pelvic pain and pelvic floor muscle dysfunction. A pelvic floor examination is an important part of the workup for pelvic floor dysfunction to assess for non-genitourinary causes of urinary symptoms, amongst others. The goal of this article from the USA is to describe the physiatric pelvic floor physical exam and how it can be utilized by practitioners to help identify potential pelvic floor dysfunction etiologies. The information gathered on this exam is helpful for the clinician to identify when pelvic floor muscle function is abnormal and may lead to urinary dysfunction. Data on physical examination to help diagnose pelvic floor dysfunction remains scarce with only a few articles on this topic in the past few years. Despite recent articles, there is still no standardized pelvic floor examination to diagnose pelvic floor dysfunction. However, a thorough pelvic floor musculoskeletal examination can help identify muscular dysfunction which may contribute to urologic symptoms or voiding disorders. Future research should be aimed at methods to develop a protocol so that the physical examination can be utilized as a reliable indicator of this issue.

WHEN AND HOW TO UTILIZE PUDENDAL NERVE BLOCKS FOR TREATMENT OF PUDENDAL NEURALGIA

Abigail Cain, Kimberly Carter, Christina Salazar, Amy Young. Clin Obstet Gynecol. 2022 Jun 3. doi: 10.1097/GRF.0000000000000715. Online ahead of print. PMID: 35703212.

Chronic pelvic pain is a common cause of pain in reproductive age women with debilitating consequences for affected women's health and quality of life. Treatment providers must be well versed in all treatment options for these patients, understanding the overlap in the management and treatment of chronic pelvic pain caused by pudendal neuralgia, myofascial pelvic pain, and vulvodynia. Pudendal blocks are a simple and quick procedure that can be performed in the office and often helps improve all the above conditions when used along with other treatment options. The authors from the USA review the anatomy and methodology on when and how to perform pudendal blocks in the office to better inform the general gynecologist on how to implement offering this treatment in the outpatient clinical setting.

AN ONLINE SURVEY OF PELVIC CONGESTION SUPPORT GROUP MEMBERS REGARDING COMORBID SYMPTOMS AND SYNDROMES

Steven J Smith, Michael Sichlau, Luke E Sewall, B Holly Smith, Brenda Chen, Neal Khurana, Peter C Rowe. Phlebology. 2022 Jul 13;268355221112567. doi: 10.1177/0268355221112567. Online ahead of print. PMID: 35831253.

Patients with pelvic congestion syndrome (PCS) often report overlapping somatic symptoms and syndromes. The objective of this study from the USA was to explore the prevalence of co-existing symptoms and self-reported syndrome diagnoses among women with PCS and to inform future research hypotheses. A brief online survey was offered to members of a PCS support group website. Responses were assessed for self-reported co-existing symptoms and formal diagnoses, including: chronic fatigue syndrome, fibromyalgia, postural tachycardia syndrome, irritable bowel syndrome, migraines, interstitial cystitis, and temporomandibular joint dysfunction. Of a total of 6000 members, there were 398 respondents; 232 (59%) had not yet been treated for PCS. Among these, the most prevalent co-existing symptoms were as follows: severe fatigue (72%), dizziness (63%), IBS symptoms (61%), brain fog (33%), migraines (49%), polyuria or dysuria (41%), excessive sweating (31%), TMJ pain (31%), and loose skin or lax joints (18%). These are much higher than reported for the general female population. The most commonly self-reported comorbid syndrome diagnoses for the overall group of 398 were: irritable bowel syndrome (29%), fibromyalgia (13%), spinal nerve problems (18%), interstitial cystitis (10%), postural tachycardia syndrome (9%), hypertension (11%), chronic fatigue syndrome (10%), and Ehlers-Danlos syndrome (6%). Other than with hypertension, these rates are variably higher than in the general population. Several self-reported co-existing symptoms and syndromes are more prevalent in members of a PCS support group relative to the reported prevalence in the general population. More formal investigation is warranted to evaluate this finding and to investigate potential etiologic links. Ehlers-Danlos Syndrome appears to be common in self-identifying PCS women.

BLADDER ENDOMETRIOSIS

A REVIEW OF URINARY TRACT ENDOMETRIOSIS

Amanda K Sherman, Lara S MacLachlan. Curr Urol Rep. 2022 Sep 1. doi: 10.1007/s11934-022-01107-8. Online ahead of print. PMID: 36048338

The purpose of this study from the USA was to describe the presenting signs and symptoms of patients with urinary tract endometriosis (UTE), appropriate workup, and to review medical and surgical therapies for symptom palliation and definitive management. UTE is a condition that clinicians should maintain a high index of suspicion for, as symptoms can be easily misdiagnosed from other causes. Surgical resection of implants appears to offer safe and durable symptom relief. Urinary tract endometriosis may present with symptoms overlapping with interstitial cystitis, nephrolithiasis, bladder overactivity, or recurrent urinary tract infections, and may or may not be cyclical in nature. Cyclical gross hematuria is considered pathognomonic, though final diagnosis must be made after a pathologic review. Without proper diagnosis and treatment, consequences such as silent renal loss from asymptomatic obstruction may result. After the diagnosis is made, initial therapy can be undertaken with hormonal treatment to palliate symptoms (most commonly in the form of combined oral contraceptives), followed by surgical resection for a definitive treatment option.

ECTOPIC ENDOMETRIOSIS IN THE PELVIC CAVITY EVOKES BLADDER HYPERSENSITIVITY VIA TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 HYPEREXPRESSION IN RATS.

Natsuho Hayashi, Naoki Kawamorita, Yuichi Ishizuka, Shingo Kimura, Yohei Satake, Akihiro Ito. Int Urogynecol J. 2022 Aug 30. doi: 10.1007/s00192-022-05335-x. Online ahead of print. PMID: 36040506

In women with chronic pelvic pain (CPP), interstitial cystitis/bladder pain syndrome (IC/BPS) and endometriosis frequently coexist. The mechanism of these diseases coexisting is explained by cross-sensitization between endometriosis and IC/BPS. The overlapped symptoms may be related to cross-sensitization with transient receptor potential vanilloid 1 (TRPV1) and/or transient receptor potential ankyrin 1 (TRPA1) hyperexpression. This study from Japan was aimed at exploring whether bladder hypersensitivity is evoked in the surgically induced ectopic endometriosis rat and whether TRPV1 and/or TRPA1 play a vital role. A total of 63 Sprague-Dawley female rats were divided into two groups, 39 for physiological examination and 24 for molecular analysis. Surgical induction of ectopic endometriosis (ENDO, n=27), surgical sham treatment (n=18), and treatment for endometriosis by GnRH analog (ENDO-G) (n=18) were performed. Bladder function was investigated by cystometry (for TRPV1 in the sham [n=6] and ENDO [n=9] groups and for TRPA1 in the sham [n=6], ENDO [n=9], and ENDO+G [n=9] groups), and TRPV1 and TRPA1 mRNA expressions were measured using real-time qPCR in the bladder and dorsal root ganglia (DRGs). On cystometry, the relative intercontraction interval (ICI) after/before resiniferatoxin (RTx; TRPV1 activator) infusion to the bladder showed no significant difference between the two groups, whereas relative ICI after/before allyl isothiocyanate (AITC; TRPA1 activator) infusion was significantly lower in the ENDO group than in the sham group. TRPA1 mRNA expression in the bladder and L5 DRG was considerably higher in the ENDO group than in the sham group on real-time qPCR. TRPA1 mRNA hyperexpression and bladder hypersensitivity after AITC infusion were reduced in the ENDO-G group. It was concluded that bladder cross-sensitization in ENDO rats occurs in association with hyperexpression of TRPA1 at both the DRG and the bladder mucosa. This can be understood by the "cross-sensitization of endometriosis to bladder" theory explaining overlapping symptoms among BPS/IC and ectopic endometriosis.

SJÖGREN'S SYNDROME

PRIMARY SJÖGREN'S SYNDROME (PSS)- RELATED PERIPHERAL NEUROPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Andreas Liampas, Konstantinos Parperis, Maria Faidra Erotocritou, Antonios Nteveros, Marianna Papadopoulou, Christos Moschovos, Mohammed Akil, Stefano Coaccioli, Georgios M Hadjigergiou, Marios Hadjivassiliou, Panagiotis Zis. Eur J Neurol. 2022 Sep 10. doi: 10.1111/ene.15555. Online ahead of print. PMID: 36086910.

Primary Sjögren's syndrome (pSS) is a chronic, systemic, autoimmune disorder characterized by lymphocytic infiltrates of the exocrine organs, leading to sicca symptoms and parotid enlargement. pSS has been linked to various neurological manifestations, including peripheral neuropathy (PN). This international team of authors aimed to provide a comprehensive analysis of the currently available evidence regarding pSS-related PN. A literature search in the PubMed database was performed and 49 papers were eligible to be included in this systematic review and meta-analysis. The pooled prevalence of PN in pSS is estimated to be 15.0% (95% CI 10.7%-20.7%). The mean age of pSS patients at PN diagnosis is 59 years. Among the patients with pSS and peripheral neuropathy, 83% are females. Neuropathic symptoms usually precede or lead to the pSS diagnosis at a 2:1 ratio in patients with pSS related PN. The commonest type of pSS-related PN is the distal axonal

polyneuropathy (80% of patients with pSS-related PN), followed by the sensory ganglionopathy. Peripheral and cranial mononeuropathies - particularly trigeminal - are also frequent. Risk factors for developing PN include increasing age and presence of vasculitis. Immune-mediated pathogenetic mechanisms are discussed. Glucocorticoids are the most commonly used treatment option of managing pSS-related PN, when associated with vasculitis, followed by the use of IVIG. PN is very common in pSS patients. Evidence on long-term prognosis of PN in pSS is limited, and further research is needed. Research into the use of immunosuppressive medication in non-vasculitic neuropathies in the context of pSS merits further consideration.

Note: this review has been included bearing in mind the interest in neuropathies in IC/BPS patients recently.

VULVODYNIA/VULVAR PAIN

IMAGE-BASED DOCUMENTATION OF VULVODYNIA PAIN LOCATION

Guettchina Telisnor, Rishabh Garg, Jennifer E Glayzer, William H Kobak, Gebre-Egziabher Kiro, Yingwei Yao, Diana J Wilkie, Judith M Schlaeger. Pain Manag. 2022 May;12(4):417-424. doi: 10.2217/pmt-2021-0110. Epub 2022 Jan 21. PMID: 35060761 PMCID: PMC8981421 (available on 2023-01-01).

Better documentation of vulvar pain is needed. The authors from the USA examined pain locations marked on general body and genital specific outlines among women with vulvodynia. 62 women (mean age 32.1 ± 9.5 years) with vulvodynia marked their pain on a digital genital specific outline (22 segments) and 59 of those women also marked their pain on a digital general body outline (48 segments). The authors used ImageJ software to determine body surface area (BSA) for each outline. On the general body outline, 24/48 segments were marked; 22/22 segments were marked on the genital specific outline. There was a moderate correlation ($r = 0.43$; $p = 0.001$) between the BSA marked on the general body outline and the BSA marked on the genital area outline. Findings support concurrent validity of the BSA as a measure of pain location using either outline.

VULVODYNIA: WHAT IS AVAILABLE ONLINE? A SYSTEMATIC REVIEW OF INFORMATION ON THE INTERNET

Jemina Loganathan, Vishalli Ghai, Ragave Ilaalagan, Stergios K Doumouchtsis, CHORUS. J Obstet Gynaecol Res. 2022 Jun 14. doi: 10.1111/jog.15324. Online ahead of print. PMID: 35699223

This multi-centre review aimed to evaluate the quality of medical information online for patients relating to vulvodynia. The authors report that to their knowledge no evaluation of online patient information exists regarding vulvodynia and, at present, there is no standardized or validated method of evaluating medical information on the internet. A clearly defined protocol was developed to generate keywords relating to vulvodynia. The three most popular search engines worldwide; google.com, yahoo.com, and bing.com, were searched in September 2020. Three assessors evaluated eligible webpages for accuracy, credibility, readability, and reliability. Forty-five webpages were eligible with 38% given HON certification or Information Standard approval. Only one webpage achieved a DISCERN score of ≥ 63 indicating excellent reliability. No webpages scored a maximum 10 points for credibility. Eleven percent of webpages were rated "accurate" with score 17 or above. The modal Flesch Kincaid Grade Level was 9 with only 15.6% having a readability grade level of 8 or less. It has been shown in previous studies that patient information available online pertaining to gynecological conditions is frequently inaccurate, with limited regulation and low reliability, and the authors believe that their findings are in agreement with this. As patients increasingly look to the internet for medical information and education, clinicians need to ensure the resources available are of a high standard and regulated. Without ensuring safe and effective healthcare resources, there is a risk of misinformation which can negatively impact clinical care.

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