

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization focused on interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
<https://www.painful-bladder.org/>

RESEARCH UPDATE – February 2024

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS, BLADDER PAIN SYNDROME, HUNNER LESION, HYPERSENSITIVE BLADDER, CHRONIC INFLAMMATORY BLADDER DISEASES, KETAMINE CYSTITIS, CHRONIC (PELVIC) PAIN, 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 open 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 open access.

We also include so-called “Preprints”. These are preliminary reports of work that have not been certified by peer review. They should therefore not be relied on to guide clinical practice or health-related behaviour. (See <https://www.medrxiv.org/content/about-medrxiv> for further information).

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.

GUIDELINES

[SUMMARY OF THE 2023 REPORT OF THE INTERNATIONAL CONSULTATION ON INCONTINENCE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME \(IC/BPS\) COMMITTEE.](#)

Philip Hanno, Mauro Cervigni, Myung Soo Choo, J. Quentin Clemens, Ming-Huei Lee, Sachin Malde, Jane Meijlink, Michael Samarinas, Tomohiro Ueda, Daniela Gold. *Continence*, Volume 8, 2023, 101056, ISSN 2772-9737, <https://doi.org/10.1016/j.cont.2023.101056>.

(<https://www.sciencedirect.com/science/article/pii/S2772973723009141>)

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Interstitial cystitis and bladder pain syndrome are essentially interchangeable as there is no accepted definition that clearly delineates the interstitial cystitis syndrome from bladder pain syndrome. IC/BPS is generally agreed to be defined as chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder when accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency when in the absence of confusable diseases. The Consultation believes that patients who meet the definition and have a Hunner lesion should be considered to have a distinct confusable disease (Hunner lesion disease — HLD) and be managed accordingly. It follows that early cystoscopy is essential in establishing whether the diagnosis is HLD or IC/BPS. As no single treatment works well over time for a majority of patients, the treatment approach should be tailored to the specific symptoms of each patient and a multidisciplinary approach may be required. A reasonable diagnostic and treatment algorithm is offered by the

Consultation. For methodology and the complete report of this international committee with complete references, please refer to the 7th edition of the International Consultation on Urological Diseases Incontinence.

[\[THE INTERPRETATION OF THE UPDATED AMERICAN UROLOGICAL ASSOCIATION GUIDELINE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN 2022\]](#) [Article in Chinese]

L Zeng, J B Bi. Zhonghua Wai Ke Za Zhi. 2024 Feb 1;62(2):122-127. doi: 10.3760/cma.j.cn112139-20230713-00006. PMID: 38310379. Abstract in English, Chinese

In 2022, American Urological Association updated the guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). A significant change has been made in treatment recommendations. The updated guideline no longer divided treatments into first-line through sixth-line tiers. Instead, treatment is categorized into behavioral/non-pharmacologic, oral medicines, bladder instillations, procedures, and major surgery. This change emphasizes the heterogeneity of IC/BPS patients and the importance of individualized treatment, overturns traditional unreasonable ideas about hierarchical and progressive treatment, and encourages patients and physicians to make treatment decisions together. At the same time, the panel emphasized the importance of early implementation of cystoscopy in patients suspected of Hunner lesions and warned against the possibility of pentosan polysulfate causing a unique retinal pigmentary maculopathy. Urinary reconstruction surgery was considered to only be used as a last resort for the treatment of IC/BPS, and there is uncertainty about the overall balance between benefits and risks/burdens. The updated guideline provides a new understanding and decision-making basis for the diagnosis and treatment of IC/BPS. However, it should be noted that the clinical characteristics of Chinese patients should be considered in practice and the application of the guideline should be localized.

[GUIDELINE NO. 445: MANAGEMENT OF CHRONIC PELVIC PAIN.](#)

Allaire C, Yong PJ, Bajzak K, Jarrell J, Lemos N, Miller C, Morin M, Nasr-Esfahani M, Singh SS, Chen I. J Obstet Gynaecol Can. 2024 Jan;46(1):102283. doi: 10.1016/j.jogc.2023.102283. PMID: 38341225.

The purpose of this guideline from Canada is to provide evidence-based recommendations for the management of chronic pelvic pain in females. This guideline is specific to pelvic pain in adolescent and adult females and excluded literature that looked at pelvic pain in males. It also did not address genital pain. The intent is to benefit patients with chronic pelvic pain by providing an evidence-based approach to management. Access to certain interventions such as physiotherapy and psychological treatments, and to interdisciplinary care overall, may be limited by costs and service availability. Medline and the Cochrane Database from 1990 to 2020 were searched for articles in English on subjects related to chronic pelvic pain, including diagnosis, overlapping pain conditions, central sensitization, management, medications, surgery, physiotherapy, psychological therapies, alternative and complementary therapies, and multidisciplinary and interdisciplinary care. The committee reviewed the literature and available data and used a consensus approach to develop recommendations. Only articles in English and pertaining to female subjects were included. The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See online Appendix A (Tables A1 for definitions and A2 for interpretations of strong and conditional [weak] recommendations). The guideline is intended for family physicians, gynaecologists, urologists, pain specialists, physiotherapists, and mental health professionals.

Tweetable abstract: Management of chronic pelvic pain should consider multifactorial contributors, including underlying central sensitization/nociplastic pain, and employ an interdisciplinary biopsychosocial approach that includes pain education, physiotherapy, and psychological & medical treatments.

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

LATEST INSIGHTS INTO THE PATHOPHYSIOLOGY OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Tornic Jurea, Engeler Daniel. Current Opinion in Urology 34(2):p 84-88, March 2024. | DOI: 10.1097/MOU.0000000000001158

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a common medical problem in both sexes affecting people of all ages. Patients might report overactive bladder symptoms with additional bladder pain at maximum bladder filling, during and after micturition. This review from Switzerland aims to highlight pathophysiological mechanisms associated with this disease. Latest literature exposes different pathophysiological mechanisms such as impaired urothelial barrier function, alteration of urothelial factors and cytokines, chronic inflammation, vascular lesions, neurogenic inflammation and processes in the central nervous system leading to central sensitization. According to the involved mechanisms, BPS/IC may be arranged in clusters according to the clinical phenotype thus helping in clinical decision-making and treatment. Moreover, patients with BPS/IC suffer from other comorbidities such as fibromyalgia, irritable bowel syndrome, chronic pain and functional syndromes and psychosomatic diseases making the management challenging for medical professionals. Bladder pain syndrome/interstitial cystitis is a complex heterogeneous medical condition involving different pathomechanisms leading to bladder pain and dysfunction, consequently, impairing quality-of-life in affected individuals. However, these mechanisms are still not fully understood, so that patient treatments often remain unsatisfactory. For this reason, continuing research is important to understand the underlying pathomechanisms to discover biomarkers and treatment targets eventually improving diagnostic and therapeutic measures of BPS/IC.

THE UROTHELIAL BARRIER IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: ITS FORM AND FUNCTION, AN OVERVIEW OF PRECLINICAL MODELS

Van Ginkel Charlotte, Hurst Robert E, Janssen Dick. Current Opinion in Urology 34(2):p 77-83, March 2024. | DOI: 10.1097/MOU.0000000000001147

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The authors from the Netherlands and the USA note that investigating bladder pain syndrome/interstitial cystitis (IC/BPS) preclinically is challenging. Various research models have been used to mimic the urothelial barrier closely and replicate the disease. The aim of this review is to discuss preclinical research related to the urothelial barrier in context of IC/BPS. In vivo models mimic IC/BPS mainly with toxic substances in the urine, with protaminesulfate and proteoglycan deglycolysation resembling a temporary impaired barrier as seen in IC/BPS. This temporary increased permeability has also been found in vitro models. Glycosaminoglycan replenishment therapy has been described, in vivo and in vitro, to protect and enhance recover properties of the urothelium. The roles of immune and neurogenic factors in the pathogenesis of IC/BPS remains relatively understudied. Preclinical studies provide opportunities to identify the involvement of specific pathologic pathways in IC/BPS. For further research is warranted to elucidate the primary or secondary role of permeability, together with inflammatory and neurogenic causes of the disease.

MULTI-OMICS ANALYSES UNCOVER METABOLIC SIGNATURES AND GENE EXPRESSION PROFILES OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Xiyanling Yi, Jin Li, Zeyu Han, Tianyi Zhang, Dazhou Liao, Xiaoyan Lv, Jianzhong Ai. Neurourol Urodyn. 2024 Feb 12. doi: 10.1002/nau.25418. Online ahead of print. PMID:

The purpose of this article from China was to explore molecular and metabolic pathways involved in interstitial cystitis (IC) with integrating multi-omics analysis for identifying potential diagnostic and therapeutic targets. Mouse models of IC/bladder pain syndrome (BPS) were established by intraperitoneal injection of cyclophosphamide and bladder tissue samples were collected for metabolomics and transcriptome analysis. The authors found a total of 82 and 145 differential

metabolites in positive ion modes and negative ion modes, respectively. Glycerophospholipid metabolism, choline metabolism in cancer, and nucleotide metabolism pathways were significantly enriched in the IC/BPS group. Transcriptome analysis demonstrated that 1069 upregulated genes and 1087 downregulated genes were detected. Importantly, the stronger enrichment for cell cycle pathway was observed in IC/BPS than that in normal bladder tissue, which may be involved in the process of bladder remodeling. Moreover, the inflammatory response and inflammatory factors related pathways were enriched in the IC/BPS group. They concluded that their findings provide critical directions for further exploration of the molecular pathology underlying IC/BPS.

NEONATAL CYSTITIS MAKES ADULT FEMALE RAT URINARY BLADDERS MORE SENSITIVE TO LOW CONCENTRATION MICROBIAL ANTIGENS

Archer AC, DeBerry JJ, DeWitte C, Ness TJ. *Res Rep Urol.* 2023;15:531-539.

<https://doi.org/10.2147/RRU.S444167>

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder. Patients with IC/BPS often experience “flares” of symptom exacerbation throughout their lifetime, initiated by triggers, such as urinary tract infections. This study from the USA sought to determine whether neonatal bladder inflammation (NBI) alters the sensitivity of adult rat bladders to microbial antigens. Female NBI rats received intravesical zymosan treatments on postnatal days P14-P16 while anesthetized; Neonatal Control Treatment (NCT) rats were anesthetized. In adults, bladder and spinal cord Toll-like receptor type 2 and 4 (TLR2, TLR4) contents were determined using ELISAs. Other rats were injected intravesically with lipopolysaccharide (LPS; mimics an *E. coli* infection; 25, 50, 100, or 200 µg/mL) or Zymosan (mimics yeast infection; 0.01, 0.1, 1, and 10 mg/mL) solutions on the following day. Visceromotor responses (VMRs; abdominal contractions) to graded urinary bladder distention (UBD, 10– 60 mm Hg, 20s) were quantified as abdominal electromyograms (EMGs). Bladder TLR2 and TLR4 protein levels increased in NBI rats. These rats displayed statistically significant, dose-dependent, robustly augmented VMRs following all but the lowest doses of LPS and Zymosan tested, when compared with their adult treatment control groups. The NCT groups showed minimal responses to LPS in adults and minimally increased EMG measurements following the highest dose of Zymosan. The microbial antigens LPS and Zymosan augmented nociceptive VMRs to UBD in rats that experienced NBI but had little effect on NCT rats at the doses tested. The greater content of bladder TLR2 and TLR4 proteins in the NBI group was consistent with increased responsiveness to their agonists, Zymosan and LPS, respectively. Given that patients with IC/BPS have a higher incidence of childhood urinary tract infections, this increased responsiveness to microbial antigens may explain the flares in symptoms following “subclinical” tract infections.

Plain Language Summary: In a rat model of interstitial cystitis, bladder inflammation during childhood resulted in increased bladder sensitivity (ie pain) to low-level infections in adults.

TGF-β INHIBITOR TREATMENT OF H₂O₂-INDUCED CYSTITIS MODELS PROVIDES BIOCHEMICAL MECHANISM FOR ELUCIDATING INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME PATIENTS

Hideto Taga, Tsunao Kishida, Yuta Inoue, Kenta Yamamoto, Shin-Ichiro Kotani, Tsujimoto Masashi, Osamu Ukimura, Osamu Mazda. *PLoS One.* 2023 Nov 6;18(11):e0293983. doi: 10.1371/journal.pone.0293983. eCollection 2023. PMID: 37931000 PMCID: PMC10627456.

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Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic disease for which no effective treatment is available. Transforming growth factor-β (TGF-β) is thought to be involved in the pathogenesis of IC/PBS, and previous studies have suggested that administrations of a TGF-β inhibitor significantly ameliorated IC/PBS in a mouse model. However, the molecular mechanisms underlying the therapeutic effect of a TGF-β inhibitor on IC/PBS has not been comprehensively analyzed. TGF-β has a variety of actions, such as regulation of immune cells and fibrosis. In this study from Japan and Taiwan, the authors induced IC/PBS-like disease in mice by an intravesical

administration of hydrogen peroxide (H₂O₂) and examined the effects of three TGF-β inhibitors, Repsox, SB431542, and SB505124, on the urinary functions as well as histological and gene expression profiles in the bladder. TGF-β inhibitor treatment improved urinary function and histological changes in the IC/PBS mouse model, and SB431542 was most effective among the TGF-β inhibitors. In the present study, TGF-β inhibitor treatment improved abnormal enhancement of nociceptive mechanisms, immunity and inflammation, fibrosis, and dysfunction of bladder urothelium. These results show that multiple mechanisms are involved in the improvement of urinary function by TGF-β inhibitor.

A BIOPHYSICALLY COMPREHENSIVE MODEL OF UROTHELIAL AFFERENT NEURONS: IMPLICATIONS FOR SENSORY SIGNALLING IN URINARY BLADDER

Satchithanathi Aruljothi, Rohit Manchanda. J Comput Neurosci. 2024 Feb 12. doi: 10.1007/s10827-024-00865-3. Online ahead of print. PMID: 38345739.

The urothelium is the innermost layer of the bladder wall; it plays a pivotal role in bladder sensory transduction by responding to chemical and mechanical stimuli. The urothelium also acts as a physical barrier between urine and the outer layers of the bladder wall. There is intricate sensory communication between the layers of the bladder wall and the neurons that supply the bladder, which eventually translates into the regulation of mechanical activity. In response to natural stimuli, urothelial cells release substances such as ATP, nitric oxide (NO), substance P, acetylcholine (ACh), and adenosine. These act on adjacent urothelial cells, myofibroblasts, and urothelial afferent neurons (UAN), controlling the contractile activity of the bladder. There is rising evidence on the importance of urothelial sensory signalling, yet a comprehensive understanding of the functioning of the urothelium-afferent neurons and the factors that govern it remains elusive to date. Until now, the biophysical studies done on UAN have been unable to provide adequate information on the ion channel composition of the neuron, which is paramount to understanding the electrical functioning of the UAN and, by extension, afferent signalling. To this end, the authors from India have attempted to model UAN to decipher the ionic mechanisms underlying the excitability of the UAN. In contrast to previous models, their model was built and validated using morphological and biophysical properties consistent with experimental findings for the UAN. The model included all the channels thus far known to be expressed in UAN, including; voltage-gated sodium and potassium channels, N, L, T, P/Q, R-type calcium channels, large-conductance calcium-dependent potassium (BK) channels, small conductance calcium-dependent (SK) channels, Hyperpolarisation activated cation (HCN) channels, transient receptor potential melastatin (TRPM8), transient receptor potential vanilloid (TRPV1) channel, calcium-activated chloride(CaCC) channels, and internal calcium dynamics. Their UAN model a) was constrained as far as possible by experimental data from the literature for the channels and the spiking activity, b) was validated by reproducing the experimental responses to current-clamp and voltage-clamp protocols c) was used as a base for modelling the non-urothelial afferent neurons (NUAN). Using their models, they also gained insights into the variations in ion channels between UAN and NUAN neurons.

[EFFECT OF TRPM8 ON PAIN SYMPTOM AND NEURONAL PROLIFERATION IN MICE WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME][Article in Chinese]

B H Fan, P Zhang. Zhonghua Yi Xue Za Zhi. 2024 Jan 30;104(5):377-384. doi: 10.3760/cma.j.cn112137-20230828-00313. PMID: 38281807 Abstract in English, Chinese.

The purpose of this article from Beijing, China was to explore the effects between transient receptor potential melastatin 8 (TRPM8) on pain symptoms and neuronal proliferation in mice with interstitial cystitis/bladder pain syndrome (IC/BPS). Female wild-type C57BL/6 mice (8-10 weeks old) were divided into control group, IC/BPS model group, and IC/BPS model+menthol group (6 mice each) by random number table method; TRPM8 knockout mice were randomly divided into TRPM8 knockout group and TRPM8 knockout model group (6 mice each). The IC/BPS model group, the IC/BPS model+menthol group, and the TRPM8 knockout model group were injected subcutaneously with

residues 65-84 of murine uroplakin 3A (UPK3A65-84). The IC/BPS model+menthol group continued to be injected with menthol. After successful modelling, the differences in pain thresholds between the groups were assessed by mechanosensitivity. The bladder wall was injected with a cell membrane red fluorescent probe (Dil), and the dorsal root ganglion (DRG) tissues were collected 10 days later. The differences in the protein and mRNA levels of TRPM8 and GAP43 in the groups were detected by Western blotting and quantitative real-time polymerase chain reaction (qRT-PCR), respectively. Immunofluorescence was used to detect the distribution of TRPM8 expression with GAP43 or Dil in DRG tissues. The relationship between TRPM8 and pain symptom and its role in neuronal proliferation in IC/BPS mice were analyzed. The models were all constructed successfully. Compared with the control group, the pain thresholds of mice in the IC/BPS model group and IC/BPS model+menthol group were reduced [(8.50±1.22), (5.50±1.05) vs (11.67±2.16), respectively, all $P<0.001$]. Compared with the control group, the expression of TRPM8 mRNA was elevated in the IC/BPS model group and IC/BPS model+menthol group, while TRPM8 was not expressed in the TRPM8 knockout group [(3.16±0.05), (6.46±0.21), and 0 vs (1.00±0.06), respectively, all $P<0.001$]. The expression of TRPM8 protein and mRNA in each group had the same trend ($P<0.001$). Compared with the control group, the expression of GAP43 mRNA in the DRG of the IC/BPS model group and the IC/BPS model+menthol group was increased, whereas the expression of GAP43 mRNA in the TRPM8 knockout model group was decreased (all $P<0.001$). The trend of GAP43 protein expression was the same as that of mRNA expression ($P<0.001$). Immunofluorescence results showed an increase in the number of GAP43-positive neurons in the DRG of the IC/BPS model group and the IC/BPS model+menthol group, and a decrease in the TRPM8 knockout group compared with the control group (all $P<0.001$). Compared with the control group, the number of Dil-positive neurons in the DRG of the IC/BPS model group and the IC/BPS model+menthol group was increased, while the TRPM8 knockout group was decreased (all $P<0.001$). It was concluded that TRPM8 can exacerbate pain symptoms in IC/BPS mice, and the mechanism may be related to the induction of sensory nerve proliferation at the DRG level.

THE EFFECTS OF A GALECTIN-3 INHIBITOR ON BLADDER PAIN SYNDROME IN MICE WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Helong Xiao, Ting Wang, Bo Gao, Junjiang Liu, Shoubin Li, Jianguo Ma. Neurourol Urodyn. 2024 Feb 14. doi: 10.1002/nau.25415. Online ahead of print. PMID: 38356381

The aim of this study from Shijiazhuang, Hebei, China was to explore the effect of blocking galectin-3 in the bladder pain syndrome associated with interstitial cystitis. A galectin-3 inhibitor was used to treat mice with cyclophosphamide-induced cystitis. The expression of galectin-3 in bladder tissues and urine was examined by immunohistochemistry and enzyme-linked immunosorbent assay (ELISA), respectively. Suprapubic-pelvic pain, bladder voiding, bladder pain-like nociceptive behavior, and referred hyperalgesia were assessed. The weights of the bladders were also measured, and inflammatory cell infiltration and inflammatory cytokine levels were examined by histopathological evaluation. The inflammatory cytokines interleukin 1 β (IL-1 β), nerve growth factor (NGF), IL-6, and tumor necrosis factor α (TNF- α) were measured by ELISA. Increases in galectin-3 levels, inflammation, bladder weight, and bladder pain-related symptoms were observed in bladders with cyclophosphamide-induced cystitis. Administration of the galectin-3 inhibitor significantly mitigated bladder pain-related symptoms and inflammatory response. In response to the 500 μ M dose of the galectin-3 inhibitor, nociceptive behaviors, nociceptive score, and bladder-to-body weight ratios were reduced by 65.1%, 65.3%, and 40.3%, respectively, while 500 μ M Gal-3 inhibitor increased pelvic pain threshold by 86.7%. Moreover, galectin-3 inhibitor treatment inhibited the inflammation. Compared to untreated CYP-induced mice, there were significant changes in the levels of IL-1 β (41.72 \pm 2.05 vs. 18.91 \pm 2.26 pg/mg tissues), NGF (9.64 \pm 0.38 vs. 1.88 \pm 0.05 pg/mg tissues), IL-6 (42.67 \pm 1.51 vs. 21.26 \pm 2.78 pg/mg tissues), and TNF- α (22.02 \pm 1.08 vs. 10.70 \pm 0.80 pg/mg tissues) in response to the highest dose of the Gal-3 inhibitor subgroup (500 μ M), and 500 μ M Gal-3 inhibitor reduced mast cell infiltration ratios by 71.8%. The galectin-3 inhibitor relieved pelvic pain, urinary

symptoms, and bladder inflammation in mice with cyclophosphamide-induced cystitis. Thus, galectin-3 inhibitors may be novel agents in interstitial cystitis treatment.

EMODIN INHIBITS BLADDER INFLAMMATION AND FIBROSIS IN MICE WITH INTERSTITIAL CYSTITIS BY REGULATING JMJD3

Junyu Lai, Xing Liu, Hongwei Su, Yongsheng Zhu, Ke Xin, Mingwei Huang, Songtao Luo, Hai Tang. Acta Cir Bras. 2023 Dec 1:38:e385123. doi: 10.1590/acb385123. eCollection 2023. PMID: 38055393 PMCID: PMC10691180

[Open access](#)

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a devastating urological chronic pelvic pain condition. In search of a potential treatment, the authors from Luzhou (Sichuan), China investigated the effect of emodin on IC/BPS inflammation and fibrosis, and explored the potential mechanism. An experimental model of interstitial cystitis was induced by cyclophosphamide, and human bladder smooth muscle cells were treated with lipopolysaccharide to establish the cell model in vitro. In both models, inflammation- and fibrosis-related indexes were measured after emodin administration. Furthermore, the specific antagonists were used to dig for the mechanisms underlying the response to emodin treatment. Emodin significantly ameliorated management of cystitis, reduced the amount of inflammatory cytokines (tumor necrosis factor- α , monocyte chemoattractant protein-1, interleukin-1 β , interleukin-8, and interleukin-6) in models, as well as reducing the synthesis of fibrosis marker including collagen1, collagen3, vimentin, fibronectin and α -smooth muscle actin. Further mechanism studies demonstrated that emodin inhibited inflammatory reaction and fibrosis through blocking lysine-specific demethylase 6B (JMJD3) expression via JAK/STAT, NF- κ B and TGF- β /SMAD pathways. The authors concluded that their study reveals the critical role of emodin-JMJD3 signalling in interstitial cystitis by regulating inflammation, fibrosis, and extracellular matrix deposition in cells and tissues, and these findings provide an avenue for effective treatment of patients with cystitis.

A PILOT STUDY OF FUNCTIONAL BRAIN MAGNETIC RESONANCE IMAGING IN BPS/IC PATIENTS: EVIDENCE OF CENTRAL SENSITIZATION

Pedro Abreu-Mendes, Diogo Dias, Francisca Magno, Guilherme Silva, José Rodrigues-Fonseca, Paulo Dinis, Francisco Cruz, Rui Almeida Pinto. February 2024. Urology Research and Practice. DOI: 10.5152/tud.2024.23209

[Open access](#)

Bladder pain syndrome/Interstitial cystitis (BPS/IC) is characterized by increased activity in bladder afferent pathways, recruitment of silent nociceptive neurons, and sensitization of the brain areas responsible for pain amplification. Default mode network (DMN) is a set of regions activated during the resting state, which reflect the brain's intrinsic activity. Conversely, the sensorimotor network (SMN) plays a key role in structural neuroplasticity. This study from Portugal aimed to evaluate DMN and SMN activity in BPS/IC patients, both with and without bladder noxious stimulus, using functional brain magnetic resonance imaging (fMRI). Six BPS/IC female patients underwent 3 Tesla fMRI brain scanners. Acquisitions consisted of 10-minute blood oxygen level-dependent echo-planar imaging. The first acquisition was with an empty bladder, painless, and the second was with suprapubic pain. Data were processed using the independent component analysis method with the MELODIC tool from the functional brain MRI of the Brain Software Library (FSL). A semi-quantitative analysis was performed afterward. The patients' age was 42.6 ± 5 years, pain intensity was 7 ± 0.7 (0-10), day and night frequency were 9.2 ± 2.2 and 2.8 ± 1.0 , and maximal bladder capacity was 260 ± 54 mL. One patient was unable to complete the study. All patients showed a comparable DMN activation in both empty and full bladder states, and all presented high SMN activation whether the bladder was empty or full. The activation of DMN at both bladder states, empty and full, and constant SMN activation without and with pain supports the role of these networks in BPS/IC. Similar findings have been reported in other chronic pain syndromes.

INHIBITION OF MICRORNA-34C REDUCES DETRUSOR ROCK2 EXPRESSION AND URINARY BLADDER INFLAMMATION IN EXPERIMENTAL CYSTITIS

Mousumi Mandal, Ahmed Rakib, Sonia Kiran, Md Abdullah Al Mamun, Somasundaram Raghavan, Santosh Kumar, Bhupesh Singla, Frank Park, M Dennis Leo, Udai P Singh. Life Sci. 2024 Jan 1:336:122317. doi: 10.1016/j.lfs.2023.122317. Epub 2023 Nov 29. PMID: 38040245 PMCID: PMC10872291

Open access

Interstitial cystitis (IC), also called painful bladder syndrome (PBS), is 2 to 5 times more common in women than in men, yet its cause and pathogenesis remain unclear. In this study from Memphis, USA, using the cyclophosphamide (CYP)-induced mouse model of cystitis, histological evaluation of the urinary bladder (UB) lamina propria (LP) showed immune cell infiltrations, indicating moderate to severe inflammation. In this study, the authors noticed a differential expression of a subset of microRNAs (miRs) in the UB cells (UBs) of CYP-induced cystitis as compared to the control. UB inflammatory scores and inflammatory signaling were also elevated in CYP-induced cystitis as compared to control. They identified eight UBs miRs that exhibited altered expression after CYP induction and are predicted to have a role in inflammation and smooth muscle function (miRs-34c-5p, -34b-3p, -212-3p, -449a-5p, -21a-3p, -376b-3p, -376b-5p and -409-5p). Further analysis using ELISA for inflammatory markers and real-time PCR (RT-PCR) for differentially enriched miRs identified miR-34c as a potential target for the suppression of UB inflammation in cystitis. Blocking miR-34c by antagomir ex vivo reduced STAT3, TGF- β 1, and VEGF expression in the UBs, which was induced during cystitis as compared to control. Interestingly, miR-34c inhibition also downregulated ROCK2 but elevated ROCK1 expression in bladder and detrusor cells. Thus, the present study shows that targeting miR-34c can mitigate the STAT3, TGF- β , and VEGF, inflammatory signalling in UB, and suppress ROCK2 expression in UBs to effectively suppress the inflammatory response in cystitis. This study highlights miR-34c as a potential biomarker and/or serves as the basis for new therapies for the treatment of cystitis.

EARLY IN LIFE STRESSFUL EVENTS INDUCE CHRONIC VISCERAL PAIN AND CHANGES IN BLADDER FUNCTION IN ADULT FEMALE MICE THROUGH A MECHANISM INVOLVING TRPV1 AND ALPHA 1A ADRENOCEPTORS

Rita Matos, Liliana Santos-Leite, Francisco Cruz, Ana Charrua. NeuroUrol Urodyn. 2024 Feb;43(2):533-541. doi: 10.1002/nau.25376. Epub 2024 Jan 4. PMID: 38178640.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder with multiple phenotypes, one of which is associated with an overactive adrenergic system. The authors from Portugal investigated if the maternal deprivation model (MDM) in female and male mice mimics IC/BPS phenotype and if the overstimulation of alpha 1A adrenoceptor (A1AAR) and the crosstalk with transient receptor potential vanilloid-1 (TRPV1) are involved in the generation of pain and bladder functional changes. C57BL/6 female and male mice were submitted to MDM. TRPV1 knockout (KO) mice were used to study TRPV1 involvement. Silodosin administration to MDM mice was used to study A1AAR involvement. The primary outcome was chronic visceral pain measured by Von Frey filaments analysis (effect size: 3 for wild type, 3.9 for TRPV1 KO). Bladder changes were secondary outcome measurements. Unpaired T test, Mann-Whitney test, one-way analysis of variance followed by Newman-Keuls multiple comparisons test, and Kruskal-Wallis followed by Dunn's multiple comparisons test were used where appropriate. MDM induces pain behavior in female and not in male mice. Bladder afferents seem sensitize as MDM also increase the number of small volume spots voided, the bladder reflex activity, and urothelial damage. These changes were similarly absent after A1AAR blockade with silodosin or by TRPV1 gene KO. The main limitation is the number/type of pain tests used. MDM induced in female mice is able to mimic IC/BPS phenotype, through mechanisms involving A1AAR and TRPV1. Therefore, the modulation of both receptors may represent a therapeutic approach to treat IC/BPS patients.

CAFTARIC ACID AMELIORATES OXIDATIVE STRESS, INFLAMMATION, AND BLADDER OVERACTIVITY IN RATS HAVING INTERSTITIAL CYSTITIS: AN IN SILICO STUDY

Saima, Irfan Anjum, Saima Najm, Kashif Barkat, Hiba-Allah Nafidi, Yousef A Bin Jordan, Mohammed Bourhia. *ACS Omega*. 2023 Jul 25;8(31):28196-28206. doi: 10.1021/acsomega.3c01450. eCollection 2023 Aug 8. PMID: 38173953 PMCID: PMC10763566.

Open access

Interstitial cystitis (IC) is the principal unwanted effect associated with the use of cyclophosphamide (CYP). It results in increased oxidative stress, overexpression of proinflammatory cytokines, and bladder overactivity. Patients receiving CYP treatment had severely depreciated quality of life, as the treatment available is not safe and effective. The goal of this study from Pakistan, Canada, Morocco and Saud Arabia was to assess the protective effect of caftaric acid in CYP-induced IC. IC was induced in female Sprague Dawley by injecting CYP (150 mg/kg, i.p.). In the present study, oral administration of caftaric acid (20, 40, and 60 mg/kg) significantly decreased inflammation. Caftaric acid significantly increased SOD (93%), CAT (92%), and GSH (90%) while decreased iNOS (97%), IL-6 (90%), TGF 1- β (83%), and TNF- α (96%) compared to the diseased. DPPH assay showed the antioxidant capacity comparable to ascorbic acid. Molecular docking of caftaric acid with selected protein targets further confirmed its antioxidant and anti-inflammatory activities. The cyclophosphamide-induced bladder overactivity had been decreased possibly through the inhibition of M3 receptors, ATP-sensitive potassium channels, calcium channels, and COX enzyme by caftaric acid. Therefore, their findings demonstrate that caftaric acid has a considerable protective role against CYP-induced IC by decreasing the oxidative stress, inflammation, and bladder smooth muscle hyperexcitability. Thus, caftaric acid signifies a likely adjuvant agent in CYP-based chemotherapy treatments.

EXPLORING THE ROLE OF DLK1 IN INDUCING NLRP3 INFLAMMASOME ACTIVATION IN BLADDER EPITHELIAL CELLS IN PATIENTS WITH INTERSTITIAL CYSTITIS

Xin Song, Tingting Lv, Weilin Fang, Jianwei Lv. *Asian J Surg*. 2024 Jan 6:S1015-9584(23)02098-5. doi: 10.1016/j.asjsur.2023.12.134. Online ahead of print. PMID: 38185550.

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Letter to Editor

NO VIABLE BACTERIAL COMMUNITIES RESIDE IN THE URINARY BLADDER OF CATS WITH FELINE IDIOPATHIC CYSTITIS

Andrea Balboni, Giovanni Franzo, Luca Bano, Lorenza Urbani, Sofia Segatore, Alessia Rizzardi, Benedetta Cordioli, Matteo Cornaggia, Alessia Terrusi, Kateryna Vasylyeva, Francesco Dondi, Mara Battilani. *Res Vet Sci*. 2024 Mar:168:105137. doi: 10.1016/j.rvsc.2024.105137. Epub 2024 Jan 2. PMID: 38181480.

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Urinary microbial diversities have been reported in humans according to sex, age and clinical status, including painful bladder syndrome/interstitial cystitis (PBS/IC). To date, the role of the urinary microbiome in the pathogenesis of PBS/IC is debated. Feline idiopathic cystitis (FIC) is a chronic lower urinary tract disorder affecting cats with similarities to PBS/IC in women and represents an important problem in veterinary medicine as its aetiology is currently unknown. In this study from Italy, the presence of a bacterial community residing in the urinary bladder of cats with a diagnosis of FIC was investigated. Nineteen cats with clinical signs and history of FIC and without growing bacteria in standard urine culture were included and urine collected with ultrasound-guided cystocentesis. Bacterial community was investigated using a culture-dependent approach consisted of expanded quantitative urine culture techniques and a culture-independent approach consisted of 16S rRNA NGS. Several methodological practices were adopted to both avoid and detect any contamination or bias introduced by means of urine collection and processing which could be relevant due to the low microbial biomass environment of the bladder and urinary tract, including

negative controls analysis. All the cats included showed no growing bacteria in the urine analysed. Although few reads were originated using 16S rRNA NGS, a comparable pattern was observed between urine samples and negative controls, and no taxa were confidently classified as non-contaminant. The results obtained suggest the absence of viable bacteria and of bacterial DNA of urinary origin in the urinary bladder of cats with FIC.

UROPROTECTIVE POTENTIAL OF CAMPESTEROL IN CYCLOPHOSPHAMIDE INDUCED INTERSTITIAL CYSTITIS; MOLECULAR DOCKING STUDIES

Joham Javed, Irfan Anjum, Saima Najm, Naila Ali, Muhammad Nasir Hayat Malik, Shah Jahan, Turki M Dawoud, Hiba-Allah Nafidi, Mohammed Bourhia. Chem Biodivers. 2023 Dec;20(12):e202301534. doi: 10.1002/cbdiv.202301534. Epub 2023 Nov 28. PMID: 37984454.

Cyclophosphamide (CYP) is commonly used to treat cancer of the ovaries, breast, lymph, and blood system and produces interstitial cystitis (IC) via its urotoxic metabolite: i. e., acrolein. The present study from Pakistan, Saudi Arabia, Canada and Morocco was aimed to investigate the uroprotective effect of campesterol (a steroidal phytochemical) in cyclophosphamide induced IC. IC was induced by CYP (150 mg/kg, i. p.) in rats. The Enzyme linked immunosorbent assays for oxidative stress markers and Polymerase Chain Reaction (PCR) for inflammatory cytokines were carried out. The Tissue Organ Bath Technique was used for the evaluation of the spasmolytic effect of campesterol. Different pharmacological antagonists have been used to explore the mechanism of action of campesterol. Treatment with campesterol (70 mg/kg) reduced nociception (55 %), edema (67 %), hemorrhage (67 %), and protein leakage significantly (94 %). The antioxidant activity of campesterol was exhibited by a fall in MDA, NO, and an elevation in SOD, CAT, and GPX levels. Campesterol presented anti-inflammatory potential by decreasing IL-1, TNF- α , and TGF- β expression levels. Histologically, it preserved urothelium from the deleterious effect of CYP. Campesterol showed a spasmolytic effect by reducing bladder overactivity that was dependent on muscarinic receptors, voltage-gated calcium and KATP channels, and cyclo-oxygenase pathways. In silico studies confirmed the biochemical findings. The findings suggest that campesterol could be valorized as a possible therapeutic agent against cyclophosphamide-induced interstitial cystitis.

HISPIDULIN TARGETS PTGS2 TO IMPROVE CYCLOPHOSPHAMIDE-INDUCED CYSTITIS BY SUPPRESSING NLRP3 INFLAMMASOME

Songlin Liu, Shuhang Li, Yuping Dong, Kun Qiao, Yang Zhao, Jianyong Yu. Naunyn Schmiedeberg Arch Pharmacol. 2024 Feb 7. doi: 10.1007/s00210-024-02987-y. Online ahead of print. PMID: 38321213 DOI: 10.1007/s00210-024-02987-y

Interstitial cystitis (IC) is a chronic bladder inflammation. Inhibition of prostaglandin G/H synthase 2 (PTGS2) is the most common method for controlling inflammation-related diseases. This study from Yantai, China aimed to analyze the effects of hispidulin on the PTGS2 and NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammation in experimental IC models. A binding activity between hispidulin and PTGS2 was measured using molecular docking. Human urothelial cells (SV-HUC-1) were stimulated by 2 ng/mL of interleukin (IL)-1 β for 24 h and cultured in a medium with different concentrations of hispidulin (2.5, 5, 10, 20 μ M) for 24 h to observe the expressions of PTGS2 and NLRP3 protein. Cells overexpressing PTGS2 were established by PTGS2 cDNA transfection. In the IL-1 β -treated cells, the NLRP3 inflammasome was measured after 20 μ M hispidulin treatment. In rats, animals were performed with three injections of 40 mg/kg cyclophosphamide (CYP) and orally treated with 50 mg/kg/day hispidulin or ibuprofen for 3 days. The bladder pain was measured using Von Frey filaments, and the bladder pathology was observed using hematoxylin and eosin (H&E) staining. The expressions of PTGS2 and NLRP3 inflammasome were also observed in the bladder tissues. A good binding activity was found between hispidulin and PTGS2 (score = - 8.9 kcal/mol). The levels of PTGS2 and NLRP3 inflammasome were decreased with the hispidulin dose increase in the IL-1 β -treated cells ($p < 0.05$). Cells overexpressing PTGS2 weakened the protective effects of hispidulin in the IL-1 β -treated cells ($p < 0.01$). In the CYP-treated

rats, hispidulin treatment improved the bladder pain through decreasing the nociceptive score ($p < 0.01$) and suppressed the bladder inflammation through suppressing the expressions of PTGS2 and NLRP3 inflammasome in bladder tissues ($p < 0.01$). Additionally, the results of ibuprofen treatment were similar to the effects of hispidulin in the CYP-treated rats. This study demonstrates that hispidulin may be a new alternative drug for the IC treatment that binds PTGS2 to perform its functions.

UROPROTECTIVE EFFECTS OF BERBERINE AND CURCUMIN IN CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS

Murat Demir, Fikret Altındağ. *Environ Toxicol.* 2024 Mar;39(3):1315-1322. doi: 10.1002/tox.24025. Epub 2023 Nov 13. PMID: 37955270.

In this study from Turkey, it was aimed to investigate the effects of berberine (BER) and curcumin (CUR) in the experimental model of cystitis induced by cyclophosphamide (CYP). A total of 36 Wistar-Albino female rats were used in the study. Rats were randomly divided into six groups ($n = 6$). Normal control group, dimethyl sulfoxide (DMSO) group, CYP group (75 mg/kg), CYP + BER (75 mg/kg CYP and 50 mg/kg BER), CYP + CUR group (75 mg/kg CYP and 50 mg/kg CUR), CYP + BER + CUR group (75 mg/kg CYP and 50 mg/kg BER and 50 mg/kg CUR). Severe edema, hyperemia, hemorrhage, necrosis, and thinning of the epithelial layer were observed in the CYP group. BER and CUR treatment significantly reduced these pathologies. Masson-Trichrome staining was severe in the CYP group and moderate in the CYP + BER, CYP + CUR, and CYP + BER + CUR groups. In the CYP group, there was a severe expression of caspase-3, TNF- α and IL-6, and mild expression of IL-10. BER and CUR treatment decreased the expression of caspase-3, TNF- α , and IL-6 and increased the expression of IL-10. The findings of the study reveal that BER and CUR treatments may reduce CYP-induced bladder damage by reducing apoptosis and inflammation and ameliorating histopathological changes.

BIOENERGETIC PROFILES OF PERIPHERAL MONONUCLEAR CELLS AND SYSTEMIC INFLAMMATION IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)

Parveen Kumar, Robert A Oster, Dean G Assimos, Timothy J Ness, Tanecia Mitchell. *PLoS One.* 2024 Feb 15;19(2):e0298981. doi: 10.1371/journal.pone.0298981. eCollection 2024. PMID: 38359038 PMCID: PMC10868762.

Open access

Inflammation is thought to contribute to the etiology of interstitial cystitis/bladder pain syndrome (IC/BPS). It is well-known that disruption in metabolism in immune cells contributes to inflammation in several inflammatory diseases. The purpose of this study from the USA was to investigate whether cellular bioenergetics is altered in monocytes and lymphocytes from women with IC/BPS, and if these alterations correlate with systemic inflammatory markers. Age and BMI matched adult healthy women (HS; $n = 18$) and women with IC/BPS ($n = 18$) were included in the study. Blood was collected to assess cellular bioenergetics in monocytes and lymphocytes using a Seahorse XF96 Analyzer and plasma cytokine levels were measured using Meso Scale Discovery immunoassays. The correlation between bioenergetic parameters, cytokines, and demographics was determined using Pearson correlation coefficients. Means of the two groups were compared using the two-group t-test. Patients with IC/BPS had reduced monocyte oxygen consumption rates and glycolytic rates compared to healthy subjects. In contrast, lymphocytes from these patients had increased oxygen consumption rates and glycolytic rates. Several cytokines and chemokines including Interferon-gamma (IFN- γ), tumor necrosis factor alpha (TNF- α), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF) levels were significantly elevated in the plasma of patients with IC/BPS. However, Transforming growth factor (TGF- β) and Interleukin-10 (IL-10) levels were significantly decreased in IC/BPS patients compared to HS. In addition, Interferon gamma (IFN- γ), TNF- α , IL-8, and TGF- β levels correlated with several bioenergetic parameters in monocytes or lymphocytes from healthy subjects. In contrast, TNF- α and IL-8 correlated with bioenergetic parameters in monocytes from IC/BPS patients. Monocyte and lymphocyte cellular bioenergetics

and plasma cytokine levels are different in patients with IC/PBS compared to HS. It appears that systemic inflammation is greater in this cohort which may negatively impact immune cell function. The relationship between cellular bioenergetics and inflammation in monocytes and lymphocytes could be important in understanding the pathogenesis of IC/PBS and warrants further investigation.

WHAT IS IN THE PIPELINE FOR NEW TREATMENTS FOR BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS?

Dias Diogo, Mendes, Pedro Abreu, Oliveira Paulo Dinis, Pinto Rui Almeida. Current Opinion in Urology 34(2):p 58-63, March 2024. | DOI: 10.1097/MOU.0000000000001159

Despite available treatments, many bladder pain syndrome/interstitial cystitis (BPS/IC) patients continue to have poor quality of life. Thus, there is an urge for new therapies. This manuscript from Portugal aims to review papers about BPS/IC treatments published in the last 2 years. During this period, several treatments were tested, most of them new and others combining treatments already used. Pentosan polysulfate, interleukin 1 antagonist, low energy shock wave, physical therapy, hypnosis, acupuncture, clorpactin, dimethyl sulfoxide and hyaluronic acid plus botulinum toxin-A showed positive results. ASP3652 and lidocaine-releasing intravesical systems failed to prove their efficacy. Validation of these studies is arduous due to the broad spectre of BPS/IC phenotypes, small number of patients enrolled, distinct outcome measures and short-term follow-up. It is also important to highlight that some authors combined therapies, and others split central and peripheric phenotypes before treatment. Therefore, soon, phenotyping and combining therapies with a step-by-step approach will be needed in BPS/IC treatment.

EFFECTS OF ELECTROACUPUNCTURE ON REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A ONE-YEAR FOLLOW-UP CASE REPORT

Ning Gao, Xuehua Zeng, Lili Wu, Zhenyu Lin, Xingbo Wang, Weiming Wang. Explore (NY). 2023 Dec 6:S1550-8307(23)00272-0. doi: 10.1016/j.explore.2023.12.001. Online ahead of print. PMID: 38072764.

Ning Gao and colleagues from China note that patients with interstitial cystitis/bladder pain syndrome (IC/BPS) commonly face a decline in their quality of life and social functioning upon discontinuation of conventional therapy, which is known for its limited efficacy and the risk of relapse. While the existing evidence is somewhat restricted, acupuncture is being explored as a potential and effective treatment option for IC/BPS. A 67-year-old woman, diagnosed with refractory IC/BPS, underwent treatment at the Medical Acupuncture Department of Sanming Integrated Traditional Chinese and Western Medicine Hospital. She reported symptoms of lower urinary system dysfunction, including urgency, frequency, and nocturia, along with chronic pelvic pain, and a persistent feeling of pressure and discomfort lasting over 8 years. The patient's visual analog scale (VAS) score for pelvic pain was 7 points prior to receiving acupuncture treatment. Throughout the day, she had more than 10 urinations, and at night, she urinated about once per hour. The O'Leary-Sant interstitial cystitis symptom index/interstitial cystitis problem index (ICSI/ICPI) score was 34 points, and the pelvic pain and urgency frequency (PUF) score was 19 points. The patient's complaints were significantly alleviated after 12 sessions of electroacupuncture treatment at BL32, BL33, BL35, and SP6 over 4 weeks. The patient claimed total relief from pelvic pain, with a VAS score of 0. The patient achieved a PUF score of 4 points and an ICSI/ICPI score of 7 points. In addition, there was a significant reduction in the frequency and urgency of urination. The patient experienced a frequency of 4-5 urinations during the day and 1-2 times at night. Subsequently, the patient's mental state and sleep quality were improved. The patient's symptoms did not change at one-year follow-up. Electroacupuncture has proven to be an effective management method for IC/BPS, as evidenced by the patient's alleviated lower urinary system symptoms and reduced pelvic pain.

IMPROVEMENT IN CHRONIC PELVIC PAIN, ORTHOSTATIC INTOLERANCE AND INTERSTITIAL CYSTITIS SYMPTOMS AFTER TREATMENT OF PELVIC VEIN INSUFFICIENCY

Steven J Smith, Michael J Sichlau, B Holly Smith, Dacre Rt Knight, Brenda Chen, Peter C Rowe. Phlebology. 2023 Dec 5:2683555231219737. doi: 10.1177/02683555231219737. Online ahead of print. PMID: 38050791.

Comorbidities associated with venous origin chronic pelvic pain (VO-CPP) were evaluated pre and post venous treatment to assess change. In this study from the USA, 45 women with VO-CPP were treated with venous stenting and/or embolization. Four surveys assessed symptoms pre- and post-treatment: IPPS (chronic pelvic pain), PUF (interstitial cystitis), OHQ (dysautonomia), and modified ROME III (IBS). Prevalence of joint hypermobility was investigated. Ages were 18-65. Pretreatment, 64% and 49% of women were in the severe range for PUF and OHQ, respectively. 40% and 56% met criteria for IBS and Ehlers-Danlos syndrome/Hypermobility Spectrum Disorder (EDS/HSD), respectively. 17 received an iliac stent, 5 pelvic embolization, and 23 both. Post-treatment, average scores improved: IPPS (by 55%), PUF (34%), and OHQ (49%). Rome III improved only slightly. Pelvic pain, interstitial cystitis, and dysautonomia were frequently found with VO-CPP and improved after venous treatment. EDS/HSD and IBS were common in these women.

BLADDER PAIN SYNDROME AKA INTERSTITIAL CYSTITIS – A CONDITION WITH SEVERE UNMET MEDICAL NEED: AN EXPLORATION OF BRIMAPITIDE AS A POTENTIAL TREATMENT OPPORTUNITY.

Taubert Erich, van der Aa, Frank, Heesakkers John. Current Opinion in Urology 34(2):p 52-57, March 2024. | DOI: 10.1097/MOU.0000000000001150

The purpose of this article from the Netherlands is to present recent findings of KU002 (brimapitide) as a novel treatment option for interstitial cystitis/bladder pain syndrome (IC/BPS). IC/BPS is a complex and poorly understood heterogeneous syndrome, with many burdensome symptoms that severely affect patients' quality of life. Treatment options beyond conservative and nonpharmacologic approaches remain limited, and there is an unmet medical need for effective medical treatments. While there are multiple ongoing clinical trials in this area, only a few explore new treatment options. This article summarizes current ongoing development and reports the findings of one such trial. In a phase 1/2a exploratory trial, intravesical instillation of brimapitide confirmed local action while eliciting in minimal systemic exposure, resulting in a promising and favorable safety profile. Efficacy exploration suggests that brimapitide reduces pain, improves signs and symptoms of IC/BPS and improves the general wellbeing of the study participants.

IMAGE SEGMENTATION FOR HIGH-DENSITY SURFACE ELECTROMYOGRAPHY MAPPINGS OF PELVIC FLOOR MUSCLE ACTIVITY OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Michael Houston, Nicholas Dias, Theresa Spitznagle, Marcie Harris-Hayes, H Henry Lai, Yingchun Zhang. Annu Int Conf IEEE Eng Med Biol Soc. 2023 Jul:2023:1-4. doi: 10.1109/EMBC40787.2023.10340839. PMID: 38083706.

Interstitial cystitis/bladder pain syndrome (IC/BPS) can result in pelvic floor muscle (PFM) overactivity. Current clinical assessment protocols include basic electromyographic assessment of PFM activation; however, they do not provide a comprehensive assessment localized to each region of the PFM. In this study from the USA, Houston and colleagues examined the ability of high-definition features from intravaginal high-density surface electromyography (HD-sEMG) to assess the severity of PFM overactivity in female IC/BPS patients. HD-sEMG was collected from fifteen female IC/BPS patients and fifteen urologically healthy female controls. The 2D mappings of root mean squared amplitude (RMS) at rest normalized by maximal voluntary contraction (resting RMS ratios) were segmented via k-means to identify areas of peak activity and surrounding activity. Female IC/BPS patients exhibited significantly greater resting RMS ratios for peak activity ($p=0.0096$), surrounding activity ($p=0.0003$), and average activity ($p=0.0016$) compared to healthy female controls. Furthermore, the area of peak activity was significantly larger for female IC/BPS patients

than for healthy female controls ($p=0.0063$). Image segmentation of intravaginal HD-sEMG provides a more robust biomarker of PFM as compared to current methods.

[CURRENT POSITION OF NEUROMODULATION FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.](#)

Kendall Harry J, Schrijvers Julia, Heesakkers John PFA. *Current Opinion in Urology* 34(2):p 64-68, March 2024. | DOI: 10.1097/MOU.0000000000001148

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Despite established effectiveness in overactive bladder and nonobstructive retention, neuromodulation's application in interstitial cystitis/bladder pain syndrome (IC/BPS) remains a topic of ongoing research. The purpose of this article from the Netherlands is to review recent developments in neuromodulation as treatment of IC/BPS offering guidance for healthcare practitioners dealing with IC/BPS cases. Recent research underlines the promising role of sacral, tibial and pudendal neuromodulation in management of IC/BPS symptoms. Studies reveal encouraging outcomes, particularly in alleviating urgency and frequency symptoms. However, while urgency and frequency symptoms tend to improve, comprehensive pain relief remains a challenge. Percutaneous tibial nerve stimulation (PTNS) and transcutaneous tibial nerve stimulation (TTNS) stand out due to their minimal invasive nature. Existing literature points to the need for larger prospective studies with extended follow-up periods to validate the efficacy and sustainability of neuromodulation. Neuromodulation is a promising treatment modality for refractory IC/BPS. Due to the minimal invasive nature, they should be tried before rigorous surgery. However, the limited quantity of available data and the variability in pain relief outcomes necessitate cautious interpretation. The review emphasizes the need for further research.

[RESTORING THE BARRIER OF CHRONICALLY DAMAGED UROTHELIUM USING CHONDROITIN SULFATE GLYCOSAMINOGLYCAN-REPLENISHMENT THERAPY.](#)

Rozenberg Boy B, van Ginkel Charlotte J, Janssen Dick. *Current Opinion in Urology* 34(2):p 44-51, March 2024. | DOI: 10.1097/MOU.0000000000001149

This study from the Netherlands aims to further understand the physiological mechanism of chondroitin sulfate treatment on the urinary bladder in cases of inflammation, by investigating the effect of chondroitin sulfate therapy on recovery of urothelial barrier in an in-vitro chronic injury model. With inflammatory bladder conditions, the urothelial barrier seems decreased. Glycosaminoglycan (GAG) replacement therapy is supposed to help restore this barrier. Clinical studies on inflammatory bladder conditions are complicated because of the heterogeneous patient population, hence the need for preclinical models. In a model using porcine urothelial cells, functional barrier (TEER) and barrier markers were assessed. Chronic urothelial damage was simulated through protamine sulfate instillations with and without subsequent chondroitin sulfate instillations during 3 days. Chondroitin sulfate instillations significantly improved TEER compared to protamine sulfate treatment only (TEER difference 310 Ω .cm², $P < 0.001$). This consistent effect over 3 days resulted in a significant higher mean TEER value in the chondroitin sulfate treated group (difference 1855 Ω .cm², $P < 0.001$). Enhanced recovery of chondroitin sulfate and other barrier markers was observed. Chondroitin sulfate therapy shows promise in facilitating the recovery of the urothelial barrier in cases of chronic damage. This preclinical study lends support to the use of clinical GAG replenishment therapy for patients with a chronically impaired urothelium.

[GLYCOSAMINOGLYCAN REPLACEMENT THERAPY WITH INTRAVESICAL INSTILLATIONS OF COMBINED HYALURONIC ACID AND CHONDROITIN SULFATE IN PATIENTS WITH RECURRENT CYSTITIS, POST-RADIATION CYSTITIS AND BLADDER PAIN SYNDROME: A NARRATIVE REVIEW](#)

Śławomir Poletajew, Magdalena M Brzózka, Wojciech Krajewski, Hubert Kamecki, Łukasz Nyk, Piotr Kryst. *Pain Ther.* 2024 Feb;13(1):1-22. doi: 10.1007/s40122-023-00559-1. Epub 2023 Nov 2. PMID: 37917298 PMCID: PMC10796878

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Defects in the glycosaminoglycan layer (GAG) of the bladder mucosa have been identified as a significant contributor to the pathogenesis and clinical progression of chronic inflammatory diseases of the bladder, such as post-radiation cystitis, bladder pain syndrome and recurrent urinary tract infections. This narrative review from Poland aims to explore the contemporary evidence on the role of GAG reconstitution with intravesical installations of hyaluronic acid and chondroitin sulfate in the management of those patients, with a goal to provide valuable insights for clinical practice. The reviewed studies consistently demonstrate that GAG reconstitution can result in varying degrees of clinical improvement in patients with post-radiation cystitis, bladder pain syndrome and recurrent urinary tract infections, and is associated with a very favorable safety profile. While the available evidence is growing, its level is still limited, mainly by relatively low number of randomized controlled trials, with small sample sizes. Further research with larger, well-designed trials is needed to solidify the findings and optimize the clinical application of GAG reconstitution.

DIMETHYL SULFOXIDE : A REVIEW OF PHARMACOLOGY AND CLINICAL EFFECT ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Hikaru Tomoe. *Contenance*, Volume 8, 2023, 101058, ISSN 2772-9737,

<https://doi.org/10.1016/j.cont.2023.101058>.

(<https://www.sciencedirect.com/science/article/pii/S2772973723009165>)

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a refractory chronic cystitis of unknown origin. The author from Japan reports that intravesical instillation therapy of Dimethyl sulfoxide (DMSO) for IC/BPS was approved by the FDA in 1978, and there are reports showing its effectiveness. However, there are still many parts of the mechanism of action of DMSO that remain unclear. DMSO has high membranous permeability, and when instilled into the bladder, DMSO easily penetrates the mucosa and infiltrates the submucosal and muscular layers, and is absorbed into the bloodstream, where it is rapidly metabolized. DMSO does not cause irreversible damage to membranes during penetration and absorption, rather it has a protective effect on cells and organs. The main mechanism of action of DMSO for IC is thought to be its anti-inflammatory effect on Hunner lesions and protection against ischemic tissue damage, mediated by radical scavenging activity of both DMSO and its reduction metabolite, DMS. Furthermore, recent studies have demonstrated that intravesical instillation of DMSO is effective only for HIC. This review highlights the known pharmacology and clinical effects of DMSO on the treatment of IC/BPS.

RESEARCH ON SYMPTOMS COMPOSITION, TIME SERIES EVOLUTION, AND NETWORK VISUALISATION OF INTERSTITIAL CYSTITIS BASED ON COMPLEX NETWORK COMMUNITY DISCOVERY ALGORITHM

Lei Pang, Zijun Ding, Xiaodong Bian, Weibing Shuang. *IET Syst Biol*. 2024 Feb;18(1):1-13. doi: 10.1049/syb2.12083. Epub 2023 Nov 13. PMID: 37957441 PMCID: PMC10860720.

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The authors from Taiyuan Shanxi Province, China analyzed the symptoms composition of Interstitial Cystitis (IC), the regularity of the evolution of symptoms before and after treatment, and the visualization of the community network, to provide a reference for clinical diagnosis and treatment of Interstitial Cystitis. Based on the outpatient electronic case data of 552 patients with Interstitial Cystitis, they used a complex network community discovery algorithm, directed weighted complex network, and Sankey map to mine the data of the symptoms composition of Interstitial Cystitis, the evolution of symptoms before and after treatment and the visualization of the community network, to analyze the epidemiological characteristics of interstitial cystitis symptoms in the real world. By the community division of the complex network of interstitial cystitis symptoms, they finally obtained three core symptom communities. Among them, symptom community A (bladder-related symptoms) is the symptom community with the highest proportion of nodes (60.00%) in the complex network of Interstitial Cystitis, symptom community B (non-bladder-related symptoms 1) ranks second (32.00%) in a complex network of Interstitial Cystitis, and symptom community C (non-

bladder-related symptoms 2) has the lowest proportion (8.00%). There is a complex evolutionary relationship between the symptoms of Interstitial Cystitis before and after treatment. Among the single symptoms before and after treatment, the decreased rate of Day frequency is 93.22%, and the reduced urgency rate is 93.07%. The decline rate of Nocturia was 82.33%. From the perspective of different communities, the overall symptoms of symptom community A decreased by 34.39% after treatment, the general symptoms of symptom community B decreased by 35.37%, and the prevalent symptoms of symptom community C decreased by 71.43%. In the case of using diet regulation treatment to treat bladder pain, the cure rate of bladder pain can reach 22.67%. The cure rate of burning in bladders can get 15.38% with Percutaneous Sacral neuromodulation, 96.95% with diet regulation treatment, and 100% with Percutaneous Sacral neuromodulation. When using behavioral physiotherapy to treat bladder pain, 3.57% of the patient's symptoms change to bladder discomfort; 4% of the patient's symptoms change to bladder discomfort when using oral medicine to treat bladder pain. Symptom research methods based on community findings can effectively explore the rule of symptom outcome of Interstitial Cystitis before and after treatment, and the results are highly interpretable by professionals.

BLADDER INSTILLATION PATTERNS IN A COHORT OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Clarissa A Niino, Lauren N Tholemeier, Catherine Bresee, Amanda M De Hoedt, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. Urogynecology (Phila). 2023 Nov;29(11):914-919. doi: 10.1097/spv.0000000000001369. PMID: 38107872 PMCID: PMC10723800.

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The purpose of this study from the USA was to determine intravesical instillation patterns among women receiving treatment for interstitial cystitis/bladder pain syndrome (IC/BPS). Using the Veterans Affairs Informatics and Computing Infrastructure, active female users of the Veterans Affairs system with an ICD-9 diagnosis of IC/BPS (595.1) were randomly sampled. Patients were considered to have IC/BPS (by chart review) if they had two visits complaining of bladder-centric pain in the absence of positive urine culture ≥ 6 weeks apart or history of bladder pain with one additional visit for bladder-centric pain. The authors abstracted the dates of intravesical instillations for each patient. A "course" of instillations was defined as ≥ 1 instillations made with < 21 days between visits. They identified 641 women with confirmed diagnosis of IC/BPS, 78 of whom underwent a total of 344 intravesical instillations. On average each subject had 1.5 \pm 0.8 courses between October 2004-July 2016. Each course was an average of 3.1 \pm 2.6 instillations. 55% of courses consisted of one instillation. Only 22% of courses had 6 or more instillations, the number typically recommended to achieve clinical response. Each instillation within a course was an average of 9.4 \pm 4.0 days apart. Most instillations (77%) were a cocktail of two or more drugs. In their cohort, few women with IC/BPS received a recommended treatment course of six weekly instillations, with most receiving only one per course. Future studies are needed to determine if instillation courses were altered from the guideline due to provider practice patterns, early improvement, or poor tolerance of instillations.

CONSTRUCTION AND EVALUATION OF A COLUMN CHART MODEL AND A RANDOM FOREST MODEL FOR PREDICTING THE PROGNOSIS OF HYDRODISTENTION SURGERY IN BPS/IC PATIENTS BASED ON PREOPERATIVE CD117, P2X3R, NGF, AND TRKA LEVELS

Lei Pang, Zijun Ding, Hongqiang Chai, Weibing Shuang. BMC Med Inform Decis Mak. 2023 Dec 14;23(1):287. doi: 10.1186/s12911-023-02396-w. PMID: 38098081 PMCID: PMC10722748

[Open access](#)

This study from Shanxi, China seeks to investigate independent risk factors affecting the prognoses of patients with bladder pain syndrome/interstitial cystitis (BPS/IC) following hydrodistention surgery and to develop a column chart model and a random forest model to help predict clinical outcomes. A retrospective analysis was conducted on the clinical data of 1006 BPS/IC patients who

visited the urology department of the Fifth Hospital of Shanxi Medical University (Shanxi Provincial People's Hospital) between June 2012 and June 2022. The patients were randomly divided into a model group (n = 704) and a validation group (n = 302). In the model group, logistic regression analysis was used to identify independent risk factors, which were used to construct a prognostic nomogram. The nomogram was evaluated by analyzing the area under the curve (AUC), calibration curve, and decision curve. These results were subsequently validated via consistency analysis (n = 302). And based on the random forest algorithm, they calculate the same data and construct a random forest model. Multivariate logistic regression analysis revealed that age and the expression of the biomarkers CD117, P2X3R, NGF, and TrkA were independent prognostic factors for patients with BPS/IC (P < 0.05). Using these five indicators, a nomogram was developed to predict the risk factors for BPS/IC (scores ranged from 0 to 400). Based on the indicators, the nomogram demonstrated good prognostic performance (AUC = 0.982 and 95% confidence interval is 0.960-0.100). The correction curve indicated a high level of differentiation in the model, and the decision curve suggested positive clinical benefits. The random forest model has high accuracy and good calibration in predicting the prognosis of patients with interstitial cystitis after hydrodistention surgery. The authors concluded that age, CD117, P2X3R, NGF, and TrkA are independent prognostic factors for bladder pain syndrome/interstitial cystitis. The column chart model and random forest model constructed based on these indicators have good predictive performance for patient prognosis.

PROGRESS AND CHALLENGES IN INTRAVESICAL DRUG DELIVERY

Arpita Banerjee, Dongtak Lee, Christopher Jiang, Rong Wang, Zoe Bogusia Kutulakos, Sohyung Lee, Jingjing Gao, Nitin Joshi. Expert Opin Drug Deliv. 2024 Jan-Jun;21(1):111-129. doi: 10.1080/17425247.2024.2307481. Epub 2024 Jan 31. PMID: 38235592

Intravesical drug delivery (IDD) has gained recognition as a viable approach for treating bladder-related diseases over the years. However, it comes with its set of challenges, including voiding difficulties and limitations in mucosal and epithelial penetration. These challenges lead to drug dilution and clearance, resulting in poor efficacy. Various strategies for drug delivery have been devised to overcome these issues, all aimed at optimizing drug delivery. Nevertheless, there has been minimal translation to clinical settings. This review from the USA provides a detailed description of IDD, including its history, advantages, and challenges. It also explores the physical barriers encountered in IDD, such as voiding, mucosal penetration, and epithelial penetration, and discusses current strategies for overcoming these challenges. Additionally, it offers a comprehensive roadmap for advancing IDD into clinical trials. Physical bladder barriers and limitations of conventional treatments result in unsatisfactory efficacy against bladder diseases. Nevertheless, substantial recent efforts in this field have led to significant progress in overcoming these challenges and have raised important attributes for an optimal IDD system. However, there is still a lack of well-defined steps in the workflow to optimize the IDD system for clinical settings, and further research is required to establish more comprehensive in vitro and in vivo models to expedite clinical translation.

THE TUMOR NECROSIS FACTOR-A LEVEL IN PLATELET-RICH PLASMA MIGHT BE ASSOCIATED WITH TREATMENT OUTCOME IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME OR RECURRENT URINARY TRACT INFECTION

Jia-Fong Jhang, Yuan-Hong Jiang, Teng-Yi Lin, Hann-Chorng Kuo. Int J Mol Sci. 2023 Dec 21;25(1):163. doi: 10.3390/ijms25010163.

Open access

Using platelet-rich plasma (PRP) injections to treat urological diseases has attracted great attention. This study from Taiwan investigated the impact of cytokine concentrations in PRP on the treatment outcome of patients with recurrent urinary tract infection (rUTI) and interstitial cystitis/bladder pain syndrome (IC/BPS). Forty patients with IC/BPS and twenty-one patients with rUTI were enrolled for

four-monthly repeated PRP injections. PRP was collected at the first injection and analyzed with multiplex immunoassays for 12 target cytokines. In patients with IC/BPS, a Global Response Assessment (GRA) score ≥ 2 was defined as a successful outcome. In rUTI patients, ≤ 2 episodes of UTI recurrence during one year of follow-up was considered a successful outcome. Nineteen (47.5%) patients with IC/BPS and eleven (52.4%) patients with rUTI had successful outcomes. The IC/BPS patients with successful outcomes had significantly lower levels of tumor necrosis factor- α (TNF- α) in their PRP than those with unsuccessful outcomes ($p = 0.041$). The rUTI patients with successful outcomes also had a lower level of TNF- α ($p = 0.025$) and a higher level of epidermal growth factor ($p = 0.035$) and transforming growth factor- $\beta 2$ ($p = 0.024$) in PRP than those with unsuccessful outcomes. A lower level of TNF- α in PRP might be a potentially predictive factor of treatment outcome.

PHARMACOLOGICAL PROPERTIES OF SHIONONE: POTENTIAL ANTI-INFLAMMATORY PHYTOCHEMICAL AGAINST DIFFERENT DISEASES

Varun Jaiswal, Hae-Jeung Lee. *Molecules*. 2023 Dec 28;29(1):189. doi: 10.3390/molecules29010189. PMID: 38202771 PMCID: PMC10780092.

[Open access](#)

The authors from Korea write that Shionone is a triterpenoid that is the primary constituent of an important ancient Chinese medicine named Radix Asteris. It has emerged as an attractive candidate against different important diseases, including interstitial cystitis, colitis, cancer, Parkinson's disease, and urinary tract infections, and was found to have a protective effect on multiple organs, including the colon, kidneys, lungs, brain, and bladder. The anti-inflammation activity of shionone may be considered an important property that imparts the positive health outcomes of shionone. Important molecular targets and markers such as TNF- α , STAT3, NLRP3, and NF- κ B were also found to be targeted by shionone and were verified in different diseases. This suggests the possible potential of shionone against other diseases associated with these targets. Pharmacokinetic studies also support the therapeutic potential of shionone and provide the initial track that may be pursued for its development. Yet, the compilation of the pharmacological activities of shionone and its important genes and pathway targets are absent in the existing literature, which would direct its development as a therapeutic and/or supplement. Hence, the present review provides a compilation of information concerning pharmacological activities, highlights the existing holes, and proposes a specific direction for the expansion of shionone as a therapeutic against different diseases and conditions.

PREPARATION AND CHARACTERIZATION OF A NOVEL COMPOSITE ACELLULAR MATRIX/HYALURONIC ACID THERMOSENSITIVE HYDROGEL FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Wei Guo, Haichao Liu, Jiaying Zhang, Jianzhong Zhang, Fei Wang, Peng Zhang, Yunbo Yang. *J Biomed Mater Res A*. 2024 Mar;112(3):449-462. doi: 10.1002/jbm.a.37643. Epub 2023 Nov 16. PMID: 37975156.

Bladder mucosa damage that causes harm to the interstitium is a recognized pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS). The intravesical instillation of drugs is an important second-line therapy, but it is often necessary to use drugs repeatedly in the clinic because of their short residence time in the bladder cavity, which alters the therapeutic effect. To overcome this drawback, this study from Beijing and Langfang, China developed a novel composite acellular matrix/hyaluronic acid (HA) thermosensitive hydrogel (HA-Gel) using rabbit small intestinal submucosa extracellular matrix (ECM) as the thermosensitive material and HA as the drug component and examined its composition, microstructure, thermodynamic properties, temperature sensitivity, rheological properties, biocompatibility, drug release, hydrogel residue, and bacteriostatic properties. The study showed HA-Gel was liquid at temperatures of 15-37.5°C and solid at 37.5-50°C, its swelling rate decreased with increasing temperature, and its lower critical

solution temperature occurred at approximately 37.5°C. This property made the hydrogel liquid at room temperature convenient for intravesical perfusion and turned into a solid about 1 min after entering the body and rising to body temperature to increase its residence time. Subsequent experiments also proved that the gel residue time of HA-Gel in vivo and the drug release time of HA in vivo could reach more than 5 days, which was significantly higher than that of HA alone, and it had good biocompatibility and antibacterial properties. Therefore, this hydrogel possesses the proper characteristics to possibly make it an ideal dosage form for IC/BPS intravesical instillation therapy.

MULTIMODAL THERAPIES AND STRATEGIES FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN TAIWAN

Wan-Ru Yu, Hann-Chorng Kuo. *Low Urin Tract Symptoms*. 2024 Jan;16(1):e12508. doi: 10.1111/luts.12508. Epub 2023 Nov 21. PMID: 37987028.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disease characterized by bladder pain, frequency, and nocturia. The most common pathologies include chronic inflammation and bladder urothelium dysfunction. According to the bladder condition with or without Hunner's lesions, IC/BPS can be divided into "IC" in patients with Hunner's lesion (HIC) and "BPS" in those without Hunner's lesion (NHIC). Previous studies have reported greater central sensitization and interorgan cross-talk in patients with NHIC. Multimodal treatments have been recommended in clinical guidelines under the biopsychosocial model. The bladder-gut-brain axis has also been speculated, and multimodal therapies are necessary. Unfortunately, currently, no treatment has been reported durable for IC/BPS. Patients with IC/BPS usually experience anxiety, depression, holistic physical responses, and even threats to social support systems. The lack of durable treatment outcomes might result from inadequate diagnostic accuracy and differentiation of clinical phenotypes based on the underlying pathophysiology. Precision assessment and treatment are essential for optimal therapy under definite IC/BPS phenotype. This article from Taiwan reviewed currently available literature and proposed a diagnosis and treatment algorithm. Based on bladder therapy combined with suitable physical and psychological therapies, a well-grounded multimodal therapy and treatment algorithm for IC/BPS following a diagnostic protocol are indispensable.

OBSTRUCTIVE SLEEP APNEA AND BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IN WOMEN

İbrahim Güven Çoşğun, Abdullah Gürel. *Sleep Breath*. 2023 Dec 26. doi: 10.1007/s11325-023-02967-1. Online ahead of print. PMID: 38147287.

The relationship between obstructive sleep apnea (OSA) and bladder pain syndrome/interstitial cystitis (BPS/IC) remains uncertain. Therefore, this study from Turkey aimed to compare the frequency of BPS/IC seen in women diagnosed with OSA and in women without OSA. The study included a patient group of women with OSA and a control group of women without OSA. All the study participants were administered the Berlin Questionnaire, Epworth Sleepiness Scale, Interstitial Cystitis Symptom Index (ICSI), and the Interstitial Cystitis Problem Index (ICPI). Differences between the women with OSA and the control group were examined. The study sample consisted of 46 women with OSA and 46 controls. No significant difference was determined between the OSA and control groups concerning age and body mass index ($p = 0.810$, $p = 0.060$, respectively). The ESS was greater in the OSA group than in the control group ($p = 0.007$). The median (IQR) ICSI was 8 (4-11.25) in women with OSA and 5 (1.75-7.15) in controls ($p < 0.001$). The median (IQR) ICPI was 7 (6.00-10.25) in women with OSA and 6 (1.75-8.00) in controls ($p < 0.001$). The ICSI symptoms and subsequent problems in daily life caused by the symptoms (ICPI) were experienced at a higher rate in patients with OSA than in the control group. There is an association between BPS/IC and OSA.

VALIDATION OF DISTINCT BLADDER PAIN PHENOTYPES UTILIZING THE MAPP RESEARCH NETWORK COHORT

Oluwarotimi Sewedo Nettey, Cindy Gu, Nicholas James Jackson, A Lenore Ackerman. *Int Urogynecol J*. 2024 Feb 1. doi: 10.1007/s00192-024-05735-1. Online ahead of print. PMID: 38300276

As interstitial cystitis/bladder pain syndrome (IC/BPS) likely represents multiple pathophysiologies, the authors from the USA sought to validate three clinical phenotypes of IC/BPS patients in a large, multi-center cohort using unsupervised machine learning (ML) analysis. Using the female Genitourinary Pain Index and O'Leary-Sant Indices, k-means unsupervised clustering was utilized to define symptomatic phenotypes in 130 premenopausal IC/BPS participants recruited through the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) research network. Patient-reported symptoms were directly compared between MAPP ML-derived phenotypic clusters to previously defined phenotypes from a single center (SC) cohort. Unsupervised ML categorized IC/BPS participants into three phenotypes with distinct pain and urinary symptom patterns: myofascial pain, non-urollogic pelvic pain, and bladder-specific pain. Defining characteristics included presence of myofascial pain or trigger points on examination for myofascial pain patients ($p = 0.003$) and bladder pain/burning for bladder-specific pain patients ($p < 0.001$). The three phenotypes were derived using only 11 features (fGUPI subscales and ICSI/ICPI items), in contrast to 49 items required previously. Despite substantial reduction in classification features, unsupervised ML independently generated similar symptomatic clusters in the MAPP cohort with equivalent symptomatic patterns and physical examination findings as the SC cohort. The reproducible identification of IC/BPS phenotypes, distinguishing bladder-specific pain from myofascial and genital pain, using independent ML analysis of a multicenter database suggests these phenotypes reflect true pathophysiologic differences in IC/BPS patients.

MECHANISMS OF OXIDATIVE STRESS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Ashu Mohammad, Mallory A Laboulaye, Chen Shenhar, Amy D Dobberfuhl. Nat Rev Urol. 2024 Feb 7. Online ahead of print. PMID: 38326514 DOI: 10.1038/s41585-023-00850-y

Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by bladder and/or pelvic pain, increased urinary urgency and frequency and nocturia. The authors from the USA note that the pathophysiology of IC/BPS is poorly understood, and theories include chronic inflammation, autoimmune dysregulation, bacterial cystitis, urothelial dysfunction, deficiency of the glycosaminoglycan (GAG) barrier and urine cytotoxicity. Multiple treatment options exist, including behavioural interventions, oral medications, intravesical instillations and procedures such as hydrodistension; however, many clinical trials fail, and patients experience an unsatisfactory treatment response, likely owing to IC/BPS phenotype heterogeneity and the use of non-targeted interventions. Oxidative stress is implicated in the pathogenesis of IC/BPS as reactive oxygen species impair bladder function via their involvement in multiple molecular mechanisms. Kinase signalling pathways, nociceptive receptors, mast-cell activation, urothelial dysregulation and circadian rhythm disturbance have all been linked to reactive oxygen species and IC/BPS. However, further research is necessary to fully uncover the role of oxidative stress in the pathways driving IC/BPS pathogenesis. The development of new models in which these pathways can be manipulated will aid this research and enable further investigation of promising therapeutic targets.

ANALGESIC EFFECT OF THE KAMPO FORMULA YOKUKANSAN VIA THE SUPPRESSION OF SUBSTANCE P IN AN EXPERIMENTAL RAT MODEL OF HUNNER-TYPE INTERSTITIAL CYSTITIS

Yoshiki Tsunokawa, Mana Tsukada, Tatsuki Inoue, Masashi Tamaoka, Toshiki Mugita, Oyunchimeg Chuluunbat, Yoshiko Maeda, Takashi Fukagai, Yoshio Ogawa, Masataka Sunagawa. Cureus. 2024 Jan 14;16(1):e52238. doi: 10.7759/cureus.52238. eCollection 2024 Jan. PMID: 38352105 PMCID: PMC10862183 DOI: 10.7759/cureus.52238

Open access

Yokukansan (YKS), a Kampo formula used in traditional Japanese medicine, has an analgesic effect, and is used for various pain disorders. This study from Japan investigated its analgesic effects on Hunner-type interstitial cystitis (HIC) and its mechanism of action in animal models. Methods: Rats with toll-like receptor-7 agonist (loxoribine)-induced HIC were used. Eight-week-old female Wistar rats were divided into three groups: control, HIC, and HIC-administered YKS (YKS + HIC). Bladder pain

was assessed based on escape behaviour using the von Frey test. Three days after HIC induction, the bladder and spinal cord were excised, and the expression of substance P (SP) was examined. Results: The pain threshold decreased significantly in the HIC group compared to that in the control group, but this decrease was suppressed by further YKS administration. The expression of SP in the bladder wall and spinal cord increased significantly in the HIC group compared to that in the control group; however, this increase was suppressed by YKS administration. SP is involved in the onset of bladder pain via neurokinin 1 receptors in bladder tissue. YKS may be useful for managing HIC-induced pain, and the suppression of SP secretion is one of its mechanisms of action.

BLADDER CAPACITY AS A BENCHMARK FOR PATIENT STRATIFICATION IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Maxwell Sandberg, Dylan T. Wolff, Wyatt Whitman, Gopal Badlani, Catherine A. Matthews, Robert Evans, Stephen J. Walker. Contenance, Volume 8, 2023, 101051, ISSN 2772-9737, <https://doi.org/10.1016/j.cont.2023.101051>.

(<https://www.sciencedirect.com/science/article/pii/S2772973723009098>)

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In a previous study the authors from the USA reported that molecular profiling of bladder mucosal tissue from a modest number of IC/BPS patients resulted in a clear separation based on anesthetic bladder capacity (BC), with 400 cc representing the apparent breakpoint between *low* and *non-low* BC. The purpose of the current study was to revisit this earlier stratification finding, using a combination of molecular and clinical data, from a large and heterogeneous patient cohort. To provide an updated assessment of IC/BPS patient stratification based on anesthetic BC, whole genome gene expression data from 48 mucosal biopsy samples (41 IC/BPS patients; 7 controls) were analyzed with unsupervised clustering and principal component analysis (PCA) to identify primary clusters of patients. This identified three primary individual clusters: (1) IC/BPS patients with a BC between 200–500 cc (n=19), (2) IC/BPS patients with a BC of 501–1500 cc (n=22), and (3) controls. Next, complete demographic, clinical, and questionnaire data prospectively collected from an additional 450 patients from their patient registry were used to conduct a combined analysis to verify this relationship. Characteristics of all 491 IC/BPS patients were compared between those having the current low BC cutoff (≤ 400 cc) and the proposed new cutoff (≤ 500 cc) by utilizing independent samples t-test (continuous variables) and chi square tests (categorical variables; $p \leq 0.05$ was considered significant). A statistical comparison of the demographic and clinical characteristics of the entire 491 IC/BPS patient cohort showed that those with a bladder capacity ≤ 500 cc were older, were more likely to have Hunner lesions, and had higher symptom scores. This group also had a lower average number of non-urolologic associated symptoms, pelvic pain syndromes, and neurologic, immune, or systemic pain syndromes. By combining newly acquired molecular data with clinical and demographic characteristics in a large cohort of IC/BPS patients, the authors concluded that anesthetic BC ≤ 500 cc provides a clinically meaningful biomarker for the bladder-centric IC/BPS phenotypic subgroup.

HUNNER LESION

THE IMMUNE SYSTEM IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND THERAPEUTIC AGENTS.

John Fallon, Inna Tabansky Stern, Micheline Laurent, Lori Birder, Robert M. Moldwin, Joel N.H. Stern. Contenance, Volume 8, 2023, 101057, ISSN 2772-9737, <https://doi.org/10.1016/j.cont.2023.101057>.

Open access

In this paper from the USA, the authors note that Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is defined by bladder pain and lower urinary tract symptoms (LUTS) in the absence of a definable etiology. Urinary tract infection is not the only definable etiology. Multiple clinical phenotypes appear within the IC/BPS patient population (Clemens, 2019) . This is likely the reason that an

etiology for the disorder has not yet been identified. The heterogeneity of this population is also the probable cause for multiple failures of therapeutic trials (Nickel and Moldwin, 2018). One IC/BPS phenotype that is readily distinguishable on cystoscopy is characterized by Hunner lesions: focal, erythematous mucosal patches with abnormal capillary architecture, edema, and scattered hemorrhages. (Akiyama et al., 2019) Current evidence suggests both local and/or centralized pathologic processes may be associated with pain experienced in IC/BPS (IC/BPS), the formation of bladder lesions is an identifiable local event in patients with IC/BPS with Hunner lesion (IC/BPS-HL). (Lai, 2021) This review will highlight recent developments in understanding the pathophysiology of IC/BPS as it relates to the immune system. The authors discuss relevant immune cells, gene expression profiles, cytokine milieu, and relevant treatment modalities.

FEMALE PELVIC ORGAN-PRESERVING ROBOT-ASSISTED SIMPLE CYSTECTOMY AND INTRACORPOREAL ILEAL NEOBLADDER RECONSTRUCTION ON A YOUNG WOMAN WITH HUNNER-TYPE INTERSTITIAL CYSTITIS

Hiroyuki Oue, Shiori Miyachi, Shinichiro Higashi, Takeshi Sasaki, Manabu Kato, Satoru Masui, Kouhei Nishikawa, Katsunori Uchida, Tomohiro Ueda, Takahiro Inoue. IJU Case Rep. 2023 Nov 23;7(1):73-76. doi: 10.1002/iju5.12671. eCollection 2024 Jan. PMID: 38173456 PMCID: PMC10758895 DOI: 10.1002/iju5.12671

[Open access](#)

Cystectomy is the last treatment option for Hunner-type interstitial cystitis. However, consensus regarding optimal patient selection or treatment approaches is lacking. In this study from Japan, a 27-year-old woman presented to a regional hospital with bladder pain and frequent urination. Antimicrobial therapy was administered; however, her symptoms persisted and she was finally diagnosed with HIC. Multiple endoscopic fulgurations of Hunner's lesions with bladder hydrodistension or intravesical therapy were performed; however, the symptoms persisted. A urethral catheter was inserted 1 month before she visited the clinic because of a severely contracted bladder. The authors performed female pelvic organ-preserving robot-assisted simple cystectomy and intracorporeal ileal neobladder reconstruction. The patient's postoperative course was uneventful and her symptoms resolved. This is the first report of pelvic organ-preserving robot-assisted simple cystectomy and intracorporeal ileal neobladder reconstruction in a young woman with HIC.

POTENTIAL ROLE OF MACROPHAGE POLARIZATION IN THE PROGRESSION OF HUNNER-TYPE INTERSTITIAL CYSTITIS

Kwang Jin Ko, Gahyun Kim, Hyun Hwan Sung, Woong-Yang Park, Kyu-Sung Lee. Int J Mol Sci. 2024 Jan 8;25(2):778. doi: 10.3390/ijms25020778. PMID: 38255860 PMCID: PMC10815545.

[Open access.](#)

Hunner-type interstitial cystitis (HIC) is a chronic inflammatory condition of the bladder. However, it remains unclear whether there is a causal relationship between the presence of Hunner lesions and seemingly normal-appearing areas in the bladder (non-Hunner lesions). This study from Korea aimed to investigate the fundamental aspects of HIC by examining potential genetic differences between Hunner and non-Hunner lesions and elucidate their role as potential markers in the progression and suppression of the disease. This cross-sectional study enrolled patients with HIC (n = 10) who underwent supratrigonal cystectomy along with augmentation cystoplasty. Full-thickness bladder tissue was collected from Hunner and non-Hunner lesions in the same patient. Normal bladder tissue biopsies were also obtained as controls. Whole transcriptome analysis was performed to analyze the gene expression patterns and immune cell populations. The mucosal layers of patients exhibited similar pathway dysregulation across Hunner and non-Hunner lesions, with immunerelated pathways being prominently affected. In the mucosal layer, genes related to anti-inflammatory and immune suppression were downregulated in Hunner lesions compared to non-Hunner lesions. Moreover, in Hunner lesions, genes related to macrophage differentiation and polarization, such as VSIG4, CD68, MAFB, and LIRB4, were downregulated. The cell fraction of M2 macrophages was

found to decrease in Hunner lesions. Immunohistochemical staining revealed an elevated fraction of M1 macrophages and a reduced fraction of M2 macrophages in Hunner lesions compared to those in non-Hunner lesions. In the muscular layer, transcriptomic evidence of muscle thickness was observed in both Hunner and non-Hunner lesions; however, the difference was not significant. Hunner lesions showed a reduced expression of anti-inflammatory and immunosuppressive factors compared to non-Hunner lesions, along with alterations in immune cell populations. This study suggests the possibility that macrophage polarization is related to the progression from non-Hunner lesions to Hunner lesions, suggesting its relevance to the characteristics of autoimmune diseases.

UROLOGIC CHRONIC PELVIC PAIN SYNDROME

ECOLOGICAL MOMENTARY ASSESSMENT OF PELVIC PAIN AND URINARY URGENCY VARIABILITY IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME AND THEIR ASSOCIATION WITH ILLNESS IMPACT AND QUALITY OF LIFE: FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN SYMPTOM PATTERNS STUDY

Bradley A Erickson, James W Griffith, Guo Wensheng, You Mengying, Ted Herman, Catherine S Bradley, J Quentin Clemens, John T Farrar, Priyanka Gupta, Karl J Kreder, H Henry Lai, Bruce D Naliboff, Diane K Newman, Larissa V Rodriguez, Theresa Spitznagle, Siobhan Sutcliffe, Suzette E Sutherland, Bayley J Taple, J Richard Landis. *Neurourol Urodyn*. 2024 Jan 22. doi: 10.1002/nau.25363. Online ahead of print. PMID: 38247366.

Open access

This MAPP study from the USA tested the hypothesis that ecological momentary assessment (EMA) of pelvic pain (PP) and urinary urgency (UU) would reveal unique Urologic Chronic Pelvic Pain Syndrome (UCPPS) phenotypes that would be associated with disease specific quality of life (QOL) and illness impact metrics (IIM). A previously validated smart phone app (M-app) was provided to willing Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) participants. M-app notifications were sent 4-times daily for 14 days inquiring about PP and UU severity. A clustering algorithm that accounted for variance placed participants into PP and UU variability? clusters. Associations between clusters and QOL and IIM were then determined. A total of 204 participants enrolled in the M-app study (64% female). M-app compliance was high (median 63% of surveys). Cluster analysis revealed k = 3 (high, low, none) PP clusters and k = 2 (high, low) UU clusters. When adjusting for baseline pain severity, high PP variability, but not UU variability, was strongly associated with QOL and IIM; specifically worse mood, worse sleep and higher anxiety. UU and PP clusters were associated with each other ($p < 0.0001$), but a large percentage (33%) of patients with high PP variability had low UU variability. It was concluded that PP variability is an independent predictor of worse QOL and more severe IIM in UCPPS participants after controlling for baseline pain severity and UU. These findings suggest alternative pain indices, such as pain variability and unpredictability, may be useful adjuncts to traditional measures of worst and average pain when assessing UCPPS treatment responses.

VALIDATION OF A SIMPLE BODY MAP TO MEASURE WIDESPREAD PAIN IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME: A MAPP RESEARCH NETWORK STUDY

J Quentin Clemens, Kenneth Locke Jr, J Richard Landis, Karl Kreder, Larissa V Rodriguez, Claire C Yang, Frank F Tu, Steven E Harte, Andrew Schrepf, John T Farrar, Siobhan Sutcliffe, Bruce D Naliboff, David A Williams, Niloofar Afari, Theresa Spitznagle, Bayley J Taple, H Henry Lai. *Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network*. *Neurourol Urodyn*. 2024 Jan 25. doi: 10.1002/nau.25400. Online ahead of print. PMID: 38270336 DOI: 10.1002/nau.25400

In patients with urologic chronic pelvic pain syndrome (UCPPS), the presence of widespread pain appears to identify a distinct phenotype, with a different symptom trajectory and potentially different response to treatment than patients with pelvic pain only. A 76-site body map was administered four times, at weekly intervals, to 568 male and female UCPPS participants in the

MAPP Network protocol. The 76 sites were classified into 13 regions (1 pelvic region and 12 nonpelvic regions). The degree of widespread pain was scored from 0 to 12 based on the number of reported nonpelvic pain regions. This continuous body map score was regressed over other measures of widespread pain, with UCPPS symptom severity, and with psychosocial variables to measure level of association. These models were repeated using an updated body map score (0-12) that incorporated a threshold of pain ≥ 4 at each site. Body map scores showed limited variability over the 4 weekly assessments, indicating that a single baseline assessment was sufficient. The widespread pain score correlated highly with other measures of widespread pain and correlated with worsened UCPPS symptom severity and psychosocial functioning. Incorporating a pain severity threshold ≥ 4 resulted in only marginal increases in these correlations. These results support the use of this 13-region body map in the baseline clinical assessment of UCPPS patients. It provides reliable data about the presence of widespread pain and does not require measurement of pain severity, making it relatively simple to use for clinical purposes.

HYPERTENSION AND UROLOGIC CHRONIC PELVIC PAIN SYNDROME: AN ANALYSIS OF MAPP-I DATA

Rosalynn R Z Conic, Terrie Vasilopoulos, Karthik Devulapally, Rene Przkora, Andrew Dubin, Kimberly T Sibille, Aaron D Mickle. BMC Urol. 2024 Jan 28;24(1):21. doi: 10.1186/s12894-024-01407-w. PMID: 38281923 PMCID: PMC10822153.

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Urologic chronic pelvic pain syndrome (UCPPS), which includes interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis (CP/CPSP), is associated with increased voiding frequency, nocturia, and chronic pelvic pain. The cause of these diseases is unknown and likely involves many different mechanisms. Dysregulated renin-angiotensin-aldosterone-system (RAAS) signalling is a potential pathologic mechanism for IC/BPS and CP/CPSP. Many angiotensin receptor downstream signalling factors, including oxidative stress, fibrosis, mast cell recruitment, and increased inflammatory mediators, are present in the bladders of IC/BPS patients and prostates of CP/CPSP patients. Therefore, the authors from the USA aimed to test the hypothesis that UCPPS patients have dysregulated angiotensin signalling, resulting in increased hypertension compared to controls. Secondly, they evaluated symptom severity in patients with and without hypertension and antihypertensive medication use. Data from UCPPS patients ($n = 424$), fibromyalgia or irritable bowel syndrome (positive controls, $n = 200$), and healthy controls ($n = 415$) were obtained from the NIDDK Multidisciplinary Approach to the Study of Chronic Pelvic Pain I (MAPP-I). Diagnosis of hypertension, current antihypertensive medications, pain severity, and urinary symptom severity were analyzed using chi-square test and t-test. The combination of diagnosis and antihypertensive medications use was highest in the UCPPS group ($n = 74$, 18%), followed by positive ($n = 34$, 17%) and healthy controls ($n = 48$, 12%, $p = 0.04$). There were no differences in symptom severity based on hypertension in UCPPS and CP/CPSP; however, IC/BPS had worse ICSI ($p = 0.031$), AUA-SI ($p = 0.04$), and BPI pain severity (0.02). Patients ($n = 7$) with a hypertension diagnosis not on antihypertensive medications reported the greatest severity of pain and urinary symptoms. This pattern of findings suggests that there may be a relationship between hypertension and UCPPS. Treating hypertension among these patients may result in reduced pain and symptom severity. Further investigation on the relationship between hypertension, antihypertensive medication use, and UCPPS and the role of angiotensin signalling in UCPPS conditions is needed.

UROLOGIC CHRONIC PELVIC PAIN SYNDROME FLARES: A COMPREHENSIVE, SYSTEMATIC REVIEW AND META-ANALYSIS OF THE PEER-REVIEWED FLARE LITERATURE

Emily S Barker, Kimberley Chiu, Victoria L Brown, Haidy Morsy, Lauren H Yaeger, Arya Catna, Ratna Pakpahan, Robert Moldwin, Barbara Shorter, Jerry L Lowder, H Henry Lai, Siobhan Sutcliffe. J Urol. 2024 Mar;211(3):341-353. doi: 10.1097/JU.0000000000003820. Epub 2023 Dec 18. PMID: 38109700.

In this study from the USA, the authors sought to systematically review and summarize the peer-reviewed literature on urologic chronic pelvic pain syndrome flares, including their terminology, manifestation, perceived triggers, management and prevention strategies, impact on quality of life, and insights into pathophysiologic mechanisms, as a foundation for future empirical research. They searched 6 medical databases for articles related to any aspect of symptom exacerbations for interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. A total of 1486 abstracts and 398 full-text articles were reviewed, and data were extracted by at least 2 individuals. Overall, they identified 59 articles, including 36 qualitative, cross-sectional, or case-control; 15 cohort-based; and 8 experimental articles. The majority of studies described North American patients with confirmed diagnoses. "Flare" was a commonly used term, but additional terminology (eg, exacerbation) was also used. Most flares involved significant increases in pain intensity, but fewer data were available on flare frequency and duration. Painful, frequent, long-lasting, and unpredictable flares were highly impactful, even over and above participants' nonflare symptoms. A large number of perceived triggers (eg, diet, stress) and management/prevention strategies (eg, analgesics, thermal therapy, rest) were proposed by participants, but few had empirical support. In addition, few studies explored underlying biologic mechanisms. Overall, they found that flares are painful and impactful, but otherwise poorly understood in terms of manifestation (frequency and duration), triggers, treatment, prevention, and pathophysiology. These summary findings provide a foundation for future flare-related research and highlight gaps that warrant additional empirical studies.

IC/BPS – THE PATIENT EXPERIENCE WITH PROVIDERS

[BELIEVING WOMEN: A QUALITATIVE EXPLORATION OF PROVIDER DISBELIEF AND PAIN DISMISSAL AMONG WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME FROM THE MAPP RESEARCH NETWORK](#)

Victoria L Brown, Aimee James, Jean Hunleth, Catherine S Bradley, John T Farrar, Priyanka Gupta, H Henry Lai, Jerry L Lowder, Robert Moldwin, Larissa V Rodriguez, Claire C Yang, Siobhan Sutcliffe. *Int Urogynecol J*. 2024 Jan;35(1):139-148. doi: 10.1007/s00192-023-05677-0. Epub 2023 Nov 22. PMID: 37991567.

Although allusions to the importance of a good physician-patient relationship are present throughout the interstitial cystitis/bladder pain syndrome (IC/BPS) literature, qualitative analysis of patients' perspectives on the clinical encounter is lacking, particularly among women who are most commonly affected by IC/BPS. Therefore, the authors from the USA adopted a patient-centered experiential approach to understanding female patients' perception of clinical encounters. They re-analyzed previously collected data from a qualitative study on patient flare experiences including eight focus groups of female IC/BPS patients (n = 57, mean = 7/group). Qualitative analysis applied grounded theory to index all physician-patient interactions, then thematically coded these interactions to elucidate common experiences of clinical encounters. Women with IC/BPS shared common experiences of provider disbelief and pain dismissal. Discussions with participants demonstrated the extent to which these negative encounters shape patients' health care-seeking behavior, outlook, and psychosocial well-being. Appearing in more than one guise, provider disbelief and dismissal occurred as tacit insinuations, explicit statements, silence, oversimplification, and an unwillingness to listen and discuss alternative treatment. As a result, women adopted several strategies including: rotating specialists; "testing" physicians; self-advocacy; self-management; avoiding the stigma of chronic pain; crying; and opting for alternative medicine over biomedicine. The prevalence of provider disbelief and pain dismissal among women with IC/BPS indicates a need to improve physician-patient communication, informed by the struggles, anxieties, and gendered inequities that female patients with chronic pain experience in their diagnostic journey. Results suggest that further investigation into the power dynamics of clinical encounters might be required.

LOWER URINARY TRACT

[LOWER URINARY TRACT INFLAMMATION AND INFECTION: KEY MICROBIOLOGICAL AND IMMUNOLOGICAL ASPECTS](#)

Kayle Dickson, Juan Zhou, Christian Lehmann. *J Clin Med.* 2024 Jan 5;13(2):315. doi: 10.3390/jcm13020315. PMID: 38256450 PMCID: PMC10816374.

[Open access](#)

The urinary system, primarily responsible for the filtration of blood and waste, is affected by several infectious and inflammatory conditions. Focusing on the lower tract, this review from Canada outlines the physiological and immune landscape of the urethra and bladder, addressing key immunological and microbiological aspects of important infectious/inflammatory conditions. The conditions addressed include urethritis, interstitial cystitis/bladder pain syndrome, urinary tract infections, and urosepsis. Key aspects of each condition are addressed, including epidemiology, pathophysiology, and clinical considerations. Finally, therapeutic options are outlined, highlighting gaps in the knowledge and novel therapeutic approaches.

[NON CLINICAL MODEL TO ASSESS THE MECHANISM OF ACTION OF A COMBINED HYALURONIC ACID, CHONDROITIN SULFATE AND CALCIUM CHLORIDE: HA+CS+CaCl₂ SOLUTION ON A 3D HUMAN RECONSTRUCTED BLADDER EPITHELIUM](#)

Laura Brambilla, Valeria Frangione, Marisa Meloni. *Med Devices (Auckl).* 2024 Jan 30;17:47-58. doi: 10.2147/MDER.S433261. eCollection 2024. PMID: 38312113 PMCID: PMC10838052

[Open access](#)

Medical Device Regulation (EU) 2017/745 requires the principal mode of action (MoA) to be demonstrated by experimental data. The MoA of Ialuril® Prefill (combined as HA+CS+CaCl₂: sodium hyaluronate 1.6%, sodium chondroitin sulphate 2% w/v and calcium chloride 0.87%) Class III medical device, indicated for intravesical instillation to reduce urinary tract infections, has been evaluated on a 3D reconstructed human bladder epithelium (HBE). Three experimental designs; i) E. coli strain selection (DSM 103538, DSM 1103) to investigate the HA+CS+CaCl₂ properties in modifying bacterial growth in liquid broth (CFU 4h and 24h) at 80%, 50% and 25% concentrations; ii) evaluation of film forming properties on HBE after 15 min exposure by quantifying caffeine permeation across the epithelium; iii) capacity to counteract E. coli adhesion and biofilm formation on colonized HBE by viable counts and ultrastructural analysis by scanning electron microscopy (SEM) using ciprofloxacin as the reference antimicrobial molecule. No significant differences were observed in bacterial viability for both the E. coli strains. HA+CS+CaCl₂ reduced caffeine permeation of 51.7% and 38.1% at 1h and 2h, respectively and determined a significant decrease in caffeine permeation rate at both timepoints supporting HA+CS+CaCl₂ capacity to firmly adhere to the bladder epithelium creating a physical barrier on the surface. The viable counts in HBE treated tissues then infected with E. coli resulted not different from the negative control suggesting that the device did not inhibit E. coli growth. SEM images showed homogenous product distribution over the HBE surface and confirmed the capacity of HA+CS+CaCl₂ to adhere to the bladder epithelium, counteracting biofilm formation. The results support the capacity of HA+CS+CaCl₂ to counteract bacterial invasion by using a physico-mechanical mode of action: this medical device represents a valid alternative to antibiotics in the treatment of recurrent UTIs.

CHRONIC PELVIC PAIN, PELVIC FLOOR

[PELVIC PAIN SYNDROMES](#)

John Heesakkers, Dick Janssen. *Curr Opin Urol.* 2024 Mar 1;34(2):43. doi: 10.1097/MOU.0000000000001156. Epub 2024 Feb 8. PMID: 38321977

Editorial - Click on title to read.

USING MYOFASCIAL THERAPY TO IMPROVE PSYCHOLOGICAL OUTCOMES, QUALITY OF LIFE, AND SEXUAL FUNCTION IN WOMEN WITH CHRONIC PELVIC PAIN-A CASE SERIES

Esther Diaz-Mohedo, Fidel Hita-Contreras, Eduardo Castro-Martin, Andrzej Pilat, Borja Perez-Dominguez, Geraldine Valenza-Peña. Healthcare (Basel). 2024 Jan 24;12(3):304. doi: 10.3390/healthcare12030304. PMID: 38338190 PMCID: PMC10855135

[Open access](#)

Chronic pelvic pain represents a prevalent condition afflicting women. Research has highlighted the presence of psychological distress and sexual dysfunction in these individuals. Regrettably, myofascial pelvic pain often goes unnoticed and untreated despite its integral role in chronic pelvic pain. By employing a longitudinal case series design, the authors from Spain studied eighteen women afflicted with chronic pelvic pain. Over a 12-week period, these participants underwent 15 sessions of myofascial therapy. Data encompassing sociodemographic particulars, the Hospital Anxiety and Depression Scale, the Medical Outcomes Study Short Form 12 questionnaire, and the Female Sexual Function Index were collected at baseline, 12 weeks post-intervention, and again at the 24-week mark. After a span of 12 weeks subsequent to the intervention, the participants demonstrated noteworthy enhancements ($p < 0.001$) in their depression and anxiety scores, their overall Mental Component scores in the Medical Outcomes Study Short Form 12, as well as sexual function. Importantly, these gains were sustained at the 24-week juncture post-therapy. The findings stemming from the prospective case study underscore the potential utility of myofascial therapy for women grappling with chronic pelvic pain. This form of intervention yields significant advancements in alleviating anxiety, depression, health-related quality of life, and sexual function.

COGNITIVE BEHAVIORAL THERAPY FOR CHRONIC PELVIC PAIN: WHAT IS IT AND DOES IT WORK?

Jeffrey M Lackner, J Quentin Clemens, Christopher Radziwon, Teresa L Danforth, Tova S Ablove, Susan S Krasner, Alison M Vargovich, Patricia C O'Leary, Tracy Marotto, Bruce D Naliboff. J Urol. 2024 Jan 16;101097JU0000000000003847. doi: 10.1097/JU.0000000000003847. Online ahead of print. PMID: 38228093

Urologic chronic pelvic pain syndrome (UCPPS), which encompasses interstitial cystitis/bladder pain syndrome in women and men and chronic prostatitis/chronic pelvic pain syndrome in men, is a common, often disabling urological disorder that is neither well understood nor satisfactorily treated with medical treatments. The past 25 years have seen the development and validation of a number of behavioral pain treatments, of which cognitive behavioral therapy (CBT) is arguably the most effective. CBT combines strategies of behavior therapy, which teaches patients more effective ways of behaving, and cognitive therapy, which focuses on correcting faulty thinking patterns. As a skills-based treatment, CBT emphasizes "unlearning" maladaptive behaviors and thoughts, and replacing them with more adaptive ones that support symptom self-management. This review from the USA describes the rationale, technical procedures, and empirical basis of CBT. While evidence supports CBT for treatment-refractory chronic pain disorders, there is limited understanding of why or how CBT might work, for whom it is most beneficial, or the specific UCPPS symptoms (eg, pain, urinary symptoms) it effectively targets. This is the focus of EPPIC (Easing Pelvic Pain Interventions Clinical Research Program), a landmark NIH trial examining the efficacy of low-intensity CBT for UCPPS. Relative to a nonspecific comparator featuring self-care recommendations of AUA guidelines. Systematic efforts to increase both the efficiency of CBT and the way it is delivered (eg home-based treatments) are critical to scaling up CBT, optimizing its therapeutic potential, and reducing the public health burden of UCPPS.

CHRONIC PELVIC PAIN, VULVAR PAIN DISORDERS, AND PROTEOMICS PROFILES: NEW DISCOVERIES, NEW HOPES

Chiara Di Tucci, Ludovico Muzii. Biomedicines. 2023 Dec 19;12(1):1. doi: 10.3390/biomedicines12010001. PMID: 38275362 PMCID: PMC10813718

[Open access](#)

This paper from Italy notes that chronic pelvic pain (CPP) is generally defined as non-cyclic pain perceived in the pelvic area that has persisted from three to six months or longer and is unrelated to pregnancy. The etiology of CPP is complex, multifactorial, with heterogeneous presentation, and includes several diseases such as endometriosis, adenomyosis, and interstitial cystitis/bladder pain syndrome. It may also be associated with sexual dysfunction, musculoskeletal disorders, and comorbid psychiatric symptoms. Vulvar pain disorders (VPDs) are typically categorized separately from chronic pelvic pain; among all VPDs, vulvodynia is a chronic vulvar pain of unknown etiology, lasting at least 3 months and that might be associated with other potentially linked factors. Proteomics represents a useful approach to study the proteome profiles of clinical samples. In this review, the authors have considered a selection of articles that have analyzed the protein abundance and novel protein species from various biological samples, including eutopic/ectopic endometrium, urine, serum, follicular, peritoneal fluid, and cervical mucus, potentially involved in the pathogenesis and progression of CPP and VPDs. These findings could represent valuable targets for paving the way for the differential diagnosis and therapeutic management of CPP and VPDs, thereby optimizing both the prevention and treatment of these conditions.

CHRONIC PELVIC PAIN; MORE THAN JUST THE BLADDER.

Messelink Bert, Flink Ida, dos Santos Ana, Adamse Corine. Current Opinion in Urology 34(2):p 69-76, March 2024. | DOI: 10.1097/MOU.0000000000001134

In this article from the Netherlands and Sweden, the authors note that chronic pelvic pain is much of a burden to those who suffer from it. Additionally, in many patients medical doctors, such as urologists are unable to identify a cause or clear pathology that can explain the pain. Still numerous patients and doctors keep on searching for a cause, focussing particularly on the pelvic organs. Lots of diagnostics and treatment methods are used but often without success. In recent years, the authors note that they have gained increased insight into the mechanisms of pain and adapted the terminology accordingly. Two aspects of chronic pelvic pain have gained more attention. First, the myofascial aspects, especially the role of the pelvic floor muscles in maintaining the pain and as a therapeutic option. Second, the role of the brain and the psychological aspects intertwine with the pain and its consequences also open up for alternative management options. In terminology chronic pain is now included in the ICD-11, a historical change. Introducing chronic primary pain (no cause found) helps us to look away from the organ and deal with the patient as a whole human being. The findings reported here are helpful for your daily practice. Looking from a broad perspective gives the patient the feeling of being seen and heard. Working together in a multidisciplinary team makes your work easier and gives more satisfaction.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

PENTOSAN POLYSULFATE MACULOPATHY

J Ben Margines, Samuel D. Hobbs. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2023 Dec 19. PMID: 36944010 Bookshelf ID: NBK589706. Free Books & Documents.

[Open access](#)

Pentosan polysulfate (PPS) is a semisynthetic pentasaccharide heparinoid with anticoagulant properties and was initially used in the 1950s as a thrombolytic due to the ability of the molecule to bind the glycocalyx of circulating red blood cells. It is the only medication approved by the United States Food and Drug Administration to treat interstitial cystitis (IC). Interstitial cystitis is characterized by bladder pain (suprapubic, pelvic, urethral, vaginal, or perineal) caused by filling and relieved by emptying with petechial bladder mucosal hemorrhages on endoscopy and decreased bladder compliance on urodynamics. This disease is very common: it affects over one million Americans, the vast majority female. In the bladder, PPS is postulated to bind to the urothelium and replace disrupted glycosaminoglycans to protect the urothelium. Less frequently, PPS is used for

other indications, including irritable bowel syndrome, pelvic pain syndrome, and inner bladder wall cracks. The recommended dosage for PPS is 100 mg three times a day. Twenty-two years after its approval as a second-line agent for interstitial cystitis, a six-patient case series described a progressive maculopathy associated with long-term use of the drug, an association that researchers have demonstrated and characterized multiple times.

BLADDER ENDOMETRIOSIS

IMAGING OF URINARY BLADDER AND URETERAL ENDOMETRIOSIS WITH EMPHASIS ON DIAGNOSIS AND TECHNIQUE

Anuradha S Shenoy-Bhangle, Isabella Vinagre Pires-Franco, Lauren J Ray, Jinjin Cao, Aoife Kilcoyne, Natally Horvat, Luciana Pardini Chamie. Acad Radiol. 2023 Nov 22;S1076-6332(23)00608-6. doi: 10.1016/j.acra.2023.10.053. Online ahead of print. PMID: 37996365

Endometriosis is a chronic inflammatory gynecological condition affecting 10-15% of women in the reproductive age group. The urinary tract is the second most common extragenital organ system affected by endometriosis, and the urinary bladder and ureter are the two most common sites involved. Involvement of the urinary bladder can cause chronic debilitating symptoms, whereas ureteral involvement may lead to asymptomatic loss of renal function. Both conditions are frequently unsuspected, leading to a delay in diagnosis. Therefore, it is important to recognize this entity early, for which knowledge of imaging appearances and techniques is helpful. In this review article from the USA and Brazil, the authors describe (a) endometriosis background, pathogenesis, definitions and clinical symptoms, (b) imaging appearance, with emphasis on ultrasound and MRI findings of urinary bladder and ureteric endometriosis, (c) ultrasound technique and MRI sequences useful for making the correct diagnosis, (d) overview of the treatment options and key imaging findings that are important to the surgeon for surgical planning, and (e) a structured reporting template useful for multidisciplinary patient management.

BRAINSTEM NUCLEI RESPONSIVE TO CYSTOMETRY IN BOTH ENDOMETRIOSIS AND CYSTITIS RAT MODELS: C-FOS IMMUNOHISTOCHEMISTRY STUDY

Ayah A Bashkami, Ezidin G Kaddumi, Mohamad Al-Saghbini, Afnan J Kenana. NeuroUrol Urodyn. 2024 Feb 13. doi: 10.1002/nau.25419. Online ahead of print. PMID: 38348646

Although the co-occurrence of interstitial cystitis (IC) and endometriosis (ENDO) is remarkably high, the exact pathophysiology for this co-occurrence is unknown. The convergence of the inputs from the involved structures to the same neuronal centers may suggest neuronal hyperexcitability as a mechanism for this co-occurrence. The present study from Jordan aimed to investigate the association between IC and ENDO, by studying the changes in brainstem responses to cystometry in a rat model of ENDO and cyclophosphamide (CYP)-induced IC using c-fos immunohistochemistry. Following cystometry the brainstem areas that had significant increase in c-fos expression in ENDO alone included: periaqueductal gray (PAG) nuclei, dorsal raphe nucleus, raphe obscurus nucleus, kolliker- Fuse areas, and area postrema. However, the brainstem areas that had increased significantly in the c-fos expression in the ENDO and CYP treated animals included: gigantocellular nucleus, lateral paragigantocellular nucleus, caudoventrolateral nucleus, rostroventrolateral/caudoventrolateral nucleus, lateral reticular nucleus, locus coeruleus, lateral PAG, raphe pallidus nucleus, raphe magnus nucleus, rostroventrolateral nucleus, dorsal motor nucleus of vagus, and solitary tract nucleus. Whereas only lateral parabrachial nucleus showed significant increase in c-fos expression in CYP treated animals alone. The results of the present study demonstrate the overlap of brainstem nuclei that are excited by urinary bladder under ENDO and IC conditions. The pattern of hyperexcitability of the brainstem nuclei may help in understanding the pathophysiology of IC and ENDO conditions.

KETAMINE CYSTITIS**KETAMINE CYSTITIS FOLLOWING KETAMINE THERAPY FOR TREATMENT-RESISTANT DEPRESSION - CASE REPORT**

Minna Chang, Mario F Juruena, Allan H Young. *BMC Psychiatry*. 2024 Jan 2;24(1):9. doi: 10.1186/s12888-023-05468-3. PMID: 38166893 PMCID: PMC10763323

[Open access](#)

Ketamine is a novel and exciting putative antidepressant medication for patients with treatment-resistant depression. A complication commonly seen in frequent and heavy recreational use of ketamine is ulcerative cystitis, which presents with lower urinary tract symptoms (LUTS) and upper renal tract damage and can be seen in over 25% of regular users. Although Ketamine-induced cystitis (KIC) is a recognised complication in recreational use of ketamine, its occurrence in therapeutic use of ketamine in depression has so far not been reported. The exact pathogenesis of KIC is currently unknown, making treatment and prevention advice much more difficult. Early diagnosis of KIC and immediate cessation of ketamine has been shown to improve adverse urinary tract symptoms and prevent further damage. Chang and colleagues from London, UK present a case of a 28-year-old female who was started on ketamine treatment for depression, and who then developed symptoms of KIC, which was confirmed by urine microscopy, culture and analysis. They note that to their knowledge, this is the first reported case of KIC in a patient receiving treatment-dose ketamine as part of their antidepressant therapy.

SJÖGREN'S SYNDROME**INTERSTITIAL CYSTITIS IN SJÖGREN'S SYNDROME**

Hirota Yamamoto, Yoshinori Taniguchi. *N Engl J Med*. 2024 Feb 8;390(6):548. doi: 10.1056/NEJMicm2308925. Epub 2024 Feb 3. PMID: 38314846.

In this article from Japan, Yamamoto and Taniguchi describe a 66-year-old woman with primary Sjögren's syndrome who presented with a 1-month history of lower abdominal pain and urinary urgency. CT of the abdomen showed bladder-wall thickening and hydronephrosis.

ARTIFICIAL INTELLIGENCE & MACHINE LEARNING**GENERAL OVERVIEW OF ARTIFICIAL INTELLIGENCE FOR INTERSTITIAL CYSTITIS IN UROLOGY**

Yongwon Cho, Jong Mok Park, Seunghyun Youn. *Int Neurourol J*. 2023 Nov;27(Suppl 2):S64-72. doi: 10.5213/inj.2346294.147. Epub 2023 Nov 30. PMID: 38048820 PMCID: PMC10715831.

[Open access.](#)

Our understanding of interstitial cystitis/bladder pain syndrome (IC/BPS) has evolved over time. The diagnosis of IC/BPS is primarily based on symptoms such as urgency, frequency, and bladder or pelvic pain. While the exact causes of IC/BPS remain unclear, it is thought to involve several factors, including abnormalities in the bladder's urothelium, mast cell degranulation within the bladder, inflammation of the bladder, and altered innervation of the bladder. Treatment options include patient education, dietary and lifestyle modifications, medications, intravesical therapy, and surgical interventions. This review article from Seoul, Korea provides insights into IC/BPS, including aspects of treatment, prognosis prediction, and emerging therapeutic options. Additionally, it explores the application of deep learning for diagnosing major diseases associated with IC/BPS.

MACHINE LEARNING-BASED CLASSIFICATION OF TRANSCRIPTOME SIGNATURES OF NON-ULCERATIVE BLADDER PAIN SYNDROME

Akshay Akshay, Mustafa Besic, Annette Kuhn, Fiona C Burkhard, Alex Bigger-Allen, Rosalyn M Adam, Katia Monastyrskaya, Ali Hashemi Gheinani. *bioRxiv Preprint*. 2024 Jan 8:2024.01.08.574189. doi: 10.1101/2024.01.08.574189. PMID: 38260635 PMCID: PMC10802429.

[Open access](#)

Lower urinary tract dysfunction (LUTD) presents a global health challenge with symptoms impacting a substantial percentage of the population. The absence of reliable biomarkers complicates the accurate classification of LUTD subtypes with shared symptoms such as non-ulcerative Bladder Pain Syndrome (BPS) and overactive bladder caused by bladder outlet obstruction with Detrusor Overactivity (DO). This study from the U&SA and Switzerland introduces a machine learning (ML)-based approach for the identification of mRNA signatures specific to non-ulcerative BPS. Using next-generation sequencing (NGS) transcriptome data from bladder biopsies of patients with BPS, benign prostatic obstruction with DO and controls, their statistical approach successfully identified 13 candidate genes capable of discerning BPS from control and DO patients. This set was subsequently validated using Quantitative Polymerase Chain Reaction (QPCR) in a larger patient cohort. To confirm their findings, the authors applied both supervised and unsupervised ML approaches to the QPCR dataset. Notably, a three-mRNA signature TPPP3, FAT1, and NCALD, emerged as a robust classifier, effectively distinguishing patients with non-ulcerative BPS from controls and patients with DO. This signature was universally selected by both supervised and unsupervised approaches. The ML-based framework used to define BPS classifiers not only establishes a solid foundation for comprehending the specific gene expression changes in the bladder of the patients with BPS but also serves as a valuable resource and methodology for advancing signature identification in other fields. The proposed ML pipeline demonstrates its efficacy in handling challenges associated with limited sample sizes, offering a promising avenue for applications in similar domains.

DYSURIA

[DYSURIA](#)

Parth Mehta, Stephen W. Leslie, Anil Kumar Reddy Reddivari.

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2023 Nov 12.

PMID: 31751108 Bookshelf ID: NBK549918. Free Books & Documents

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Dysuria is the sensation of pain and/or burning, stinging, or itching of the urethra or urethral meatus associated with urination. It is a prevalent urinary symptom experienced by most people at least once in their lifetime. Dysuria typically occurs when urine comes in contact with the inflamed or irritated urethral mucosal lining. This is exacerbated by and associated with detrusor muscle contraction and urethral peristalsis, which stimulates the submucosal pain receptors, resulting in pain or a burning sensation during urination. True dysuria requires differentiation from other symptoms, which can also occur due to pelvic discomfort from various bladder conditions such as interstitial cystitis, prostatitis, and suprapubic or retropubic pain. This distressing condition can be caused by multiple underlying factors, including urinary tract infections (UTIs), bladder inflammation, sexually transmitted infections (STIs), or even more serious conditions like kidney stones. Understanding dysuria's broad differential is critical in further management. Clinicians should recognize that further evaluation is warranted when dysuria is present. This will lead to improved recognition of potential abnormalities, which, in turn, will dictate treatment strategies and improve patient outcomes.

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