

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 – June 2025

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 These are preliminary reports of work that have not been certified by peer review.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 Lesion Disease, Hunner’s ulcer, Hunner IC and Classic IC are synonymous.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

USA

[ADVANCING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME \(IC/BPS\) DIAGNOSIS: A COMPARATIVE ANALYSIS OF MACHINE LEARNING METHODOLOGIES.](#)

Janicki JJ, Zwaans BMM, Bartolone SN, Ward EP, Chancellor MB. Diagnostics (Basel). 2024 Dec 5;14(23):2734. doi: 10.3390/diagnostics14232734. PMID: 39682641; PMCID: PMC11640490.

Open access

This USA study aimed to improve machine learning models for diagnosing interstitial cystitis/bladder pain syndrome (IC/BPS) by comparing classical machine learning methods with newer AutoML approaches, utilizing biomarker data and patient-reported outcomes as features. The authors applied various machine learning techniques to biomarker data from the previous IP4IC and ICRS studies to predict the presence of IC/BPS, a disorder impacting the urinary bladder. Data were sourced from two nationwide, crowd-sourced collections of urine samples involving 2009 participants. The models utilized included logistic regression, support vector machines, random forests, k-nearest neighbors, and AutoGluon. Expanding the dataset for model training and evaluation resulted in improved performance metrics compared to previously published findings. The implementation of AutoML methods yielded enhancements in model accuracy over classical techniques. The top-performing models achieved a receiver-operating characteristic area under the curve (ROC-AUC) of up to 0.96. This research demonstrates an improvement in model performance relative to earlier studies, with the top model for binary classification incorporating objective urinary biomarker levels. These

advancements represent a significant step toward developing a reliable classification model for the diagnosis of IC/BPS.

USA

[INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: MATCHING THERAPIES TO THE PATIENT.](#)

Moldwin, J.F., Moldwin, R.M. *Curr Bladder Dysfunct Rep* **20**, 4 (2025).

<https://doi.org/10.1007/s11884-025-00772-y>

Open access

The aim is to establish broad clinical subgroups of patients and match them to a more tailored approach with improved clinical outcomes. Patient experience over the past four decades and investigative initiatives such as The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) have led to the development of four broad categories of IC/BPS patients: bladder-centric (which is further sub-divided into those with Hunner lesion disease (HLD) and those without (IC/BPS)); widespread/centralized pain; and myofascial pelvic floor tenderness. Other systems of patient categorization, such as UPOINT, now INPUT, highlight the complexities of patient assessment. Reanalysis of previous failed clinical trials and common sense suggests that matching the therapy's mechanism of action to the patient's phenotype may yield better therapeutic outcomes. Although the IC/BPS population is known to be phenotypically heterogeneous, therapeutic approaches afforded by most current guidelines have been relatively rigid, only accounting for those patients with and without Hunner lesions. Segregating the IC/BPS population further into distinct phenotypic groups that may respond to targeted therapy is relatively simplistic but represents an essential first step toward precision care

Randomized controlled trial. Netherlands

[CARRY-OVER EFFECTS IN GAG THERAPY EFFICACY TRIAL SOLUTION FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS \(GETSBI STUDY\): AN INTERIM ANALYSIS.](#)

van Ginkel C, Groenewoud JMM, Hoogeboom TJ, Heesakkers J, Martens F, Janssen D. *BMJ Open*. 2025 Jun 5;15(6):e092757. doi: 10.1136/bmjopen-2024-092757. PMID: 40473282.

This double blind, multicentre, randomised, placebo-controlled GAG-therapy Efficacy Trial Solution for Bladder pain syndrome/Interstitial cystitis (GETSBI) study from the Netherlands aims to evaluate the efficacy of intravesical glycosaminoglycans therapy with hyaluronic acid and chondroitin sulfate in symptomatic bladder pain syndrome/interstitial cystitis (BPS/IC) patients with Hunner lesions. This trial encompasses multiple methodologies, including a standard randomised controlled trial (RCT), a cross-over trial and an N-of-1 trial. An N-of-1 trial is a multiple crossover trial, usually randomised and often blinded, conducted in a single patient (1). The N-of-1 methodology is, however, only valid under the condition that there is no carry-over effect, meaning a carry-over of effect from an a-priori intervention period into the placebo period. Therefore, it is important to examine any potential carry-over effects to determine the validity of the study protocol concerning the N-of-1 trial part and thereby justifying recruitment. This concerns an interim analysis for potential carry-over effects in a secondary care setting with 21 participants who had concluded part one from the GETSBI study at time of this analysis (October 2023). The primary outcome of the study is the change from baseline in pain intensity, measured by visual analogue scale (VAS) pain. To assess for carry-over effects, the placebo responses on VAS pain were compared between groups with (n=10) and without (n=11) potential carry-over effects. The threshold for a clinically relevant carry-over effect was set at a difference on VAS pain >0.50 points. Data were analysed using descriptive statistics, T-tests, effect sizes and 95% CI. Statistical significance was set at $\alpha=0.05$. The mean baseline VAS pain did not differ ($p=0.12$) between group A (n=10, VAS 7.52, SD=0.52) and group B (n=11, VAS 6.02, SD=2.47). The mean placebo responses on VAS pain for groups A and B were 0.97 (SD=1.85) and 1.47 (SD=1.81), respectively. The mean carry-over effect was 0.50 (SD=1.83), which was not statistically significant with a 95% CI of -1.17 to 2.17 and $p=0.5369$. This interim analysis shows that an N-of-1 trial probably will be feasible for evaluating non-curative treatment efficacy in chronic disease using only half the

patients as are required for a classic RCT. Future analysis will provide a direct comparison of outcomes between the RCT, crossover and the N-of-1 part for a complete evaluation.

USA, Canada

DEVELOPMENT OF A UNIQUE CROSSLINKED GLYCOSAMINOGLYCAN FOR SOFT TISSUE REPAIR: TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Heidebrecht RW Jr, Jozefiak TH, Shain HC, Skrabut EM, Saunders D, Smith N, Towner RA, Hurst R. *PLoS One*. 2025 Jan 24;20(1):e0317790. doi: 10.1371/journal.pone.0317790. PMID: 39854411; PMCID: PMC11760559.

Open access

Chemical modification of naturally derived glycosaminoglycans (GAGs) expands their potential utility for applications in soft tissue repair and regenerative medicine. Here the authors report the preparation of a novel crosslinked chondroitin sulfate (~200 to 2000 kilodaltons) that is both soluble in aqueous solution and microfilterable. They refer to these materials as “SuperGAGs.” One can further conjugate these materials with diverse capture agents to further modify polymer properties and add new capabilities. A representative material (GLX-100) demonstrated durable restoration of bladder impermeability in a gold standard animal model of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). Histologic examination of the animal bladders treated with a GLX-100 SuperGAG conjugated to biotin as a reporter demonstrated that the residence time of GLX-100 is superior to chondroitin sulfate (a product that is currently used for clinical treatment of patients with IC/BPS). As expected, this novel crosslinked GAG biopolymer was restricted to the luminal surface of the bladder wall. In this communication they describe a simple and versatile synthesis of a crosslinked glycosaminoglycan (GAG) biopolymer for soft tissue repair. Chondroitin sulfate (~12 kD) was crosslinked to form a water soluble and microfilterable polymer with approximately 200 to 2000 kD molecular weight. The synthesis presented here allows for control of molecular weight while avoiding formation of an extended block gel. Moreover, the procedure enables further chemical modification of the SuperGAG through the selection of a capture agent. A set of agents have been used, demonstrating the preparation of a family of SuperGAGs with diverse capabilities. The authors report that they can optimize polymer properties, adjust adherence to various tissues, add reporters, and engage the biochemistry of surrounding tissues with peptides and other bioactives.

In vitro. Netherlands

HYALURONIC ACID: FUNCTION AND LOCATION IN THE UROTHELIAL BARRIER FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS, AN IN VITRO STUDY.

Van Ginkel CJ, Baars CDM, Tiemessen DM, Jansen CFJ, Martens FMJ, Schalken JA, Janssen DAW. *PLoS One*. 2025 Feb 26;20(2):e0318277. doi: 10.1371/journal.pone.0318277. PMID: 40009603; PMCID: PMC11864510.

Open access

Disruption of the glycosaminoglycan (GAG)-layer and urothelial barrier is an important aspect of the pathophysiology of bladder pain syndrome/ interstitial cystitis. Intravesical hyaluronic acid (HA) is often used in treatments for IC/BPS, however the role in the urothelial barrier is unknown. This study from the Netherlands aims to clarify the location and functional contribution of HA in the urothelium, using an in vitro model. Immunohistochemistry was performed on human and porcine biopsies and on porcine cell cultures to evaluate the location of HA. Functional contribution was assessed through transepithelial electrical resistance measurements and the effects on gene expression in a differentiated primary porcine urothelial cell model. HA was found throughout in the urothelium and most abundant around the basal layer. Digestion of HA increased impermeability of the urothelium, contrasting with the effect of protamine sulfate (PS). After HA digestion, quantitative PCR analysis revealed upregulation of HA-synthesizing gene (HAS3) and the inflammatory marker (IL8). Treatment with HA and/or chondroitin sulfate therapy in undamaged cells upregulated genes related to GAG synthesis, barrier markers and inflammation. In PS-damaged cells, GAG therapy only upregulated

genes associated with HA synthesis and inflammation, without affecting barrier recovery speed. These results emphasize the interaction of HA on urothelial cell inflammation and barrier repair physiology. HA seems to not directly restore the urothelial luminal GAG layer but influences barrier integrity through its interactions with urothelial cells.

Randomized controlled trial. China

EVALUATION OF CLINICAL EFFICACY OF PELVIC ULTRASOUND MONITORING COMBINED WITH SCALE SCORING IN THE TREATMENT OF INTERSTITIAL CYSTITIS BY INTRAVESICAL INSTILLATION REGIMEN COMBINED WITH HYDRODISTENTION AND TRANSURETHRAL FULGURATION.

Liu L, Xue L, Zhou J, Dong B, Li Y, Li Z, Dong Y, Han C. *BMC Urol.* 2025 May 7;25(1):117. doi: 10.1186/s12894-025-01764-0. PMID: 40336023; PMCID: PMC12060316.

Open access

Interstitial cystitis (IC) is a chronic condition with complex symptoms, including pelvic pain and urinary frequency. Current treatments often involve a combination of therapies, but their effectiveness remains a topic of ongoing investigation. This study from China aimed to evaluate the clinical efficacy of a treatment regimen combining intravesical instillation of heparin and alkalized lidocaine, hydrodistention, and transurethral fulguration, using pelvic ultrasound monitoring and symptom scales to assess patient outcomes. From June 2016 to June 2023, patients who were diagnosed as interstitial cystitis in urology department of the Xuzhou central hospital were selected. All patients received intravesical instillation regimen of 2% lidocaine 10 ml + 5% sodium bicarbonate 5 ml + heparin 25000 IU for 6 months, and they were randomly divided into two groups according to the simple randomization (coin toss): hydrodistention and transurethral fulguration (HD/TF) group and non-HD/TF group. The 24-h urination frequency, nocturia frequency, pelvic ultrasound measurement results (bladder volume at maximum filling state, bladder wall thickness after urination, residual urine volume), O'Leary-Sant interstitial cystitis symptom index (ICSI), O'Leary-Sant interstitial cystitis problem index (ICPI), pelvic pain and urgency/frequency (PUF), pain visual analogue score (VAS), self-rating anxiety scale (SAS) were recorded before treatment and 3 and 6 months after treatment. A total of 68 patients were included in this study, including 13 males (19.12%) and 55 females (80.88%), with an average age of 59.07 ± 8.15 years. According to the simple randomization, 68 patients were randomly divided into HD/TF group ($n = 30$) and non-HD/TF group ($n = 38$). After the 3rd and 6th months of treatment, the 24-h urination frequency and nocturia frequency in both groups decreased significantly ($P < 0.05$), and the 24-h urination frequency and nocturia frequency after the 3rd and 6th months of treatment in HD/TF group decreased significantly compared with that in non-HD/TF group ($P < 0.05$). After the 3rd and 6th months of treatment, the bladder volume at maximum filling state in the two groups increased and the residual urine volume decreased ($P < 0.05$). In addition, the bladder volume at maximum filling state of the HD/TF group increased significantly compared to the non-HD/TF group after 3rd and 6th months of treatment ($P < 0.05$), while the bladder wall thickness after urination decreased compared to the non-HD/TF group after 3rd months of treatment ($P < 0.05$). There was no significant difference in residual urine volume between HD/TF group and non-HD/TF group before and after treatment ($P > 0.05$). The postoperative scores at 3rd and 6th months of ICPI, ICSI, PUF, SAS and VAS in both groups were significantly lower than those before treatment ($P < 0.05$), and The postoperative scores at 3rd and 6th months of ICPI, ICSI, PUF, SAS and VAS in HD/TF group were significantly lower than those in non-HD/TF group ($P < 0.05$). Intravesical instillation of heparin/alkalized lidocaine combined with hydrodistention and transurethral fulguration is an effective treatment for interstitial cystitis, which can significantly reduce patient pain and improve patient prognosis. Moreover, the use of pelvic ultrasound to monitor indicators such as bladder volume at maximum filling state and residual urine volume, combined with ICSI, ICPI, PUF, VAS, and SAS scores, has high application value for evaluating the efficacy of intravesical instillation regimen combined with hydrodistention and transurethral fulguration in the treatment of interstitial cystitis.

Systematic review and meta-analysis. China

[SAFETY AND EFFICACY OF INTRAVESICAL INSTILLATION OF BOTULINUM TOXIN-A IN THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND OVERACTIVE BLADDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.](#)

Zhou Y, He Z, Xiang T, Cao X, Cong H, Liu Q, Sun H, Liao L. *Front Pharmacol.* 2025 Apr 15;16:1586845. doi: 10.3389/fphar.2025.1586845. PMID: 40303921; PMCID: PMC12037478.

Open access

The effectiveness and safety of the instillation of botulinum toxin A (BTX-A) remain subjects of controversy. The meta-analysis was performed to assess the efficacy and safety of a novel intravesical instillation of BTX-A for managing overactive bladder (OAB) or interstitial cystitis/bladder pain syndrome (IC/BPS). The randomized controlled trials were retrieved from PubMed, EMBASE, and the Cochrane Library databases up to 29 January 2024. The studies included in the analysis focused on the intravesical instillation of BTX-A in patients with OAB or IC/BPS. The data extraction was independently conducted by two reviewers. The random effects model was utilized for the assessment in order to compute the overall effect sizes. The heterogeneity tests and subgroup analyses were conducted. The meta-analysis and subgroup analysis did not reveal any statistically significant differences. However, the results of the meta-analysis indicated that intravesical instillation of BTX-A could reduce episodes of urgency urinary incontinence (UUI) (overall weighted mean difference [WMD] = -0.85; 95% confidence interval [CI]: -2.99 to 1.29). In subgroup analysis, an increase in void volume (VV) at 4 weeks of follow-up (WMD = -31.99; 95% CI: -70.53 to 6.54) was observed compared to that at 12 weeks (WMD = -1.73; 95% CI: -16.98 to 13.53). In contrast to the groups receiving more than 200 units of BTX-A, patients in the group receiving 200 units or fewer of BTX-A (WMD = -16.89; 95% CI: -41.14 to 7.35) exhibited a significantly greater increase in VV. It was concluded that the intravesical instillation of BTX-A appears to be a viable administration route that may reduce UUI and VV to some extent. In terms of safety, intravesical instillation of BTX-A demonstrated a reduced risk of UTI and post-void residual compared to the placebo group.

Systematic Review and Meta-Analysis. China

[THE EFFICACY AND SAFETY OF DIMETHYL SULFOXIDE INTO THE BLADDER FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS.](#)

Li HR, Shen SH, Gao XS, Peng L, Luo DY. *Neurourol Urodyn.* 2025 Apr 10. doi: 10.1002/nau.70036. Epub ahead of print. PMID: 40205912.

This study from China investigated the efficacy and safety of intravesical DMSO instillation for the treatment of interstitial cystitis/bladder pain syndrome. The following databases were searched for relevant studies: PubMed, EMBASE, MEDLINE, Cochrane Library, and Web of Science (updated August 10, 2024). All studies on intravesical DMSO met the inclusion criteria and were evaluated using various quality assessment methods based on the type of study. Data were then analyzed using Review Manager 5.4 (Cochrane Collaboration software). The primary outcomes and indicators included the Interstitial Cystitis Symptom Index, the Interstitial Cystitis Problem Index, and Pain Scores. The secondary outcomes were bladder diary metrics and Pelvic Pain and Urgency/Frequency Symptom Scale (PUF). This systematic review and meta-analysis included 5 randomized controlled trials and 9 single-arm or cohort studies, involving 554 patients. The combined statistics indicated an average pretreatment Interstitial Cystitis Symptom Index score was 14.27, an average Interstitial Cystitis Problem Index Score was 12.72, and an average Pain Score was 7.06. Compared to pretreatment values, the results indicated that the Interstitial Cystitis Symptom Index score decreased by 5.59 (95% CI: -6.68 to -4.50, $p < 0.00001$), the Interstitial Cystitis Problem Index score decreased by 5.14 (95% CI: -6.45 to -3.83, $p < 0.00001$), and the Pain Score decreased by 3.27 (95% CI: -3.95 to -2.60, $p < 0.00001$). Additionally, the overall incidence rate of adverse events in patients was 37.6%. Although 37% of cases had adverse events, the majority were considered mild and acceptable. Evidence-based statistical analysis of the literature on intravesical DMSO treatment for interstitial cystitis/bladder pain syndrome indicates that this therapy is both effective and safe. Therefore, intravesical DMSO

instillation can be considered a standard treatment method for interstitial cystitis/bladder pain syndrome.

China

[PLATELET-RICH PLASMA IMPROVES CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS IN RAT MODELS THROUGH THE TOLL-LIKE RECEPTOR 4/NUCLEAR FACTOR-KAPPA B SIGNALLING PATHWAY.](#)

Wu Y, Chen L, Xu M, Yao L, Yang S, Ang X, Chen W. *Clin Exp Nephrol.* 2025 Mar 25. doi: 10.1007/s10157-025-02660-5. Epub ahead of print. PMID: 40133553.

This study from China investigated the therapeutic effect of platelet-rich plasma (PRP) on a cyclophosphamide (CYP)-induced interstitial cystitis (IC) rat model. A CYP-induced IC rat model (75 mg/kg every 3 days, with a total of five injections) was used to evaluate the therapeutic effects of PRP. Here, PRP was administered via bladder irrigation (every 2 days, with a total of three irrigations), and bladder tissue was analysed for inflammation and histological changes. The toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) signalling pathway was assessed using real-time quantitative polymerase chain reaction and ribonucleic acid sequencing. In addition, lipopolysaccharide (LPS)-induced SV-HUC-1 cells (10 µg/LPS and 2.5 mM adenosine triphosphate) were employed to investigate the inflammatory response and the effects of PRP on the TLR4/NF-κB signalling pathway. The PRP treatment significantly improved the bladder tissue condition in the CYP-induced IC rat model, as evidenced by reduced inflammation and histological damage. The damage and shedding of the superficial epithelium of the bladder mucosa were notably decreased following PRP bladder instillation. Importantly, the expression of ZO-1, a key marker of epithelial integrity, was upregulated in PRP-treated rats, indicating enhanced bladder epithelial function. High-throughput analysis revealed that PRP alleviated bladder mucosal injury in the IC rat model through the TLR4/NF-κB signalling pathway. In LPS-induced SV-HUC-1 cells, PRP treatment also increased ZO-1 expression, decreased CDH1 expression and regulated the TLR4/NF-κB signalling pathway. It was concluded that platelet-rich plasma treatment may improve the expression of ZO-1 and CDH1 in urinary epithelium in vitro by mediating the TLR4/NF-κB pathway, which is effective in the treatment of IC.

China

[ELECTROACUPUNCTURE NEURAL STIMULATION MITIGATES BLADDER DYSFUNCTION AND MECHANICAL ALLODYNIA IN CYCLOPHOSPHAMIDE INDUCED CYSTITIS THROUGH DOWNREGULATION OF THE BDNF-TRKB SIGNALING PATHWAY.](#)

Su Y, Yang F, Xie JC, Zhang C, Luo RX, Li WS, Liu BL, Su MZ. *eNeuro.* 2025 Mar 10;12(3):ENEURO.0329-24.2025. doi: 10.1523/ENEURO.0329-24.2025. Epub ahead of print. PMID: 40064496; PMCID: PMC11913400.

Open access

Central sensitization is a major factor in bladder pain syndrome/interstitial cystitis (BPS/IC), making effective pain management crucial. This study from China explores the potential of electroacupuncture (EA) as a therapeutic approach to alleviate pain and improve bladder function in a rat model of BPS/IC induced by cyclophosphamide. Their findings demonstrate that EA therapy significantly reduces mechanical allodynia, enhances urinary function, and decreases neuroinflammation by modulating brain-derived neurotrophic factor–tyrosine kinase receptor B signaling in the spinal dorsal horn. The research highlights EA's capability to inhibit excitatory neural transmission and provide relief in chronic pain conditions. These results offer new insights into the mechanisms of EA therapy, potentially improving treatment strategies for BPS/IC and similar pain syndromes.

China

TRPC3 CONTRIBUTES TO CYCLOPHOSPHAMIDE-INDUCED CYSTITIS PROGRESSION BY ENHANCING BLADDER FIBROSIS THROUGH ACTIVATION OF THE TGF- β /SMAD PATHWAY.

Luo R, Li W, Huang J, Liu Z, Zhang C, Ding H, Chen J. *Front Pharmacol.* 2025 Apr 9;16:1565156. doi: 10.3389/fphar.2025.1565156. PMID: 40271070; PMCID: PMC12014565.

Open access

Bladder pain syndrome/Interstitial cystitis (BPS/IC) is a chronic urological disorder affecting 2.7%–6.5% of the population. The condition is characterized by significant bladder-related pain, with approximately 50% of IC/BPS patients exhibiting bladder fibrosis. Transient receptor potential cation channel subfamily C member 3 (TRPC3), a protein linked to fibrosis in heart and kidneys, emerged as a potential therapeutic target for this condition. In this study from China, using a cyclophosphamide-induced cystitis rat model, the authors employed RNA sequencing for transcriptional profiling, Western blot for protein quantification, and Masson staining for fibrotic assessment. Cellular-specific TRPC3 expression patterns were elucidated through single-cell transcriptomic analysis. TRPC3 inhibition was implemented via intraperitoneal administration of Pyrazole 3. The study assessed mechanical pain sensitivity and bladder function through von Frey testing and cystometry. Significant findings revealed TRPC3 RNA and protein expression was markedly upregulated in cystitis rats. TRPC3 inhibition substantially improved mechanical pain sensitivity and reduced micturition frequency. TRPC3 is predominantly expressed in fibroblasts and fibrosis-related pathways are upregulated in cystitis rats. The increased fibrosis markers and collagen fiber deposition are both reversed by TRPC3 inhibition. And the TGF- β /Smad signaling pathway was notably activated and subsequently downregulated with TRPC3 inhibition. TRPC3 activation contributes significantly to bladder fibrosis in IC/BPS. Inhibiting TRPC3 ameliorates symptoms by modulating TGF- β /Smad pathway, suggesting it as a promising therapeutic target for managing this challenging condition with limited current treatment options.

Japan

LIPIDOMIC ANALYSIS COUPLED WITH MACHINE LEARNING IDENTIFIES UNIQUE URINARY LIPID SIGNATURES IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Iwaki T, Kurano M, Sumitani M, Niimi A, Nomiya A, Kamei J, Taguchi S, Yamada Y, Sato Y, Nakamura M, Yamada D, Minagawa T, Fukuhara H, Kume H, Homma Y, Akiyama Y. *World J Urol.* 2025 Apr 18;43(1):233. doi: 10.1007/s00345-025-05628-y. PMID: 40249505; PMCID: PMC12008056.

Open access

The purpose of this study from Japan was to identify biomarkers for diagnosis and classification of interstitial cystitis/bladder pain syndrome (IC/BPS) by urinary lipidomics coupled with machine learning. Urine samples from 138 patients with IC/BPS, including 116 with Hunner lesion (HL) and 22 with no HL, and 71 controls were assessed by lipid chromatography-tandem mass spectrometry. Single and paired lipid analyses of differentially expressed lipids in each group were conducted to assess their diagnostic ability. Machine learning models were constructed based on the identified urinary lipids and patient demographic data, and a five-fold cross-validation method was applied for internal validation. Levels of urinary lipids were adjusted to account for urinary creatinine levels. A total of 218 urinary lipids were identified. Single lipid analysis revealed that urinary levels of C24 ceramide and LPC (14:0) distinguished HL and no HL, with an area under the receiver operating characteristics curve of 0.792 and 0.656, respectively. Paired lipid analysis revealed that summed urinary levels of C24 ceramide and LPI (18:3), and subtraction of PG (36:5) from PC (38:2) distinguished HL and no HL even more accurately, with an area under the curve of 0.805 and 0.752, respectively. A machine learning model distinguished HL and no HL, with the highest area under the curve being 0.873 and 0.750, respectively. Limitations include the opaque black box nature of machine learning techniques. It was concluded that urinary levels of C24 ceramide, along with those of C24 ceramide plus LPI (18:3), could be potential biomarkers for HL. Machine learning-coupled urinary lipidomics may play an important role in the next-generation AI-driven diagnostic systems for IC/BPS.

Gene case study. Italy**POTENTIAL ROLE OF *ABCF2* GENE IN PUDENDAL NERVE NEUROPATHY AND INTERSTITIAL CYSTITIS.**

Musumeci A, Vinci M, Treccarichi S, Ragalmuto A, Bruno G, Tinniriello G, Farina J, Federico C, Saccone S, Calì F, Porru D. *Genes (Basel)*. 2025 Feb 26;16(3):281. doi: 10.3390/genes16030281. PMID: 40149433; PMCID: PMC11942409.

Open access

Symptoms of pudendal nerve neuropathy may overlap with various symptoms of interstitial cystitis (IC). As documented, there is a well-established correlation between the genes involved in ATP metabolism, neuropathy, and IC. ATP-binding cassette (ABC) transporters genes, in fact, are vital for ATP signaling. This study from Italy aims to associate the *ABCF2* gene with a suspected pudendal nerve neuropathy and IC. Histological analysis was conducted for diagnosing IC while the genetic variant was identified by whole exome sequencing (WES) Trio and confirmed through Sanger. The authors report a patient with IC, confirmed by histological examination, presenting with a suspected bladder and pudendal nerve neuropathy, though not analytically confirmed. Histological analysis revealed urothelial detachment caused by a dense subepithelial lymphocytic infiltrate, predominantly composed of mast cells, which serve as key diagnostic markers for interstitial cystitis (IC). WES analysis identified the heterozygous genetic variant c.1253T>G p.Phe418Cys within *ABCF2* gene, precisely in its functional domain which actively operates in the hydrolysis of ATP energizing various biological systems. As reported, this gene displays high expression patterns in bladder tissue. The variant, absent in the healthy brother, was inherited from the father which presents mosaicism. The *in silico* prediction analyses classified this variant as pathogenic, identifying potential alterations in the protein structure. Although the precise role of *ABCF2* should be supported by further studies, the authors hypothesize that its disruption might impair ATP metabolism, likely altering the nociceptive response and leading to the patient's neuropathy. Further analyses are imperative to validate this research, for laying the groundwork for a specific therapy targeting the genetic dysregulation involved in this condition.

China**IDENTIFICATION AND VALIDATION OF IMMUNE AND DIAGNOSTIC BIOMARKERS FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME BY INTEGRATING BIOINFORMATICS AND MACHINE-LEARNING.**

Zhou T, Zhu C, Zhang W, Wu Q, Deng M, Jiang Z, Peng L, Geng H, Tuo Z, Zou C. *Front Immunol*. 2025 Jan 23;16:1511529. doi: 10.3389/fimmu.2025.1511529. PMID: 39917301; PMCID: PMC11799275.

Open access

The etiology of interstitial cystitis/painful bladder syndrome (IC/BPS) remains elusive, presenting significant challenges in both diagnosis and treatment. To address these challenges, the authors from China employed a comprehensive approach aimed at identifying diagnostic biomarkers that could facilitate the assessment of immune status in individuals with IC/BPS. Transcriptome data from IC/BPS patients were sourced from the Gene Expression Omnibus (GEO) database. They identified differentially expressed genes (DEGs) crucial for gene set enrichment analysis. Key genes within the module were revealed using weighted gene co-expression network analysis (WGCNA). Hub genes in IC/BPS patients were identified through the application of three distinct machine-learning algorithms. Additionally, the inflammatory status and immune landscape of IC/BPS patients were evaluated using the ssGSEA algorithm. The expression and biological functions of key genes in IC/BPS were further validated through *in vitro* experiments. A total of 87 DEGs were identified, comprising 43 up-regulated and 44 down-regulated genes. The integration of predictions from the three machine-learning algorithms highlighted three pivotal genes: *PLAC8* (AUC: 0.887), *S100A8* (AUC: 0.818), and *PPBP* (AUC: 0.871). Analysis of IC/BPS tissue samples confirmed elevated *PLAC8* expression and the presence of immune cell markers in the validation cohorts. Moreover, *PLAC8* overexpression was found to promote the proliferation of urothelial cells without affecting their migratory ability by inhibiting the Akt/mTOR/PI3K signaling pathway. The authors concluded that their study identifies potential

diagnostic candidate genes and reveals the complex immune landscape associated with IC/BPS. Among them, PLAC8 is a promising diagnostic biomarker that modulates the immune response in patients with IC/BPS, which provides new insights into the future diagnosis of IC/BPS.

China

TRANSIENT RECEPTOR POTENTIAL MELASTATIN 8 CONTRIBUTES TO CYSTITIS-INDUCED NEURONAL SPROUTING AND PAIN HYPERSENSITIVITY THROUGH AKT/MTOR SIGNALING PATHWAY IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Wu L, Chang R, Zhang P. *Low Urin Tract Symptoms*. 2024 Nov;16(6):e12537. doi: 10.1111/luts.12537. PMID: 39528242.

The aim of this study was to investigate the mechanism of TRPM8 in neuroproliferation and pain, as well as the relevance of the Akt/mTOR signaling pathway in mice with IC/BPS. The model of IC/BPS was established in wild and TRPM8^{-/-} mice. The mechanical sensitivity was measured. The number of neurite segments, length of neurites, and density of neurites were all counted. IL-6 and norepinephrine levels were detected by ELISA, Western blot was used to detect protein levels of TRPM8, Akt, p-Akt, mTOR, p-mTOR. Immunofluorescence was used to detect TRPM8 expression and distribution in neurites, neurons, and sensory nerves in mouse bladder tissue. Pain threshold in the IC/BPS group was decreased, and neurite segments, length, and density were all significantly enhanced when compared to the control group. The parameters in the IC/BPS model + Menthol group were more statistically significant. Neurite number and density were lower in TRPM8 knockout-model mice than in IC/BPS model mice. The expression of TRPM8 and the ratios of p-Akt/Akt and p-mTOR/mTOR rose in the IC/BPS model group. In TRPM8 knockout-model mice, the ratios of p-Akt/Akt and p-mTOR/mTOR were not substantially different from those in the control group. TRPM8 knockout-model mice had considerably lower levels of serum IL-6 and urine norepinephrine than IC/BPS model mice. It was concluded that TRPM8 can induce pain hypersensitivity and sensory nerve proliferation by activating Akt/mTOR pathway and raising the expression of IL-6 and norepinephrine in IC/BPS models. These findings offer new perspectives on IC/BPS treatment.

USA

NOVEL APPLICATION OF T1P MAGNETIC RESONANCE IMAGING FOR NONINVASIVE ASSESSMENT OF BLADDER HYPERPERMEABILITY BIOMARKERS: A FOCUS ON GLYCOSAMINOGLYCAN CONTENT.

Suyama JA, Statum SM, Mohana-Borges AVR, Cheng X, Ma Y, Esko JD, Anger JT, Chung CB, Alperin M. *Neurol Urodyn*. 2025 May 4. doi: 10.1002/nau.70058. Epub ahead of print. PMID: 40320728.

Bladder wall hyperpermeability due to glycosaminoglycan depletion is implicated in interstitial cystitis/bladder pain syndrome pathogenesis. This study from the USA sought to validate T1p MRI as a noninvasive imaging sequence for assessing bladder wall hyperpermeability biomarkers, with a focus on bladder glycosaminoglycan content, in protamine sulfate-induced models of interstitial cystitis/bladder pain syndrome. Rat bladders (n = 8) treated with saline (control), protamine sulfate, pentosan polysulfate, or protamine sulfate + pentosan polysulfate (rescue) were imaged in situ using T1p and standard MRI sequences. Predominant bladder glycosaminoglycans, chondroitin and heparan sulfate, were measured in subsequently harvested rat bladders via aniline tagging coupled with mass spectrometry. Human bladder biopsies (n = 12) were similarly imaged before and after protamine sulfate treatment, and post-imaging glycosaminoglycan analysis was performed. Data were compared between groups using one-way ANOVA or paired Student t-test. T1p relaxivity was correlated with chemically measured glycosaminoglycan content using linear regression. Protamine sulfate-treated rat bladders had decreased glycosaminoglycans and higher T1p relaxivity relative to controls. Pentosan polysulfate also decreased glycosaminoglycans versus controls and did not mitigate protamine-mediated glycosaminoglycan depletion. Importantly, T1p relaxivity correlated with chemical glycosaminoglycan quantification (chondroitin sulfate: r = 0.86, p < 0.01; heparan sulfate r = 0.80, p = 0.02). In human biopsies, T1p relaxivity increased after protamine sulfate treatment versus baseline (154.2 ± 5.9 vs. 131.0 ± 4.4 ms, p < 0.001), consistent with decreased glycosaminoglycans,

while chemical analyses failed to capture statistically significant changes in bladder glycosaminoglycans. T1p MRI accurately measured glycosaminoglycans in rat bladders and differentiated protamine sulfate-treated bladder biopsies from unperturbed specimens in humans. T1p MRI warrants further investigation as a novel biomarker of bladder glycosaminoglycan content in interstitial cystitis/bladder pain syndrome.

Clinical study. Taiwan

FOCAL OR DIFFUSE BLADDER WALL THICKNESS ON BLADDER COMPUTED TOMOGRAPHY INDICATES MORE SEVERE BLADDER WALL INFLAMMATION IN PATIENTS WITH INTERSTITIAL CYSTITIS.

Yu WR, Jiang YH, Jhang JF, Kuo HC. World J Urol. 2025 Feb 4;43(1):100. doi: 10.1007/s00345-025-05451-5. PMID: 39903306.

The classification of different phenotypes of interstitial cystitis/ bladder pain syndrome (IC/BPS) provides different pathophysiology and associated treatment strategies. Most clinical studies have focused on bladder symptoms and cystoscopic findings. This study from Taiwan analyzed bladder wall thickness (BWT) and compared bladder conditions, urinary biomarkers, and histopathology among patients of IC/BPS with different BWT. A total of 182 patients with cystoscopy-proven IC/BPS underwent abdominal computed tomography (CT) before intervention. The BWT on CT was classified as smooth, focal thickness, and diffuse thickness. Clinical symptoms, urodynamic findings, cystoscopic characteristics, presence of Hunner's lesion, urinary biomarkers, and bladder histopathology were compared among the three subgroups. Among the patients, 85 had smooth, 64 had focal, and 33 had diffuse BWT. There was a significant trend of patients with focal and diffuse BWT being significantly older with higher symptom scores, smaller bladder capacity, higher grade of glomerulations, and incidence of Hunner's IC. Pathological findings revealed that patients with diffused BWT, followed by those with focal thickness, had the greatest uroepithelial cell denudation and plasma cell infiltration. Patients with diffuse BWT has higher rate of inflammatory cell infiltration, nerve bundle hyperplasia, and granulation tissue. The urinary levels of tumor necrosis factor-alpha and oxidative stress biomarkers in IC/BPS patients with different BWT were significantly higher than those in the controls. BWT in CT scans can reflect chronic inflammation of the bladder wall in patients with IC/BPS, which is clinically relevant for the diagnosis and treatment of IC subtypes.

Comparative study. China

THE ROLE OF NETRIN-1 IN THE DIAGNOSIS AND PROGNOSIS OF BLADDER PAIN SYNDROME /INTERSTITIAL CYSTITIS: A COMPARATIVE STUDY.

Ang XJ, Xia KG, Qian YM, Zhang YL, Wei XL, Li HB, Li M, Chen WG. World J Urol. 2025 Jun 3;43(1):351. doi: 10.1007/s00345-025-05659-5. PMID: 40459754; PMCID: PMC12133911.

The purpose of this study from China was to investigate the diagnostic and prognostic value of netrin-1 in Bladder Pain Syndrome /Interstitial Cystitis (BPS/IC). A total of 40 BPS/IC patients, 20 patients with overactive bladder (OAB), and 20 healthy controls were included. Baseline data of all participants were collected. Plasma netrin-1 expression levels were measured before treatment and two months after treatment. Statistical significance of differences among the three groups was analyzed. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic and prognostic value of netrin-1. The netrin-1 expression level in the BPS/IC group was 777.37 ± 268.02 pg/ml, which was significantly higher than in the other two groups ($P < 0.001$). No significant difference in netrin-1 expression was observed between the OAB group and the healthy control group. Netrin-1 expression was positively correlated with ICSI, ICPI, and VAS scores. The netrin-1 expression level two months after treatment in the BPS/IC group was 485.06 ± 135.99 pg/ml, which was significantly lower than before treatment. It was concluded that Netrin-1 can serve as a diagnostic and prognostic biomarker for BPS/IC. However, the underlying mechanisms of netrin-1 in BPS/IC remain unclear and require further investigation.

Clinal Trial. Taiwan

INTRAVESICAL INJECTION OF PERIPHERAL BLOOD MONONUCLEAR CELL FOR THE TREATMENT OF INTERSTITIAL CYSTITIS: A PRELIMINARY REPORT.

Tsai CP, Cheng KL, Yang E, Huang LY, Wang FH, Hung MJ, Su HL. *PLoS One*. 2025 May 21;20(5):e0324535. doi: 10.1371/journal.pone.0324535. PMID: 40397968; PMCID: PMC12094792.

Open access

Interstitial cystitis (IC) is a complex syndrome characterized by symptoms such as bladder pain, urgency, frequency, and nocturia, without the presence of urinary tract infection or any other identifiable pathology. Traditional treatments, including medication and bladder instillation, are often ineffective in about 30% of patients. Currently, efforts are focused on developing therapies based on the possible pathogenesis of IC. This study from Taiwan is a phase one clinical trial which aimed to investigate the safety and efficacy of autologous peripheral blood mononuclear cell (PBMC) intravesical injections, which have the potential to promote tissue regeneration, as a novel treatment for IC. The study involved isolating PBMCs using the Sepax Cell Separation System and injecting these cells beneath the bladder mucosa layer of patients with IC. Clinical efficacy was evaluated using voiding diaries, questionnaires, and cystoscopic examinations before and 3 months after treatment. Twelve patients with refractory IC participated in this study. Observed side effects, such as pain or urinary tract infection, were mild and transient which demonstrated the safety of this treatment modality. Although the treatment response varied among patients, a third of the patients experienced moderate to significant progress according to the GRA score. Four patients exhibited improvement in bladder glomerulations during postoperative follow-up cystoscopy. In conclusion, the overall safety profile of PBMCs injections appears to be favourable. Further research is needed to optimize treatment protocols and understand the factors influencing individual responses to this therapy.

China

S100A9 AS A POTENTIAL NOVEL TARGET FOR EXPERIMENTAL AUTOIMMUNE CYSTITIS AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Zhao J, Zhou M, Yang C, Liu YW, Yang T, Sun B, Li B, Zheng J, Dai S, Yang Z, Wang X. *Biomark Res*. 2025 May 9;13(1):72. doi: 10.1186/s40364-025-00763-5. PMID: 40346703; PMCID: PMC12065242.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic inflammatory disease of the bladder for which no effective therapy is currently available. Understanding the pathogenesis of IC/BPS and identifying effective intervention targets are of great clinical importance for its effective treatment. The authors from China report that their work focuses on elucidating the key targets and underlying mechanisms of IC/BPS. They established an experimental autoimmune cystitis (EAC) mouse model and generated gene knockout mice to elucidate key mediators triggering chronic inflammatory damage in IC/BPS through using single-cell RNA sequencing, proteomic sequencing, and molecular biology experiments. Their study revealed that the infiltration and activation of macrophages, T cells, and mast cells exacerbated inflammatory bladder damage in both IC/BPS and EAC mice. Notably, cell-cell communication among bladder immune cells was significantly enhanced in EAC mice. Macrophages, as the main cell types altered in EAC mice, received and transmitted the most intensity signalling. Mechanistically, macrophages synthesized and secreted S100A9, which in turn facilitated macrophage polarization and promoted the production of pro-inflammatory cytokines. S100A9 emerged as an important pro-inflammatory and pathogenic molecule in IC/BPS and EAC. Further analysis demonstrated that S100A9 activation enhanced the inflammatory response and exacerbated bladder tissue damage in IC/BPS patients and EAC mice via TLR4/NF- κ B and TLR4/p38 signalling pathways. Importantly, inhibition of S100A9 with paquinimod, as well as genetic knockout of S100A9, significantly attenuated the pathological process. The authors concluded that S100A9 is an important pro-inflammatory and pathogenic molecule in IC/BPS and EAC. Targeting S100A9-initiated signalling pathways may offer a novel therapeutic strategy for IC/BPS.

China

ASSOCIATION OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS WITH HYPERLIPIDEMIA: A CASE-CONTROL STUDY.

Zhang ZY, Zhang Z, Ling M, Shi BW, Zhang ZW. *Int Urogynecol J.* 2025 May 7. doi: 10.1007/s00192-025-06149-3. Epub ahead of print. PMID: 40332521.

Metabolic factors have been proposed to be related to the bladder pain syndrome/interstitial cystitis (BPS/IC) pathogenesis. In this study from China, the authors investigated the association between metabolic factors, especially blood lipids, and BPS/IC. The present study adopted a case-control design, comparing several metabolic indicators in 106 women with BPS/IC versus 164 women without BPS/IC, all of whom were diagnosed at the Hospital between January 2013 and December 2022. The case-control odds ratio (OR) and 95% confidence interval (CI) for metabolic indicators were estimated using logistic regression. The associations between indicators and BPS/IC classifications were assessed using ordinal multinomial logistic regression. The propensity score-matching method was used to eliminate bias from age and body mass index (BMI), and the BPS/IC group had a greater hypercholesterolemia prevalence than the control group (16.3% vs 7.1%, $p = 0.046$), with an OR > 2.4 ($p < 0.05$). Ordinal multinomial logistic regression between indicators and BPS/IC classifications showed that age and triglycerides correlated with the BPS/IC lesion grade. However, when the data were corrected for age and BMI, triglycerides still correlated with lesion grade. It was concluded that the BPS/IC group had a greater hypercholesterolemia prevalence than the control group. Hypercholesterolemia may be a risk factor. Cystoscopic lesion grade correlated with age and triglyceride level. These results indicate a potential association between hyperlipidemia and the BPS/IC pathogenesis.

Taiwan

APPLYING K-MEANS CLUSTER ANALYSIS TO URINARY BIOMARKERS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A NEW PERSPECTIVE ON DISEASE CLASSIFICATION.

Jiang YH, Jhang JF, Wang JH, Wu YH, Kuo HC. *Int J Mol Sci.* 2025 Apr 14;26(8):3712. doi: 10.3390/ijms26083712. PMID: 40332347; PMCID: PMC12028259.

Open access

This study from Taiwan applied K-means cluster analysis to urinary biomarker profiles in interstitial cystitis/bladder pain syndrome (IC/BPS) patients, aiming to provide a new perspective on disease classification and its clinical relevance. The authors retrospectively analyzed urine samples from 127 IC/BPS patients and 30 controls. The urinary levels of 10 inflammatory cytokines and three oxidative stress markers (8-hydroxy-2-deoxyguanosin [8-OHdG], 8-isoprostane, and total antioxidant capacity [TAC]) were quantified. K-means clustering was performed to identify biomarker-based patient subgroups. IC/BPS patients exhibited significantly elevated urinary levels of Eotaxin, MCP-1, NGF, 8-OHdG, 8-isoprostane, and TAC compared to controls (all $p < 0.05$). K-means clustering identified four distinct subgroups. Cluster 4, characterized by the highest levels of inflammatory and oxidative stress biomarkers, comprised 85% ESSIC type 2 IC/BPS patients and exhibited the lowest visual analogue scale (VAS) pain scores and maximal bladder capacity (MBC). Correlation analysis revealed distinct cluster-specific associations between biomarker levels and clinical parameters, including the VAS pain score, MBC, the grade of glomerulation, and treatment outcomes. Applying K-means clustering to urinary inflammatory and oxidative stress biomarkers provides a new perspective on disease classification, identifying IC/BPS subtypes with distinct clinical and biochemical characteristics. This approach may refine disease phenotyping and guide personalized treatment strategies in the future.

Taiwan

CLUSTERING OF URINARY BIOMARKERS TO IDENTIFY INTERSTITIAL CYSTITIS SUBTYPES AND DIFFERENT CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES.

Tian JH, Tsai CY, Yu WR, Jiang YH, Jhang JF, Kuo HC. *Biomedicines.* 2025 Feb 5;13(2):369. doi: 10.3390/biomedicines13020369. PMID: 40002782; PMCID: PMC11852991.

Open access

Interstitial cystitis/bladder pain syndrome (IC/BPS) is mysterious and difficult to diagnose without cystoscopic hydrodistention. This study from Taiwan aimed to explore non-invasive and highly reliable urine biomarkers to identify Hunner's IC (HIC) and different non-Hunner's IC (NHIC) subtypes. 422 women with and without clinically diagnosed IC/BPS ($n = 376$ and 46 , respectively) were retrospectively enrolled. Patients were diagnosed with HIC or NHIC by cystoscopic hydrodistention under anesthesia. Then, the maximal bladder capacity (MBC) and glomerulation grade were determined. Thirteen urine inflammatory cytokines, chemokines, and oxidative stress biomarkers based on the previously reported predictors of IC/BPS were assayed using commercial microsphere kits. The dataset was randomly divided into training (70%) and test (30%) sets for model construction and validation using logistic regression and stepwise variable selection techniques. To construct the predictive models, univariate analysis was performed to evaluate the discriminative power of each urinary biomarker, measured by the area under the curve (AUC). Biomarkers with AUC values < 0.6 were excluded from further modeling. Multivariate logistic regression was then employed, with variables selected through stepwise forward selection based on log-likelihood criteria. For dichotomization, cutoff values were determined using quartile ranges from the control group. The final model's performance was assessed using AUC, accuracy, sensitivity, and specificity in both training and test sets. By setting the screening criterion to $AUC \geq 0.60$, the potential urinary biomarkers for identifying IC/BPS cases were eotaxin, monocyte chemoattractant protein-1, tumor necrosis factor- α (TNF- α), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and 8-isoprostane. Those for identifying HIC from the IC/BPS cohort were interleukin (IL)-6, IL-8, interferon γ -inducible protein 10 (IP-10), and regulated on activation, normal T-cell expressed and secreted (RANTES). A diagnostic algorithm using a cluster of urinary biomarkers included TNF- $\alpha \geq 0.95$ pg/mL or 8-OHdG ≥ 22.34 pg/mL and 8-isoprostane ≥ 22.34 pg/mL for identifying IC/BPS from the overall cohort; for identifying HIC from the IC/BPS cohort, the urinary IP-10 ≥ 3.74 pg/mL or IP-10 ≥ 19.94 pg/mL was added. Using a cluster of urinary biomarkers such as TNF- α or 8-OHdG and 8-isoprostane can identify IC/BPS from a study cohort, and adding the urinary IP-10 can distinguish HIC from IC/BPS cases.

Slovenia

[MATCHED SERUM- AND URINE-DERIVED BIOMARKERS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Kuret T, Sterle I, Romih R, Veranič P. *PLoS One*. 2024 Dec 31;19(12):e0309815. doi: 10.1371/journal.pone.0309815. PMID: 39739829; PMCID: PMC11687793.

Open access

Setting up the correct diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS), a chronic inflammatory disease of the bladder, is a challenge, as there are neither diagnostic criteria nor reliable and non-invasive disease biomarkers available. The aim of this study from Slovenia was to simultaneously determine matched serum- and urine-derived biomarkers of IC/BPS, which would provide additional insights into disease mechanisms and set the basis for further biomarker validation. This study included 12 female patients with IC/BPS and 12 healthy controls. A total of 33 different biomarkers were measured, including cytokines and chemokines, proteins involved in extracellular matrix remodeling, adhesion molecules, growth factors, and markers of oxidative stress using enzyme linked immunoassays and multiplex technology. Heatmaps and principal component analysis based on significantly altered biomarkers, revealed urine- and serum-associated IC/BPS signatures that clearly differentiated IC/BPS patients from controls. Four biomarkers, including CCL11, BAFF, HGF and MMP9, were significantly upregulated in both serum and urine of patients with IC/BPS compared to controls. Serum levels of MMP9 were associated with disease severity and could distinguish well between IC/BPS patients with and without Hunner's lesions. Systemic levels of MMP9 can therefore mirror the local pathology within the bladders of IC/BPS patients, and MMP9 may prove to be a useful target for the development of novel therapeutic interventions. Utilizing a comprehensive panel of both urine and serum biomarkers, identified here, holds promise for disease detection in IC/BPS patients.

Taiwan

REVEALING DISTINCT TREATMENT MECHANISMS AND OUTCOME CORRELATIONS IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AFTER DIFFERENT BLADDER THERAPIES THROUGH URINARY BIOMARKER ANALYSIS.

Chiu YC, Tsai PC, Jhang JF, Kuo HC. Int Urol Nephrol. 2025 Jan 29. doi: 10.1007/s11255-025-04388-3. Epub ahead of print. PMID: 39878889.

Urinary cytokine changes may serve as biomarkers to assess treatment outcomes for interstitial cystitis/bladder pain syndrome (IC/BPS). This study from Taiwan analyzed the changes in urinary cytokines following various bladder therapies and explored their clinical significance in therapeutic mechanisms. A total of 122 patients with IC/BPS treated with platelet-rich plasma (PRP), botulinum toxin-A (BoTN-A), hyaluronic acid (HA), or low-energy shock wave (LESW) were evaluated. Urinary inflammatory and oxidative stress biomarkers were measured at baseline and at 3 months posttreatment. Treatment outcomes were assessed using the Global Response Assessment (GRA), a 10-point visual analog score for pain, and the O'Leary-Saint Symptom Score (OSS). A GRA ≥ 2 was considered indicative of effective treatment. Significant symptom improvement was observed in patients treated with PRP and BoNT-A but not with LESW or HA. At 3 months post-treatment, PRP therapy led to decreased urinary 8-isoprostane and total antioxidant capacity levels, while BoNT-A therapy reduced monocyte chemotactic protein-1 and 8-hydroxy-2'-deoxyguanosine levels. HA therapy did not alter urinary biomarker levels, whereas LESW therapy increased macrophage inflammatory protein-1 beta and tumor necrosis factor- α levels. Patients with significant urinary biomarker reductions (GRA ≥ 2) demonstrated clinical improvement at 3 months. The authors concluded that PRP or BoNT-A exhibits anti-inflammatory effects, reflected by reductions in urinary cytokine levels, correlating with positive treatment outcomes. Urinary cytokine changes may play a role to evaluate the mechanisms of action of various treatments in patients with IC/BPS.

China

REGULATION OF AUTOPHAGY BY THE CDK1/P53/P21 FEEDBACK LOOP IN AN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME CELL MODEL: IMPLICATIONS FOR INFLAMMATORY RESPONSE.

Wang K, Shi J, Chen Z, Zhuang Y, Xue D. Int Urogynecol J. 2025 May 30. doi: 10.1007/s00192-025-06169-z. Epub ahead of print. PMID: 40447865.

The Cdk1/p53/p21 feedback loop could play an important role in maintaining a consistently high urinary tract epithelial permeability. This study from China is aimed at elucidating whether this feedback loop is associated with the inadequate autophagic response and the heightened inflammatory response in interstitial cystitis/bladder pain syndrome (IC/BPS). To construct the IC/BPS cell model, HTB4 cells were first treated with 1% H₂O₂ for 1 h, followed by a 24-h exposure to TNF α (10 ng/ml). The protein expression levels of LC3-I/II and Beclin 1 were assessed using Western blot analysis. Autophagosome formation was visualized using monodansylcadaverine (MDC) staining. The secretion levels of inflammatory cytokines, including IL-6, IL-8, and TNF α , were quantified using enzyme-linked immunosorbent assay. Additionally, malondialdehyde (MDA) levels and the activities of antioxidant enzymes (GSH and SOD2) were measured. Compared with normal urothelial HTB4 cells, the number of autophagosomes and the levels of LC3-I/II and Beclin 1 are significantly increased in IC/BPS cells. These cells also exhibit markedly higher levels of inflammatory markers (TNF α , IL-6, IL-8) and MDA, alongside notably reduced levels of the antioxidants GSH and SOD2. Compared with IC/BPS cells or IC/BPS cells co-transfected with p21 siRNA and Cdk1 control, the IC/BPS cells co-transfected with p21 siRNA and Cdk1 inhibitor exhibit a significant increase in terms of autophagosome numbers and the LC3-I/II level. Additionally, the levels of inflammatory factors are significantly decreased in the IC/BPS cells co-transfected with p21 siRNA and Cdk1 inhibitor. It was concluded that in IC/BPS, the Cdk1/p53/p21 feedback loop could regulate the level of autophagy and inflammatory response. This discovery identifies promising new therapeutic targets for IC/BPS, which may pave the way for innovative clinical approaches to this complex disorder.

China**CHARACTERISTIC GENES AND IMMUNE LANDSCAPE OF INTERSTITIAL CYSTITIS.**

Wang J, Zhou Y, Hu J, Han J, Feng J, Guo K, Chen W, Yun Y, Li Y. *PLoS One*. 2025 May 28;20(5):e0320249. doi: 10.1371/journal.pone.0320249. PMID: 40435311; PMCID: PMC12119006.

Open access

Interstitial cystitis (IC) was still a disease with the exclusive diagnosis and lacked an effective gold standard. It was of great significance to find diagnostic markers for IC. This study from China was aimed to screen characteristic genes via machine learning algorithms, characterize the immune landscape of IC, and show correlations between characteristic genes and immune cell subtypes. RNA sequencing data sets on IC were downloaded from Gene Expression Omnibus (GEO) database, including [GSE57560](#), [GSE11783](#) and [GSE621](#), whose corresponding platforms were [GPL16699](#), [GPL570](#) and [GPL262](#) respectively. Three machine learning algorithms were applied for identification of characteristic gene for IC. Single sample Gene Set Enrichment Analysis (ssGSEA) was applied to figure out the immune cell infiltration (ICI) of IC and normal tissue samples. Correlation analysis was performed via Spearman test. Receiver operator characteristic curve (ROC) was used to evaluate diagnostic efficacy of key genes. CCL18, MMP10 and WIF1 were identified as characteristic gene via machine learning algorithms. MMP10 and CCL18 were with higher expression in IC tissues compared with normal bladder tissues, while WIF1 had lower expression in IC tissues ($P < 0.05$). These three genes had good diagnostic efficacy for IC. Compared with normal bladder tissues, 18 immune cell subtypes were up-regulated in interstitial cystitis tissues ($P < 0.05$). MMP10 and CCL18 were positively correlated to immune scores in IC, while WIF1 was negatively correlated to immune scores ($P > 0.05$). The authors screened the feature genes, CCL18, MMP10 and WIF1, among the differentially expressed genes (DEGs) by three different machine learning algorithms. They showed good diagnostic performance in both training and testing cohorts and were potential diagnostic markers for IC. They paint the immune landscape of IC. In IC tissue, immune cell subtypes infiltrated extensively. Most immune cell subtypes were up-regulated in IC tissue, including mast cells, activated CD4 T cells, and regulatory T cells that suppress immune responses. MMP10 and CCL18 had positive correlation to ICI, while WIF was negatively correlated with ICI. MMP10 and CCL18 may be the driving factors of immune response or their expression levels may be increased by immune response. The effect of characteristic genes of IC on immune cell subtypes still needed to be further explored.

China**INHIBITION OF HPSE/SDC-2 AXIS-INDUCED EPITHELIAL-MESENCHYMAL TRANSITION FOR TREATING IC/BPS.**

Chen Z, He Y, Zhang J, Ge Q, Du T, Fan Z, Zhou J, Yang X, Shen B, Wei Z. *PLoS One*. 2025 May 23;20(5):e0321730. doi: 10.1371/journal.pone.0321730. PMID: 40408331; PMCID: PMC12101628.

Open access

Interstitial cystitis/bladder pain syndrome (IC/BPS) plagues patients and clinicians with its unclear etiology and pathogenesis, and ineffective treatments. Destruction of epithelial tissue and proliferation of interstitial tissue are typical pathological features of IC/BPS, in which epithelial-mesenchymal transition (EMT) may play an important role. Both the increased urination frequency observed in mice with acute cystitis induced by cyclophosphamide (CYP) and the disruption of the anti-leakage barrier in urothelial cells induced by LPS are associated with the occurrence of EMT. The expression of heparanase 1 (HPSE) and syndecan-2 (SDC-2) is up-regulated in the bladder mucosa of patients with IC, and both of them can promote the development of EMT. Improvement of lower urinary tract symptoms and restoration of the uroepithelial cell anti-leakage barrier in mice with CYP-induced cystitis after treatment with the HPSE inhibitor OGT2115 and inhibited the development of EMT. The authors then verified that HPSE binds to SDC-2 and that SDC-2 is a key intermediate protein in the pro-EMT role of HPSE, and that EMT was inhibited by knockdown of SDC-2. SDC-2 exerts its biological function by inhibiting the ubiquitinated degradation of TGF- β R1. Here they identified a novel

mechanism by which the HPSE/ SDC-2 axis promotes EMT development and thus causes epithelial dysfunction and altered voiding behaviour, providing a new direction for the treatment of IC/BPS.

China

[ACTIVE COMPOUNDS, TARGETS, AND MECHANISMS OF SALVIA MILTIORRHIZA BUNGE IN TREATING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Wang L, Yu B, Wang Y, Qu X, Tang W. *Immun Inflamm Dis.* 2025 Apr;13(4):e70173. doi: 10.1002/iid3.70173. PMID: 40226969; PMCID: PMC11995424.

Open access

This study from China investigated the active compounds, molecular targets, and biological mechanisms of *Salvia miltiorrhiza* Bunge (SM) in treating interstitial cystitis/bladder pain syndrome (IC/BPS) through network pharmacology and a cyclophosphamide-induced cystitis model. A network pharmacology approach was used to assess the effects of SM and luteolin in IC/BPS. Female C57BL/6 mice were divided into four groups: CON, CON + Luteolin, CYP, and CYP + Luteolin, with luteolin (100 mg/kg) administered for CYP-induced cystitis. Histological and molecular analyses, including H&E staining, TUNEL, ELISA, Western blot, and urodynamics, were performed to explore the mechanisms. Network pharmacology showed 65 active ingredients and 148 potential targets of SM in the treatment of IC/BPS, of which luteolin had the highest potential. TP53, AKT1, CCND1, EGFR, and ERBB2 are the core targets, and PI3K-Akt and p53 are important signaling pathways for luteolin in the treatment of IC/BPS. Compared with the CYP group, the CYP + Luteolin group showed significantly lower bladder tissue scores; reduced expression of malondialdehyde, inflammatory factors (IL-18, IL-1 β , IL-6), and apoptosis-related proteins (cleaved-Caspase-3, Bax, cleaved-Caspase-8); significantly increased expression of total SOD and glutathione; and improved bladder function. Animal experiments have shown that luteolin can block the activation of the PI3K-Akt and p53 signaling pathways. It was concluded that SM has a variety of potentially active components for the treatment of IC/BPS, of which luteolin has the highest potential. Luteolin can inhibit inflammation, oxidative stress, and apoptosis through the p53 and PI3K-Akt signaling pathways and plays a role in treating IC/PBS.

Korea

[ANTI-INFLAMMATORY EFFECT OF SEA BUCKTHORN IN AN HCL-INDUCED CYSTITIS RAT MODEL.](#)

Yoon HS, Yu J, Kang S, Yoon H. *Investig Clin Urol.* 2025 Jan;66(1):67-73. doi: 10.4111/icu.20240196. PMID: 39791586; PMCID: PMC11729227.

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Although the mechanism underlying interstitial cystitis/bladder pain syndrome (IC/BPS) remains unclear, oxidative stress is suggested to be implicated in IC/BPS development. Sea buckthorn (SB; *Hippophae rhamnoides* L.) contains several compounds with antioxidant properties. In addition, intravesical application of hydrochloric acid (HCl) in rats induces histological changes similar to those observed in humans with IC. Therefore, the aim of this Korean study was to evaluate the anti-inflammatory effects of SB in an HCl-induced rat cystitis model. Twenty 8-week-old female Sprague–Dawley rats were instilled with HCl in their bladders to create an IC/BPS model. The model rats were divided into three groups and orally administered distilled water (control, n=4), concentrated SB (n=8), or pentosan polysulfate (PPS, n=8) daily. Pathologic inflammation grade (H&E staining), number of mast cells per square millimeter (toluidine blue staining), fibrotic changes (Masson's trichrome staining), and apoptosis (terminal deoxynucleotidyl transferase dUTP nick end labeling staining) of bladder tissue samples were compared among the groups. Compared to the control group, the SB and PPS groups showed reduced edema (5.25 $\pm$ 0.96 vs. 2.25 $\pm$ 0.46 vs. 2.50 $\pm$ 0.54, p=0.004, p=0.005, respectively), number of mast cells (12.5 $\pm$ 3.6 vs. 6.8 $\pm$ 1.9 vs. 6.6 $\pm$ 1.8, p=0.010, p=0.002, respectively), ratio of fibrotic submucosal tissue (63.9% $\pm$ 7.0% vs. 43.6% $\pm$ 9.9% vs. 40.5% $\pm$ 5.2%, p<0.001, p<0.001, respectively), and ratio of apoptotic nucleus (40.7% $\pm$ 11.7% vs. 7.7% $\pm$ 6.5% vs. 5.1% $\pm$ 4.9%, p<0.001, p<0.001, respectively). SB exhibited anti-inflammatory effects comparable to those of PPS in the HCl-induced chemical cystitis model.

Randomized Controlled Trial. USA

[AUGMENTATION OF INTERSTITIAL CYSTITIS-BLADDER PAIN SYNDROME TREATMENT WITH MEDITATION AND YOGA: A RANDOMIZED CONTROLLED TRIAL.](#)

Dao AN, Komesu YM, Jansen SM, Petersen TR, Meriwether KV. *Obstet Gynecol.* 2025 Feb 1;145(2):186-195. doi: 10.1097/AOG.0000000000005820. Epub 2025 Jan 2. PMID: 39746210.

This study investigated whether yoga and meditation added to usual care improves treatment response in women with interstitial cystitis-bladder pain syndrome. This randomized trial compared women with interstitial cystitis-bladder pain syndrome receiving standard care alone (control group) with those receiving standard care plus meditation and yoga (mind-body group). Standard care was defined as behavioral changes or medications recommended by the American Urological Association. Individuals in the control group received standard care, and those in the mind-body group received standard care augmented with a commercially available meditation application and standardized yoga tutorial video. Both groups continued their current interstitial cystitis-bladder pain syndrome standard care treatments. The primary outcome was the modified GRA (Global Response Assessment), comparing responders (moderately, markedly improved) with nonresponders at 12 weeks. On power analysis assuming $\alpha=5\%$ and $\beta=80\%$, a sample size of 82 participants was required to find 30% difference on the GRA between groups. Weekly GRA scores over 12 weeks were also compared. Secondary outcomes included ICPI (Interstitial Cystitis Problem Index)/ICSI (Interstitial Cystitis Symptom Index), pain, pain interference, anxiety/depression, and self-efficacy scores and treatment escalation over 12 weeks. Among 97 randomized participants (49 mind-body group, 48 control group), groups did not differ in characteristics or symptoms at baseline. The mind-body group had more GRA responders compared with the control group at 12 weeks (31/43 [72.1%] vs 10/39 [25.6%], relative risk [RR] 2.8, 95% CI, 1.6-4.6), corroborated by superior weekly GRA results over 12 weeks. The mind-body group had superior beneficial change on the ICPI (RR 1.8, 95% CI, 0.5-3.1), ICSI (RR 1.9, 95% CI, 0.2-3.6), and pain (RR 1.4, 95% CI, 0.4-2.5) scores than the control group at 12 weeks. The mind-body group required less treatment escalation than the control group (2/45 [4.4%] vs 14/42 [33.3%], RR 0.13, 95% CI, 0.03-0.55). The addition of meditation and yoga to standard interstitial cystitis-bladder pain syndrome care was associated with improved treatment response and required fewer additional interventions compared with standard care alone.

USA

[SELF-EFFICACY IN MANAGING FEMALE SEXUAL DYSFUNCTION IN INTERSTITIAL CYSTITIS.](#)

Sutherland S, Kelly AG, Walsh EG, Dmochowski RR, Burton R, McKernan LC. *Urology.* 2025 May 27:S0090-4295(25)00466-2. doi: 10.1016/j.urology.2025.05.010. Epub ahead of print. PMID: 40441309.

Open Access

The purpose of this study from the USA was to examine relations between clinical features and female sexual dysfunction in a sample of women with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS), with a focus on sexual self-efficacy, or confidence in ability to manage symptoms. Female sexual dysfunction (FSD) is prevalent in IC/BPS. Several areas of sexual functioning are impacted, including experiences of pain during and after sex which is significantly disruptive to quality of life. Despite evidence that emotional health and FSD relate, less is known about how to address FSD in IC/BPS. Sixty-eight female participants [$m = 43.89$ ($SD = 13.15$) years] with IC/BPS reported demographics, diagnostic symptoms of IC/BPS, pain, mood, sexual self-efficacy, and sexual function. Regression explored the relation of urologic symptoms, pain and emotional distress to FSD, and the additional predictive utility of sexual self-efficacy when assessing this relationship. While pelvic and mood

symptoms effectively predicted FSD, the addition of sexual self-efficacy to the model produced significant model improvement, such that greater self-efficacy was associated with better sexual functioning, and variance in FSD was no longer predicted by pain or depression. Results emphasize the influential role that confidence in ability to manage symptoms plays in FSD, beyond known influences such as mood or symptom severity. Complementing existing treatment with education or intervention including skills-building to increase patient confidence in ability to manage sexual pain may improve sexual function in IC/BPS. A model of intervention appropriate for physician implementation in the clinical setting is discussed, and potential self-management strategies are reviewed.

USA

[ESTABLISHING EVIDENCE FOR THE PAINFUL INTERCOURSE SELF-EFFICACY SCALE-INTERSTITIAL CYSTITIS.](#)

Kelly AG, Sutherland SL, Walsh EG, Finn MTM, Ryden AM, McKernan LC. *Womens Health Rep (New Rochelle)*. 2025 Mar 27;6(1):344-352. doi: 10.1089/whr.2024.0152. PMID: 40308358; PMCID: PMC12040544.

Open access

Although female sexual dysfunction (FSD) and low sexual self-efficacy are common in patients with interstitial cystitis/bladder pain syndrome (IC/BPS), existing measures of these constructs do not fully capture unique challenges faced by patients with IC/BPS, such as managing sex-related symptom exacerbations, experiencing rewarding sexual activity, and maintaining intimate relationships. To address the lack of tailored measurement of FSD and sexual self-efficacy in patients with IC/BPS, the authors aimed to adapt the Painful Intercourse Self-Efficacy Scale—Interstitial Cystitis (PISES-IC) for this population. To form the PISES-IC, they added three items to the pain self-efficacy subscale of the PISES, each informed directly by qualitative interviews with patients with IC/BPS and literature review of patient-reported sexual experiences in IC/BPS. Utilizing baseline data of 71 female participants involved in a clinical trial for IC/BPS (NCT#04275297), they assessed the validity and reliability of the newly adapted PISES-IC. Results indicate that the PISES-IC is indeed a valid and reliable measure of sexual self-efficacy in the IC/BPS population and that the items informed by IC/BPS patient experiences (self-efficacy related to pain flares, rewarding sexual activity, and interference with romantic relationships) may be particularly related to FSD in patients with IC/BPS. They concluded that the PISES-IC captures aspects of sexual experiences of patients with IC/BPS that are not assessed by other existing measures. The PISES-IC can be utilized in research and clinical settings to inform patient care and to further understand sexual experiences of IC/BPS patients.

MAPP Research Network Study. USA

[TOWARDS PRECISION MEDICINE IN CLINICAL TRIALS FOR THE TREATMENT OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME: LESSONS FROM THE MAPP RESEARCH NETWORK.](#)

Stephens Shields AJ, Clemens JQ, Pontari MA, Lai HH, Moldwin R, Williams DA, Bradley CS, Farrar JT, Landis JR, Mullins C, Naliboff BD, Sutcliffe S, Walker SJ, Yang CC, Clauw DJ. *Nat Rev Urol*. 2025 Apr 30. doi: 10.1038/s41585-025-01030-w. Epub ahead of print. PMID: 40307537.

Randomized clinical trials have resulted in few approved therapies for the treatment of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, collectively referred to as urologic chronic pelvic pain syndrome. Heterogenous patient populations, mismatches of treatments to patient phenotypes, non-specific outcomes and use of standard study designs not leveraging phenotypic heterogeneity might have contributed to the inability of previous trials to demonstrate existing efficacy. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network has identified important phenotypic characteristics associated with differential symptom severity and treatment responsiveness. Based on Multidisciplinary Approach to the Study of Chronic Pelvic Pain findings and external research, empirically informed strategies were generated for defining patient populations, specifying treatments and selecting primary outcomes for future

randomized clinical trials in urologic chronic pelvic pain syndrome. Explicitly specifying the scope of eligibility criteria across heterogeneous patient subgroups defined by pain widespreadness, the presence of Hunner lesions, the presence of pain with bladder filling or relieved by voiding, the extent of chronic overlapping pain conditions, and pelvic floor tenderness is needed. Therapies should be selected based on the mechanism of action and relevance to the mechanism of pain and dominant symptomology that the patient experiences. Evidence suggests that pain and urinary symptoms should be evaluated separately. Promising trial designs for identifying effective therapies in this heterogeneous patient population include sequential multiple assignment randomized trials and adaptive designs.

MAPP Research Network Study. USA

RELATIONSHIP OF SEX AND DIAGNOSIS WITH SYMPTOMS AND ILLNESS IMPACT IN UROLOGIC CHRONIC PELVIC PAIN; A MAPP NETWORK ANALYSIS.

Naliboff BD, McWilliams T, Clemens JQ, Pontari MA, Stephens-Shields AJ, Moldwin R, Sutcliffe S, Mullins C, Landis JR. *Neurourol Urodyn.* 2025 Feb;44(2):400-408. doi: 10.1002/nau.25648. Epub 2024 Dec 20. PMID: 39704257; PMCID: PMC11788956.

Open access

This study assessed differences in clinical presentation and illness impact in men and women presenting with urologic chronic pelvic pain syndrome (UCPPS) and between men diagnosed with interstitial cystitis/bladder pain syndrome (IC/BPS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). 356 men and 605 women from six sites across the United States were assessed using a comprehensive set of demographic, symptom, and illness impact measures. Multivariable regression analyses examined differences between men and women and between men previously diagnosed with CP/CPPS or IC/BPS. In a stepwise manner, analyses tested group differences, controlling for demographic variables including symptom duration and presence of bladder pain that varied with filling and voiding. Men diagnosed with IC/BPS had the most severe UCPPS symptoms, followed by women with IC/BPS, and then men with CP/CPPS only. While men and women showed similar patterns of symptoms across most of the variables, women had increased widespread non-pelvic pain, greater pelvic floor tenderness on exam, and higher self-reported sensory sensitivity compared to men. About 60% of men diagnosed with CP/CPPS only reported bladder symptoms of painful filling or relief with voiding. A generally shared symptom pattern was found across men and women irrespective of diagnostic labels suggesting the use of key marker symptoms, such as severity of bladder symptoms and widespread pain, to better identify subgroups of UCPPS rather than diagnostic category. Women may have an increased likelihood of increased sensitivity and central sensitization than men, including those men with IC/BPS.

MAPP Research Network Study. USA

WIDESPREAD PAIN MODERATES THE RESPONSE TO CENTRALLY-ACTING THERAPIES IN AN OBSERVATIONAL COHORT OF PATIENTS WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROME: A MAPP RESEARCH NETWORK STUDY.

Schrepf A, Locke K, Moldwin R, Williams DA, Till S, Farrar J, Richard Landis J, Tu F, Rodriguez L, Lai H, Naliboff B, Kutch J, Harte SE, Harris RE, Kreder KJ, Spitznagle T, McKernan L, Yang C, Quentin Clemens J, Mullins C, Clauw DJ. *Neurourol Urodyn.* 2025 May 25. doi: 10.1002/nau.70068. Epub ahead of print. PMID: 40415481.

Urologic Chronic Pelvic Pain Syndrome (UCPPS) impacts millions of people in the United States but treatment options remain largely unsatisfying. A large number of neurobiological studies from the Multidisciplinary Approach to the study of chronic Pelvic Pain (MAPP) research network and others point to aberrant pain mechanisms in patients with UCPPS and widespread pain, but the clinical significance of widespread pain has been speculative. In the current exploratory study the authors investigated whether pain and urologic symptoms responded to centrally-directed therapies (tricyclic antidepressants/gabapentinoids) versus peripherally-directed (pelvic floor physical

therapy/hydrodistension) therapies depending on the presence or absence of widespread pain when the new treatment was initiated. Forty UCPPS patients (n = 19 widespread) underwent an evaluation of UCPPS symptoms before and after twelve weeks of either centrally-directed (n = 16) or peripherally-directed therapy. Participants were stratified post hoc into widespread (two or more non-pelvic pain sites + pelvic pain) and localized pain categories. General linear models were used to test the group X treatment interaction effect, adjusting for age, sex, and baseline outcome levels. On average, patients with widespread pain receiving centrally-directed therapies improved more than six points on the 0-28 Pelvic Pain Severity scale, while those with localized pain showed no average improvement (interaction p = 0.005). Similar effects were observed for the bladder symptom impact score (interaction p = 0.011) but not urologic symptom severity (interaction p = 0.72). While these findings are exploratory, they provide preliminary evidence for phenotype X treatment interactions in UCPPS and should be followed by confirmatory studies.

MAPP Research Network Study. USA

WIDESPREAD PAIN PHENOTYPES IMPACT TREATMENT EFFICACY RESULTS IN RANDOMIZED CLINICAL TRIALS FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN NETWORK STUDY.

Farrar JT, Locke KT Jr, Clemens JQ, Griffith JW, Harte SE, Kirkali Z, Kreder KJ, Krieger JN, Lai HH, Moldwin RM, Mullins C, Naliboff BD, Pontari MA, Rodríguez LV, Schaeffer AJ, Schrepf A, Stephens-Shields A, Sutcliffe S, Taple BJ, Williams DA, Landis JR. Pain. 2025 May 1;166(5):1179-1190. doi: 10.1097/j.pain.0000000000003455. Epub 2025 Feb 18. PMID: 39499552; PMCID: PMC12004979.

Open access

Pain clinical trials are notoriously complex and often inefficient in demonstrating efficacy, even for known efficacious treatments. A major issue is the difficulty in the a priori identification of specific phenotypes to include in the study population. Recent work has identified the extent of widespread pain as an important determinant of the likelihood of response to therapy, but it has not been tested in clinical trials for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). The authors explored this hypothesis using data from 3 previously published trials testing treatments for IC/BPS, which suggested modest benefits but did not meet a priori primary outcome statistical significance criteria. Importantly, these studies also collected symptom questionnaire data that allowed the group to retrospectively identify participants with and without widespread pain. Analyzing the treatment by the degree of widespread pain revealed a difference in outcome and statistical significance level for each trial. Participants with predominately local pain (ie, limited widespread pain symptoms) responded to therapy targeting local symptoms, whereas those with widespread pain did not. Alternatively, participants with widespread pain beyond their local pelvic pain responded to more centrally acting treatments. The results suggest that differentiating patients based on widespread vs more localized pain is a key consideration for designing future clinical trials for conditions with variable pain profiles, such as IC/BPS and potentially other pain-based syndromic disorders.

USA

RESILIENCE AMONG ADULTS WITH CHRONIC UROLOGIC PELVIC PAIN SYNDROME: A FLEXIBLE SELF-REGULATION PERSPECTIVE.

Rogers AH, Lackner JM, Radziwon C, Danforth TL, Gudleski GD. J Pain. 2025 May 15;32:105439. doi: 10.1016/j.jpain.2025.105439. Epub ahead of print. PMID: 40381976.

While coping with the heavy patient demands of chronic pain requires psychological resilience, its core mechanisms have not been systematically studied in high-impact pain disorders like Urologic Chronic Pelvic Pain Syndrome (UCPPS). Applying a flexible self-regulation (FSR) model of resilience, the authors sought to characterize how flexibility deficits in the abilities to read, decode, and respond appropriately to contextual cues (context sensitivity) and coping flexibility relative to known protective (e.g., pain-specific resilience, social support) and vulnerability factors (e.g., catastrophizing), correspond with symptom severity and quality of life (QoL) impairment in patients

with refractory UCPPS symptoms. Participants included 113 (Mean age = 43.56, SD = 14.79, 81.4% female) formally diagnosed UCPPS (Interstitial Cystitis/Bladder Pain Syndrome or Chronic Prostatitis/Chronic Pelvic Pain Syndrome) patients with refractory pelvic pain. Baseline data, completed as part of an NIH clinical trial, included FSR components, Pain Resilience Scale, social support, Positive and Negative Affect Schedule, Coping Strategies Questionnaire - Catastrophizing, pelvic pain, and urinary severity indices, and QoL (CDC Healthy Days, PROMIS physical and mental health). Regression analyses, using a Bayesian variable selection method, examined how protective and vulnerability factors were associated with symptom and QoL outcomes. As predicted, context sensitivity and coping flexibility corresponded with higher QoL. The pattern of results was more consistent for components of FSR than for dispositional psychological factors including pain resilience, negative affectivity, and pain catastrophizing. Data demonstrates the importance of resilience rooted in a theory-informed, empirically grounded flexible self-regulation conceptual model. Flexible self-regulation, a cognitive-affective construct critical to the development of resilience, is important for understanding adaptation to nociplastic pain disorders like UCPPS. Contextual-based coping based on situational flexibility corresponds with quality of life, which may be a novel therapeutic target for optimizing behavioral pain treatments for high-impact pain disorders.

Türkiye

EXPLORING DRUG REPURPOSING FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: DEFINING NOVEL THERAPEUTIC TARGETS.

Inal-Gültekin G, Çetin Z, Mangır N. Neurourol Urodyn. 2025 Feb;44(2):496-503. doi: 10.1002/nau.25651. Epub 2024 Dec 26. PMID: 39723619.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating pain condition of unknown etiology. Effective therapies for this condition could not have been developed in the last century. Drug repurposing is a practical strategy for enhancing patient access to successful therapies. It is an approach for discovering novel applications for licensed or investigational pharmaceuticals that extend beyond the initial medical indication. This work aims to identify repurposable medications through bioinformatics to discover potential drugs or compounds that can reverse the IC/BPS disease signature. The analysis involved examining the differentially expressed genes in IC/BPS patients with two distinct disease phenotypes (Hunner's lesion disease, non-Hunner's lesion disease) and controls using the datasets GSE11783, GSE28242, and GSE57560. The goal was to assess the reversal of the disease signature on the L1000CDS2 and cMAP platforms. Twenty-one compounds were repurposed, consisting of 11 small molecules, 10 chemical compounds, 3 natural products, and 6 FDA-approved drugs, currently used for clinical indications such as cancer, myelofibrosis, and diabetes. Bioinformatics can be useful for identifying therapeutic agents for IC/BPS by accessing and processing big data on molecular and cellular levels. Prospective in vivo experiments must validate repurposed drugs. The expansion of large-scale genome sequencing, gene expression studies, and clinical data for IC/BPS will improve successful drug selection.

Review. Taiwan

INTEGRATING BIOMARKER CLUSTERING FOR IMPROVED DIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A REVIEW.

Chen YC, Kuo HC. Int Urol Nephrol. 2025 Mar 15. doi: 10.1007/s11255-025-04452-y. Epub ahead of print. Erratum in: Int Urol Nephrol. 2025 Apr 2. doi: 10.1007/s11255-025-04492-4. PMID: 40088357.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic condition characterized by pelvic pain and urinary disturbances, making its diagnosis challenging due to overlapping symptoms with various lower urinary tract disorders. Current diagnostic methods primarily rely on subjective evaluations, leading to significant difficulties in accurately identifying and managing IC/BPS. This review from Taiwan explores the potential of clustering different disease biomarkers to enhance diagnostic precision for IC/BPS. The authors examined current research identifying non-invasive biomarkers, including inflammatory markers, oxidative stress indicators, and neurogenic growth

factors, while emphasizing the limitations inherent in single biomarker approaches. By employing cluster analysis, which integrates diverse biomarker data relevant to IC/BPS, current studies indicate that this integration facilitates improved sensitivity and specificity in diagnosis while enabling personalized treatment strategies. Emerging machine learning techniques further enhance this analytical framework, identifying predictive urinary biomarkers that can assist frontline clinicians in making informed diagnostic decisions. This review also highlights the need for standardized protocols in biomarker collection and analysis, advocating for multi-omics integration and longitudinal studies to uncover disease mechanisms and improve clinical practices. Ultimately, utilizing a cluster of disease biomarkers aims to provide objective diagnostic tools, thereby supporting clinicians in delivering timely and effective interventions that can significantly impact patients' quality of life.

Review. Taiwan

[PATHOPHYSIOLOGY AND POTENTIAL MULTIMODAL THERAPEUTIC STRATEGIES FOR IC/BPS.](#)

Jhang JF, Yu WR, Jiang YH, Kuo HC. Nat Rev Urol. 2025 May 15. doi: 10.1038/s41585-025-01044-4. Epub ahead of print. PMID: 40374927.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a bladder disorder with no definite aetiology and currently no effective treatment. Its clinical symptoms vary widely, and the bladder condition and extra-bladder dysfunction also show different clinical presentations. This condition is considered to have multiple factors affecting the bladder and clinical symptoms, including urothelial dysfunction, mast cell activation, autoimmune response, neurogenic inflammation, viral or bacterial infection, autonomic nervous dysfunction and central nervous sensitization. Several non-pharmacological, medical, intravesical and novel bladder therapies have been advocated, but the efficacy and durability of these treatments have not been well elucidated. Multimodal therapy has been suggested based on possible pathological mechanisms; however, the most appropriate therapeutic strategy for this disorder has not been well defined. Thus, a rational algorithm for concomitant multimodal therapy for IC/BPS has been proposed.

Review. Japan

[EXPERIMENTAL MURINE MODELS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A REVIEW.](#)

Saito T, Minagawa T, Yoshimura N, Luo Y, Akiyama Y. Histol Histopathol. 2025 May;40(5):635-644. doi: 10.14670/HH-18-837. Epub 2024 Oct 23. PMID: 39523811.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic enigmatic disease of the urinary bladder characterized by persistent bladder/pelvic pain in conjunction with lower urinary tract symptoms. IC/BPS is categorized as either Hunner-type IC (HIC) or BPS based on the presence/absence of the Hunner lesion, a reddish mucosal lesion in the bladder. HIC and BPS present with similar symptoms, however, the etiologies are completely different. Recent evidence suggests that HIC is an immune-mediated inflammatory disease of the urinary bladder. In contrast, BPS, other forms of HIC lacking Hunner lesions, is a minimally inflamed condition comprising various clinical phenotypes. Based on this evidence, basic research into IC/BPS has shifted to target each subtype of IC/BPS. Today, experimental murine models of autoimmune cystitis are used for HIC research, whereas models related to neurophysiological and psychosocial dysfunctions have been developed for BPS research. This emerging concept of a subtype-tailored approach may contribute to a better understanding of the full picture of IC/BPS, thereby improving current clinical management strategies and the development of novel therapies.

Review. India

[CHONDROITIN SULFATE: FROM BIOACTIVE MOLECULE TO VERSATILE DRUG DELIVERY SYSTEM FOR ADVANCING REGENERATIVE MEDICINE.](#)

Rajesh A, Sajeev D, R NK, Rangasamy J, C Nair S. Int J Biol Macromol. 2025 Jun;311(Pt 2):143746. doi: 10.1016/j.ijbiomac.2025.143746. Epub 2025 May 2. PMID: 40319978.

Regenerative medicine, a rapidly advancing field, holds immense promise for restoring and revitalizing damaged tissues and organs resulting from aging, diseases, or injuries, ultimately improving patient well-being. Chondroitin Sulfate (CS), a naturally occurring glycosaminoglycan, is a compelling biomaterial due to its natural origin, well-established biocompatibility, and structural complexity. Renowned for its biocompatibility, structural complexity, and varied bioactivities, CS provides significant applications beyond its recognized function in joint health and osteoarthritis treatment. Recent breakthroughs demonstrate its potential in treating complicated disorders such as interstitial cystitis, psoriasis, dry eye syndrome, and cardiovascular diseases by controlling inflammation, facilitating wound healing, and improving tissue repair. Notwithstanding its therapeutic potential, CS remains inadequately investigated in regenerative medicine and tissue engineering. Its capacity to modulate cellular signaling, promote extracellular matrix remodeling, and improve scaffold integration establishes it as a crucial facilitator of sophisticated therapeutic approaches. This review elucidates the progression of CS-based drug delivery systems, encompassing hydrogels, microparticles, nanoparticles, composites, and beads while underscoring their effectiveness in addressing conventional drug delivery obstacles such as non-specific targeting and off-target effects. Integrating CS into advanced platforms enables regulated drug release, accurate targeting, and enhanced cellular absorption while maintaining biodegradability and compatibility with tissue engineering scaffolds. Its inherent antioxidant, anti-inflammatory, and immune-modulating characteristics augment its attractiveness for individualized therapeutic applications. Recent studies highlight the adaptability of CS in developing multimodal drug delivery systems designed for regenerative medicine. Nonetheless, substantial deficiencies persist, especially in clinical validation and extensive applications. Overcoming these hurdles may fully realize CS's potential in transforming drug delivery, establishing a solid basis for the progression of regenerative therapies. By integrating biomaterial science with clinical medicine, CS-based systems are set to transform treatment approaches in regenerative medicine, providing precision, efficiency, and adaptability for individualized care.

Review. China

INNOVATIVE APPLICATIONS OF NATURAL POLYSACCHARIDE POLYMERS IN INTRAVESICAL THERAPY OF BLADDER DISEASES.

Hu K, Xiao M, Chen S, Huang Y, Hou Z, Li X, Yang L. Carbohydr Polym. 2025 Apr 15;354:123307. doi: 10.1016/j.carbpol.2025.123307. Epub 2025 Jan 22. PMID: 39978897.

Natural polysaccharide polymers, characterized by their remarkable biocompatibility, biodegradability, and structural versatility, hold great promise for intravesical therapy in treating of bladder diseases. Conditions such as bladder cancer and interstitial cystitis compromise drug efficacy by affecting the permeability of the bladder wall. Traditional therapeutic approaches are often hindered by physiological challenges, including rapid drug clearance and the intrinsic permeability barrier of the bladder. Polysaccharides like hyaluronic acid (HA) and chitosan (CS) have emerged as promising materials for intravesical drug delivery systems (IDDS), owing to their ability to repair tight junctions in the bladder wall, mitigate inflammation, and enhance permeability. This review from China provides a comprehensive overview of the mechanisms through which polysaccharide-based natural polymers regulate bladder wall permeability and highlights their advancements in delivery platforms, including nanoparticles, hydrogels, floating systems, and composite materials. By improving drug retention, enhancing bioavailability, and promoting patient adherence, these materials offer a solid foundation for the development of innovative therapeutic strategies for bladder diseases.

Literature Review. Pakistan

EXPLORING THE ANTI-INFLAMMATORY EFFECTS OF PHYTOCHEMICALS IN ATTENUATING INTERSTITIAL CYSTITIS-A LITERATURE REVIEW.

Anjum I, Nasir A, Naseer F, Ibrahim A, Rehman B, Bashir F, Tul Ain Q. *Front Pharmacol.* 2025 Feb 5;16:1483548. doi: 10.3389/fphar.2025.1483548. PMID: 39974737; PMCID: PMC11836544.

Open access

Interstitial cystitis is a fierce syndrome affecting the quality of life of thousands of individuals around the globe. It causes immense pain in the bladder and associated viscera along with inflammation-like lesions. The current medicinal and pharmacological research focuses on the protective and curative effects of phytochemicals in several ailments. Phytochemicals derived from many medicinal plants have shown potent outcomes in protection against various pathological conditions including interstitial cystitis. This review has summarized the insights of *in vitro* and *in vivo* studies regarding the effects of phytochemicals in fading the inflammation in bladder tissue and exhibiting a protective effect on the urothelium. Hemorrhagic cystitis is a common manifestation in patients undergoing chemotherapy with cyclophosphamide and related alkylating agents. Sodium 2-mercaptoethane sulfonate (Mesna) has traditionally been employed in clinical practice to counter cyclophosphamide-induced cystitis in humans. However, cyclophosphamide has been employed in developing animal models of interstitial cystitis in *in vivo* studies. Phytochemicals including quercetin, beta-caryophyllene, curcuminol, boswellic acid, caftaric acid, some flavonoids and other secondary metabolites being a consequential component of numerous medicinal plants, have displayed a significant reduction in the levels of proinflammatory cytokines including TNF- α , NF κ B, IL-1 β , NLRP3 inflammasome, IL-6, IL-2, matrix metalloproteinases etc. Uroprotective outcomes of these phytochemicals have been found to result in diminished oxidative stress and restoration of glutathione, superoxide dismutase, and related proteins in the inflamed bladder tissue. Many *in vivo* studies involving cyclophosphamide-induced interstitial cystitis have confirmed these findings. The coupling of phytotherapy with novel drug delivery systems such as nanoparticles, liposomes, nanotubes, quantum dots, etc. can help translate these beneficial effects of phytochemicals into clinical practice. Further investigations of these phytochemicals can provide intuition regarding the development of newer drug molecules having exclusive activity for attenuating interstitial cystitis.

Review. China

THE INTEGRATION OF BIOMARKERS AND PATIENT-REPORTED OUTCOMES IMPROVES PREDICTION OF INTERSTITIAL CYSTITIS SYNDROME.

Chen YC, Kuo HC. *Expert Rev Mol Diagn.* 2025 Jun;25(6):217-232. doi: 10.1080/14737159.2025.2502035. Epub 2025 May 6. PMID: 40319375.

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a chronic condition characterized by debilitating bladder pain and urinary symptoms, such as urgency and frequency. Its considerable impact on patients' quality of life is compounded by the diagnostic challenges stemming from symptom overlap with other urological disorders and insufficient standardization of diagnostic criteria. This review from China examines various key aspects of IC/BPS, including the identification of biomarkers such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), monocyte chemotactic protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) that correlate with symptom severity and underlying inflammatory processes. It discusses the importance of urinary and serum biomarkers, current challenges in clinical assessments, the variability in biomarker collection and analysis methods, and emphasizes the role of patient-reported outcomes (PROs) such as the O'Leary - Sant (ICSI/ICPI) questionnaires and the Visual Analogue Scale in capturing the patient's subjective experience and quality of life. Strengthening the integration of biomarkers with PROs is crucial for enhancing diagnostic accuracy and personalizing treatment approaches for IC/BPS patients. The review calls for future research to develop standardized protocols, which will improve patient care by facilitating a more tailored management strategy based on a comprehensive understanding of IC/BPS.

Review. Spain**RESEARCH METHODOLOGY IN ACUPUNCTURE FOR MANAGING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SCOPING REVIEW.**

Infantes Rosales MÁ, Mesías Pesqueira Á, Castellanos Díaz A, Díaz Mohedo E. Neurourol Urodyn. 2025 May 2. doi: 10.1002/nau.70061. Epub ahead of print. PMID: 40313170.

Acupuncture and moxibustion are being explored as complementary therapies with promising potential in managing interstitial cystitis/bladder pain syndrome (IC/BPS). While some studies indicate possible benefits, their scientific basis and clinical efficacy remain subjects of debate, partly due to methodological flaws in study designs involving acupuncture and related modalities, which warrant further attention and discussion. The main objective is to analyze and evaluate the research methodologies used in existing literature on acupuncture for managing IC/BPS, providing insight into the methodological challenges and opportunities in this field. National Library of Medicine (PubMed), Allied and Complementary Medicine Database (AMED), Cochrane Library, Excerpta Medica database (EMBASE), Web of Sciences (WOS), Medical Literature Analysis and Retrieval System Online (MEDLINE), Cumulated Index in Nursing and Allied Health Literature (CINAHL), Scopus, SPORTdiscus, Epistemonikos, and Physiotherapy Evidence Database (PEDro) were searched from their inception to August 2024. Data were extracted based on the study designs, primary outcome measures, adverse events (AEs), and participants' subjective views. All the experimental studies (27.3%, 6 of 22) were randomized controlled trials (RCTs), but only 2 full texts were accessible. Of the 4 RCTs, 3 involved rats. Observational research (50%) included case reports (27.3%), cohort studies (9.1%), and theoretical studies (4.5%). Additionally, reviews (22.7%) were included. The main languages were English (77.3%), Chinese (13.6%), Japanese (4.5%), and Russian (4.5%). The most frequently reported outcome was pain, followed by quality-of-life impact (symptom burden), urinary frequency and urgency, nocturia, and bladder capacity. AEs were reported in only 5 articles, all of which concluded that these effects were not significant and that acupuncture could be considered a safe and relatively noninvasive technique. One review found a risk of 1 AE/76 000 patients, with the most common side effects being minor, such as bleeding or bruising. Current evidence on acupuncture for interstitial cystitis is limited in quality, with studies often compromised by biases, small sample sizes, and lack of standardized protocols. Acupuncture is frequently part of multimodal treatments, aligning with Traditional Chinese Medicine's holistic approach to balance physical, mental, and emotional health. More high-quality experimental research is needed, focusing on standardized protocols and participant experiences to better evaluate its efficacy and safety.

Review. Iran, Austria**GAP OF RESEARCH TO PRACTICE IN IC/BPS: A SCIENTOMETRIC STUDY OF AVAILABLE EVIDENCE.**

Mostafaei H, Ashayeri H, Afshar S, Mostafaei H, Badr TA, Salehi-Pourmehr H, Hajebrahimi S. Urol Res Pract. 2025 Apr 4;50(6):332-342. doi: 10.5152/tud.2025.24086. PMID: 40243379; PMCID: PMC12015755.

Open access

The main objective of this study from Iran and Austria was to first characterize the current status of the research field of interstitial cystitis and bladder pain syndrome (IC/BPS). This was achieved by mapping, analyzing, and sub-analyzing the field with a scientometric approach, which provides insights into future research. In September 2023, the Scopus database was searched without restrictions on language and date. The following search query was used: Bladder* W/5 pain* W/3 syndrome* AND Interstitial* W/3 (Cystitis* OR Cystides) and the Scopus filters were used to exclude short surveys, book chapters, editorials, notes, and guidelines. The author, journal, institution data, keywords, average citation, countries, and sources were transformed using a Biblioshiny tool (A Shiny app for Bibliometrix), accounting for author spelling, institutional naming, and subgrouping variations. The search strategy yielded 1833 studies. The USA was the most cited country, with other countries showing significant growth in recent years. In terms of affiliations, TZU CHI University was the most relevant in this field (n = 154). The most relevant keywords were “female,” “interstitial cystitis,”

“human,” “cystitis interstitial,” “male,” and “cystalgia.” The current topics in IC/BPS research are Genome-wide association and Cannabidiols. By understanding the past, scientific gaps, and the direction of the current research, researchers can aim for their research questions and conduct their research more organized. The scientific gaps of IC/BPS can be effectively understood by paying attention to the models used in this research, which are the results of the systemic analysis of the scientific products in this research field.

Review. USA

INTERVENTIONAL PAIN MANAGEMENT IN THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Kalajian, T., Drerup, B., Drerup, J. et al. Curr Bladder Dysfunct Rep 20, 2 (2025). <https://doi.org/10.1007/s11884-024-00771-5>

Interstitial cystitis (IC)/Bladder pain syndrome (BPS) is a complicated problem commonly encountered in the fields of urology and pain management. This review article aims to provide readers with a detailed discussion outlining the most recent breakthroughs in the management of IC, specifically, emerging and first-line interventional treatments. Recent literature demonstrates that nerve blocks and neuromodulation selecting a variety of targets in the peripheral and central nervous system can be used with efficacy in treating IC/BPS. Recent research has demonstrated that rapidly evolving interventional techniques remain a promising area to effectively treat the challenging disorder of IC/BPS with acknowledgement that further research is needed in this space.

Review. USA

FEMALE PELVIC CONDITIONS: INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Beltran E. FP Essent. 2024 Dec;547:33-39. PMID: 39692795.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a likely underdiagnosed chronic pain syndrome consisting of pelvic pain lasting longer than 6 weeks plus lower urinary tract symptoms in the absence of infection or other identifiable cause. It is more common after 40 years of age. The etiology is unclear, but some patients have inflammatory findings in the bladder known as Hunner lesions. Due to its variable presentation, there is no standardized evaluation for diagnosis of IC/BPS. The history should include pain and urinary symptoms; associated comorbid disorders, including autoimmune and mental health conditions; and symptoms suggestive of other causes (eg, infection). Cystoscopy is not required but should be considered for patients with refractory symptoms and when Hunner lesions are suspected, such as in those older than 50 years or with comorbid autoimmune disorders and/or bladder-centric presentation (eg, predominance of urgency, frequency, low urine volumes). Treatment is often multimodal, including behavior modifications, stress management, and nonpharmacologic therapy (eg, pelvic floor physical therapy). Oral pharmacotherapy can be considered, but no guidelines exist on preferred agents. Referral for procedural treatments can also be considered for refractory cases. Patients should understand that no treatments are definitively successful, and recurrences and flare-ups often occur.

Preprint. USA

INTERSTITIAL CYSTITIS: A PHENOTYPE AND RARE VARIANT EXOME SEQUENCING STUDY: INTERSTITIAL CYSTITIS: A PHENOTYPE AND EXOME SEQUENCING STUDY.

Motelow JE, Malakar A, Murthy SBK, Verbitsky M, Kahn A, Estrella E, Kunkel L, Wiesenbahn M, Becket J, Harris N, Lee R, Adam R, Kiryluk K, Gharavi AG, Brownstein CA. medRxiv [Preprint]. 2025 Feb 18:2025.02.16.25322147. doi: 10.1101/2025.02.16.25322147. PMID: 40034785; PMCID: PMC11875234.

Open access

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a poorly understood and underdiagnosed syndrome of chronic bladder/pelvic pain with urinary frequency and urgency. Though IC/BPS can be hereditary, little is known of its genetic etiology. Using the eMERGE data, the authors from the USA

confirmed known phenotypic associations such as gastroesophageal reflux disease and irritable bowel syndrome and detected new associations, including osteoarthritis/osteoarthritis and Barrett's esophagus. An exome wide ultra-rare variants analysis in 348 IC/BPS and 11,981 controls extended the previously reported association with *ATP2C1* and *ATP2A2*, implicated in Mendelian desquamating skin disorders, but did not provide evidence for other previously proposed pathogenic pathways such as bladder development, nociception or inflammation. Pathway analysis detected new associations with "anaphase-promoting complex-dependent catabolic process", the "regulation of MAPK cascade" and "integrin binding". These findings suggest perturbations in biological networks for epithelial integrity and cell cycle progression in IC/BPS pathogenesis, and provide a roadmap for its future investigation.

HUNNER LESION DISEASE

China

[EXPLORING THE THERAPEUTIC POTENTIAL OF PACAP IN HUNNER-TYPE INTERSTITIAL CYSTITIS.](#)

Ke H, Zhu L, Wang Q, Xu K. *World J Urol.* 2025 Jan 4;43(1):60. doi: 10.1007/s00345-024-05429-9. PMID: 39755799.

This study aims to elucidate the role of pituitary adenylate cyclase-activating polypeptide (PACAP) in Hunner-type Interstitial Cystitis (HIC) and evaluate its potential as a therapeutic target. Bladder tissue samples were obtained from HIC patients and normal bladder tissue from bladder cancer patients. PACAP expression was assessed through immunohistochemistry. An in vitro HIC model was established using LPS-induced SV-HUC1 cells. PACAP knockdown was performed using siRNA. The expression of inflammatory markers (IL-6, IL-1 β , TNF- α) and fibrotic markers (fibronectin 1, TGF- β 1, collagen I) was evaluated via qPCR, Western blot, and ELISA. Cell migration and proliferation were analyzed using wound healing and CCK-8 assays. Transcriptomic profiling was conducted to identify differentially expressed genes (DEGs) and explore their functional significance. PACAP expression was significantly elevated in the bladder tissues of HIC patients. LPS stimulation of SV-HUC1 cells induced PACAP expression alongside increased levels of inflammatory cytokines, validating the inflammatory model. PACAP knockdown markedly suppressed IL-6, IL-1 β , and TNF- α expression and attenuated LPS-induced fibrosis by reducing fibronectin 1, TGF- β 1, and collagen I levels. Additionally, PACAP knockdown inhibited LPS-induced cell migration and proliferation, as evidenced by wound healing and CCK-8 assays. Transcriptomic analysis revealed distinct molecular alterations in HIC tissues, including PACAP upregulation, implicating it in HIC pathogenesis. PACAP plays a pivotal role in the inflammatory and fibrotic pathways of HIC. PACAP knockdown alleviates LPS-induced pathological responses, highlighting its potential as a novel therapeutic target. Further research is warranted to investigate PACAP's precise mechanisms in HIC and its translational application in clinical settings.

Korea

[TRANSURETHRAL FULGURATION OF HUNNER LESION WAS EFFECTIVE FOR PRIMARY MANAGEMENT OF PELVIC PAIN IN PATIENTS WITH INTERSTITIAL CYSTITIS: A LONG-TERM FOLLOW-UP STUDY.](#)

Jeong HJ, Kang YJ, Choo MS, Jeong SJ, Oh SJ. *Neurourol Urodyn.* 2025 Apr 3. doi: 10.1002/nau.70051. Epub ahead of print. PMID: 40176747.

This study from Korea aimed to analyze the outcomes of clinical management of patients with interstitial cystitis (IC). The authors retrospectively analyzed the electronic medical records of patients with IC who visited outpatient clinics with pelvic pain between October 2005 and December 2019. Pain was managed with cystoscopic surgery based on transurethral fulguration (TUF) for bladder ulcers. Cystectomy was performed for intractable pelvic pain. Patients were regularly followed and clinical outcomes were analyzed. Of the 275 patients, 240 patients (57 men, 23.7% and 183 women, 76.3%) underwent initial cystoscopic surgery. Overall median follow-up duration was 21.0 months and mean number of TUF was 1.0 (± 0.8). Of these 240 patients, 71 (29.6%) did not require further surgical treatment, whereas 64 (26.7%) required a second TUF for recurrent pelvic pain. The median

recurrence interval was 12.0 (interquartile range: 6.0-25.0) months. Of the 64 patients who received a second TUF, 15 (23.4%) underwent a third TUF after a median of 12.0 (interquartile range: 12.0-32.0) months. Of the 15 patients who received a third TUF, five patients required a fourth TUF because of recurrence of pain. One patient received up to a seventh TUF. Overall, 168 of 240 patients (70.0%) achieved pain control with TUF. Eighteen patients (7.5%) underwent cystectomy (six patients with urinary diversion and 12 patients with cystectomy with bladder replacement). It was concluded that TUF-based cystoscopic surgery is an effective basic treatment for pelvic pain management in patients with IC.

Clinical Trial. Korea

[A SINGLE-CENTER, PHASE 1/2A TRIAL OF HESC-DERIVED MESENCHYMAL STEM CELLS \(MR-MC-01\) FOR SAFETY AND EFFICACY IN INTERSTITIAL CYSTITIS PATIENTS.](#)

Kyung YS, Hong KS, Chung HM, Hyun Shin J, Choo MS, Kim EY, Shin JM, Kang AR, Seo JW, Park J, Park SP. *Stem Cells Transl Med.* 2025 May 19;14(5):szaf018. doi: 10.1093/stcltm/szaf018. PMID: 40387787; PMCID: PMC12087345.

Open access

This study from Korea investigated the safety and efficacy of MR-MC-01, a mesenchymal stem cell therapy derived from human embryonic stem cells, in patients with interstitial cystitis (IC), particularly those with Hunner lesions unresponsive to pentosan polysulfate sodium (PPS). Conducted as a prospective, randomized, double-blind, placebo-controlled phase I/IIa clinical trial, it enrolled 22 patients, with six completing phase I and 16 participating in phase IIa. Phase I tested 2 doses (2.0×10^7 and 5.0×10^7 cells) to determine the maximum tolerated dose (MTD), revealing no dose-limiting toxicities and only mild adverse events such as transient hemorrhage and bladder pain.

In phase IIa, 12 participants received the MTD of 5.0×10^7 cells, and 4 received placebo. Significant reductions in interstitial cystitis questionnaire (ICQ) and pain urgency frequency (PUF) scores were observed in the treatment group. Improvements were noted in nocturnal voiding frequency and Hunner lesion size, with 8 patients showing either a reduction or complete resolution of lesions after 6 months. The global response assessment (GRA) reported moderate to marked improvement in 41.67% of treated patients versus 25% in the placebo group. MR-MC-01 demonstrated no serious drug-related adverse events, highlighting its favorable safety profile. These findings suggest that MR-MC-01 not only alleviates symptoms but also promotes structural recovery in IC, making it a promising treatment option. Further large-scale, long-term studies are warranted to confirm these results and optimize therapeutic protocols

China

[THE EFFICACY OF MICRO-RADIOFREQUENCY THERAPY FOR TREATING NON-HUNNER LESION INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A RETROSPECTIVE COHORT STUDY.](#)

Zhao C, Li P, Wang C, Liu J, Xue L, Zhang Y, Meng X, Tang M. *Int Urogynecol J.* 2025 Jan;36(1):213-220. doi: 10.1007/s00192-024-06008-7. Epub 2024 Dec 16. PMID: 39680106.

The objective was to explore the efficacy of micro-radiofrequency (micro-RF) therapy for treating non-Hunner interstitial cystitis (NHIC). Forty female NHIC patients were enrolled in this retrospective study from December 2021 to December 2023, with 20 receiving intravesical micro-RF therapy and 20 undergoing hydrodistension (HD). The primary evaluation index was the treatment success rate using the Global Response Assessment (GRA) scale. Secondary indexes included changes from baseline in the visual analog scale (VAS) for pain, Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale, and urination parameters. Outcomes were analyzed via t or nonparametric tests. All 40 patients completed the treatment and follow-up; the treatment success rate of the micro-RF group (70%, 14 out of 20) was slightly higher than that of the HD group (50%, 10 out of 20) at 12 weeks post-treatment, with no significant difference (20%, $p = 0.197$). The VAS, ICSI, ICPI, PUF, day-time frequency, urgency episodes, and nocturia significantly decreased in both groups after treatment ($p < 0.05$). Further, the median

decline ranges of VAS (-4.0 vs -3.0; $p = 0.017$; 95% CI -1.45, -0.15) and ICPI (-5.0 vs -4.0; $p = 0.011$; 95% CI -2.02, -0.283) were significantly larger in the micro-RF group. There were no significant differences in ICSI (-6.5 vs -6.0, $p = 0.407$), PUF (-10.0 vs. -8.0; $p = 0.071$), and urgency episodes (-5.5 vs -4.5; $p = 0.570$). The study showed that the short-term overall efficacy of micro-RF therapy was better than hydrodistension, particularly in managing pain, and might be a new alternative treatment option for patients with NHIC.

UROBIOME, URINARY MICROBIOME

Italy

UROBIOME AND INFLAMMATION: A SYSTEMATIC REVIEW ON MICROBIAL IMBALANCES AND DIAGNOSTIC TOOLS FOR URINARY DISORDERS.

Palumbo S, Lucarelli G, Lasorsa F, Damiano R, Autorino R, Aveta A, Spena G, Perdonà S, Russo P, Giulioni C, Cafarelli A, Finati M, Siracusano S, Pandolfo SD. *Urology*. 2025 Apr 3;S0090-4295(25)00305-X. doi: 10.1016/j.urology.2025.03.050. Epub ahead of print. PMID: 40187695.

The purpose of this study from Italy was to synthesize current knowledge on urobiome alterations, innovative diagnostic advancements, and emerging therapeutic strategies targeting urobiome dysbiosis in inflammatory urinary tract disorders, including urinary tract infections, nongonococcal urethritis, and interstitial cystitis. A systematic review was conducted by screening the most important scientific databases. The search included the keywords: (microbiome) OR (microbial) OR (bacteria) OR (bacterial profile) AND (urine) OR (urinary) AND (first-morning sample) OR (first void). Only original studies in English involving human specimens were considered. Of the 760 articles initially identified, a final sample of 20 original studies met the inclusion criteria. Disruptions in the urobiome composition were associated with increased colonization by pathogens such as *Escherichia coli* and *Mycoplasma genitalium*, resulting in inflammation and recurrent urinary conditions. Advanced diagnostic techniques, including metaproteomics, metagenomics, and point-of-care assays such as *Neisseria gonorrhoeae* lateral flow assay, demonstrated enhanced capabilities for rapid pathogen detection and differentiation of inflammatory conditions. Therapeutic interventions targeting urobiome dysbiosis, particularly probiotics (*Lactobacillus rhamnosus*, *L. reuteri*, *L. crispatus*), showed promising efficacy in reducing recurrence and inflammation in clinical trials. It was concluded that urobiome dysbiosis plays a critical role in inflammatory urinary tract disorders. Innovative diagnostic methods and targeted therapeutic approaches, especially probiotics, offer substantial potential to improve patient outcomes. Further research is warranted to refine these strategies and validate their clinical applicability.

Taiwan

DEXTROSE PROLOTHERAPY'S IMPACT ON THE URINARY MICROBIOME IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Chen LK, Chang SJ, Chen CL, Yan JH, Cherng JH, Fan GY, Meng E, Hsu YC. *Int J Med Sci*. 2025 Feb 26;22(7):1516-1527. doi: 10.7150/ijms.104028. PMID: 40093799; PMCID: PMC11905267.

Open access

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic condition affecting millions globally. Dextrose prolotherapy, a minimally invasive and safe treatment, has emerged as a potential way to promote tissue healing in these patients. This study from Taiwan investigates how dextrose prolotherapy impacts the urinary microbiome, aiming to uncover the underlying mechanisms involved in its effectiveness. Midstream urine samples from healthy controls and IC/BPS patients were collected before and after administering intravesical 10% dextrose injections. Microbiome profiling was conducted using 16S rRNA gene sequencing to analyze bacterial composition. Significant differences in urinary microbiome diversity were observed between healthy controls and IC/BPS patients. Proteobacteria, Firmicutes, and Bacteroidota were more abundant in IC/BPS patients.

Importantly, dextrose prolotherapy led to a decrease in harmful bacteria (Subgroup_22, *Chryseolinea*, and *Ureaplasma*) while enriching beneficial species such as *Luteolibacter*, *Lactococcus*, and *L. lactis*, correlating with improved clinical symptoms. It was concluded that dextrose prolotherapy (DP) not only reduces the presence of harmful bacteria but also fosters the growth of beneficial microbes in IC/BPS patients. These findings suggest that the modulation of the urinary microbiome may be a key factor in its therapeutic success.

Review. China

[CONTRIBUTION OF THE MICROBIOME TO INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A MINI REVIEW.](#)

Nandwana D, Zhang Y, Feng N. *Eur Urol Focus*. 2024 Dec;10(6):893-897. doi: 10.1016/j.euf.2025.01.008. Epub 2025 Jan 28. PMID: 39880761.

Open access

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic and debilitating condition characterized by pelvic pain and urinary urgency and frequency with an unclear etiology. Emerging evidence implicates microbiome dysbiosis-disruptions in the microbial communities inhabiting the body-in IC/BPS pathophysiology. This review from China synthesizes the literature on microbial alterations in IC/BPS, including urinary, vaginal, and gastrointestinal microbiota, and their interactions with host inflammatory and metabolic pathways.

PATIENT SUMMARY: The authors reviewed studies from the past 10 years on microbial communities in the body for patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Studies have revealed significant changes in microbial species for these patients, especially in urine. However, research on whether IC/BPS can be treated with interventions to modify microbial communities in the body is still needed.

GUIDELINES AND CLASSIFICATIONS

Canada

[2025 CANADIAN UROLOGICAL ASSOCIATION GUIDELINE: SELECTED TREATMENT RECOMMENDATIONS FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Doiron RC, Tadayon B, Violette PD, Locke J, Andrews M, Nadeau G, Gray G, Cox A. *Can Urol Assoc J*. 2025 Apr;19(4):90-103. doi: 10.5489/cuaj.9182. PMID: 40168684; PMCID: PMC11973989.

Open access

In 2009, the Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) defined interstitial cystitis/bladder pain syndrome (IC/BPS) as “an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than six weeks duration, in the absence of infection or other identifiable causes.” The current American Urological Association (AUA) guideline on IC/BPS adopted the 2009 SUFU definition, and this guideline will do the same.

IUGA, AUGS

[JOINT TERMINOLOGY REPORT: TERMINOLOGY STANDARDIZATION FOR FEMALE BLADDER PAIN SYNDROME.](#)

Developed by the Joint Writing Group of the International Urogynecological Association and the American Urogynecologic Society. *Int Urogynecol J*. 2025 Feb;36(2):265-277. doi: 10.1007/s00192-024-05923-z. Epub 2025 Jan 3. PMID: 39751633.

Female bladder pain syndrome (FBPS), previously known as interstitial cystitis/bladder pain syndrome, is a life-altering and morbid condition that occurs primarily in female patients and can be variable in presentation. Given the absence of pathognomonic symptoms and sensitive diagnostic tests, significant symptomatic overlap with numerous other pelvic conditions (such as pelvic floor tension

myalgia or endometriosis) occurring in women makes diagnosis of FBPS challenging. The frequent co-occurrence of FBPS with other pain conditions and functional somatic syndromes further complicates diagnosis and management. The challenges have limited the progress made in understanding the pathophysiology of the condition and improving approaches to treatment and prevention. Improvement in standardization of the terminology used to describe this unique condition is needed to improve the accuracy of diagnosis and the clinical care for affected patients. Given the variability in presentation and the differing definitions for the condition world-wide, the American Urogynecologic Society and the International Urogynecologic Association convened a joint writing group to standardize terminology around common signs and symptoms of the condition and to clarify the diagnosis as it pertains to female patients with the condition. After careful consideration of a broad range of available data and clinical experiences, consensus opinion recommended adopting the term "FBPS" instead of the misleading "interstitial cystitis" to describe a chronic, intermittent condition of at least 3 months' duration affecting women involving symptoms of pain or discomfort localized to the bladder, often with bladder filling, which are not attributed to other pathology. This term will allow clinicians, researchers, and learners alike to standardize their understanding of FBPS.

DYSPAREUNIA

IMI-Paincare review. Multicentre

[DYSPAREUNIA IS RARELY ASSESSED IN RODENT MODELS OF ENDOMETRIOSIS AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Nunez-Badinez P, Shah R, Demetriou L, De Leo B, Meijlink J, Birch J, Schmidt N, Nagel J, Vincent K. *Reprod Fertil.* 2025 Jan 21;6(1):e230083. doi: 10.1530/RAF-23-0083. PMID: 39704692; PMCID: PMC11770405.

Open access

Dyspareunia, or pain during sex, is a common and often debilitating symptom in individuals with endometriosis and/or interstitial cystitis/bladder pain syndrome (IC/BPS). Despite its significant impact on quality of life, it is frequently overlooked in research. This IMI-Paincare review evaluates how dyspareunia has been addressed in preclinical investigations of these conditions. A systematic search was conducted using Embase from 1998 to 2021, identifying original *in vivo* preclinical studies using female rodents to model (i) endometriosis and (ii) IC/BPS. The search aimed to identify studies that assessed dyspareunia. Study quality and risk of bias were evaluated using a modified CAMARADES checklist. The analysis found 1,286 studies modelling endometriosis and 674 modelling IC/BPS, but only 18 and 1, respectively, measured dyspareunia. The most common method involved vaginal distention in rats, assessed by either behavioural escape responses or visceromotor reflexes of abdominal muscles. Despite the high prevalence of dyspareunia in these conditions, it is rarely measured in preclinical studies. The authors identify a significant gap in the literature and offer succinct recommendations for future translational research to address this important symptom.

Lay summary

Dyspareunia describes pain occurring before, during or after sexual intercourse. This poorly understood symptom is particularly common in people suffering from two chronic pain-related conditions: endometriosis and IC/BPS, severely impacting their quality of life. Therefore, effective treatments addressing painful sex in people with these conditions are needed. To see the benefits of medical research at the patient's bedside, it is important to build from basic science research to preclinical animal studies then to human studies. This study aims to assess the work that has been done so far at the 'preclinical' stage. Developments have been made in the methodology used to investigate this symptom in animals, and a summary of all the key findings may help build a platform to design future studies. Given the urgent need to develop new therapeutic strategies, attention given to painful sex by scientific medical researchers and physicians needs to improve.

CHRONIC PAIN SYNDROMES, PAIN DISORDERS, PELVIC PAIN, PELVIC DISORDERS**IMI-Paincare TRiPP study. Multicentre****SYMPTOM FLARES IN WOMEN WITH CHRONIC PELVIC PAIN: QUESTIONNAIRE STUDY WITHIN A COHORT STUDY (TRANSLATIONAL RESEARCH IN PELVIC PAIN (TRIIPP)).**

Coxon L, Lugt C, Horne AW, Evans E, Abreu-Mendes P, Arendt-Nielsen L, Aziz Q, Becker CM, Birch J, Charrua A, Demetriou L, Ferreira-Gomes J, Hoffman A, Hummelshoj L, Krassowski M, Lunde CE, Meijlink J, Missmer SA, Perro D, Zondervan KT, Sieberg CB, Cruz F, Nagel J, Vincent K. *BJOG*. 2024 Dec;131(13):1832-1840. doi: 10.1111/1471-0528.17915. Epub 2024 Jul 18. PMID: 39030801.

The purpose of this study was to quantify the variation, triggers and impact on quality of life of symptom flares in women with chronic pelvic pain (CPP) in a cross-sectional questionnaire within the Translational Research in Pelvic Pain clinical cohort study. It concerned women with CPP, with subgroups of women with endometriosis (EAP), interstitial cystitis/bladder pain syndrome (BPS), comorbid endometriosis and interstitial cystitis/bladder pain syndrome (EABP), and those with pelvic pain without endometriosis or interstitial cystitis/bladder pain syndrome (PP), a total of 100 participants. They received 100 responses of 104 questionnaires sent. Seventy-six per cent of women with CPP have ever experienced symptom flares of at least one length (short, medium and/or long). Flares are associated with painful and non-painful symptoms. There is large variation for the frequency, duration, symptoms and triggers for flares. Over 60% of participants reported flares as stopping them from doing things they would usually do, >80% reported thinking about symptoms of flares and >80% reported flares being bothersome. Flares are prevalent and clinically very important in CPP. More research is needed to elucidate the mechanisms and characteristics underlying flares. Clinical practice should include an enquiry into flares with the aim of finding strategies to lessen their burden.

IMI-Paincare TRiPP study. Multicentre**EXPLORING THE VALUE OF A WELL-ESTABLISHED CONDITIONED PAIN MODULATION PARADIGM IN WOMEN: A TRANSLATIONAL RESEARCH IN PELVIC PAIN (TRIIPP) STUDY.**

Demetriou L, Perro D, Coxon L, Krassowski M, Lunde CE, Ferreira-Gomes J, Charrua A, Abreu-Mendes P, Arendt-Nielsen L, Aziz Q, Birch J, Garbutt K, Horne A, Hoffman A, Hummelshoj L, Meijlink J, Obendorf M, Pogatzki-Zahn E, Sasamoto N, Terry K, Treede RD, Vitonis A, Vollert J, Rahmioglu N, Becker CM, Cruz F, Missmer SA, Zondervan K, Sieberg CB, Nagel J, Vincent K. *Front Pain Res (Lausanne)*. 2025 Mar 12;6:1439563. doi: 10.3389/fpain.2025.1439563. PMID: 40144516; PMCID: PMC11936887.

Open access

Conditioned pain modulation (CPM) is considered a human proxy for descending inhibitory pain pathways. However, there is wide variation in the CPM response described in the literature and ongoing debate about its utility. Here the authors explored CPM in women with ($n = 59$) and without ($n = 26$) chronic pelvic pain (CPP), aiming to determine the magnitude of effect and factors influencing variability in the CPM response. Using a pressure pain threshold test stimulus and ischaemic pressure cuff conditioning stimulus (CS), they found no significant difference in the mean CPM effect between CPP and control participants. Using a robust statistical method (± 2 standard error of measurement) to further investigate CPM, there was no significant difference in the proportion exhibiting inhibition between controls and CPP participants ($X^2 = 0.003$, $p = 0.96$). Notably, only 23.1% of the healthy controls demonstrated a “true” CPM effect ($n = 4$ inhibitory, $n = 2$ facilitatory). Despite a rich data set, they were unable to identify any single questionnaire, clinical or psychophysical covariate correlating with the CPM effect. Despite using one of the recommended CPM paradigms, they were only able to demonstrate “true” CPM in 23.1% of control participants. Thus, the absence of differences between women with and without chronic pelvic pain must be interpreted with caution. Future studies using different CPM paradigms or larger sample sizes may find different results. Although CPM in chronic pain populations is of major theoretical mechanistic interest, the lack of an established assessment standard led us to question its added value in current clinical research.

USA

CHRONIC PAIN SYNDROMES IN WOMEN.

Muchowski K. *Prim Care.* 2025 Jun;52(2):329-340. doi: 10.1016/j.pop.2025.01.006. Epub 2025 Mar 10. PMID: 40412910.

Chronic pain syndromes like fibromyalgia, chronic pelvic pain, interstitial cystitis/bladder pain syndrome, and chronic migraine cause significant disability and impair quality of life for many women. Evaluation of chronic pain can be complex because women often have overlapping syndromes as well as comorbid anxiety and depression. Multidisciplinary care including nonpharmacologic treatments like exercise and mindfulness-based therapies as well as pharmacologic medications improve function and decrease pain. With their wide knowledge base, primary care providers are well-equipped to primarily manage chronic pain in their women patients.

USA

COMMON PAIN DISORDERS IN WOMEN: DIAGNOSIS, TREATMENT, AND REHABILITATION MANAGEMENT.

Shustorovich A, Bova M, Delavaux LV. *Phys Med Rehabil Clin N Am.* 2025 May;36(2):297-310. doi: 10.1016/j.pmr.2024.11.011. Epub 2024 Dec 28. PMID: 40210363.

There is well-established epidemiologic evidence demonstrating variance in the pain disorders affecting women compared with men, although limited conclusive evidence exists regarding the pathophysiologic mechanisms to account for this difference. Six of the most common pain disorders affecting women include migraine headache, fibromyalgia, endometriosis, interstitial cystitis, temporomandibular disorders, and osteoarthritis. The sex-specific prevalence, risk factors, triggers, presentations, and treatments of these disorders are critical for physicians to appreciate and understand to provide the highest standard of care when treating these common pain conditions.

Book. StatPearls

CHRONIC PELVIC PAIN.

Dydyk AM, Singh C, Gupta N. 2025 May 2. In: *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.* PMID: 32119472.

Open access

Chronic pelvic pain is a persistent or recurrent pain in the lower abdomen or pelvis lasting at least 3 to 6 months. This condition primarily affects women but can also occur in men. Chronic pelvic pain is often associated with irritable bowel syndrome, interstitial cystitis, pelvic inflammatory disease, and mood disorders. This condition also shares features with other chronic pain syndromes, including central sensitization, where the nervous system becomes overly sensitive to pain stimuli. Diagnosis is primarily clinical, based on history and physical examination, including a digital rectal exam and assessment for cutaneous allodynia. Imaging and laboratory tests may help identify contributing comorbidities, although they are often inconclusive. Prognosis varies widely, depending on the cause, treatment response, and comorbidities.

USA

CHRONIC PELVIC PAIN IN WOMEN: EVALUATION AND TREATMENT.

Meisenheimer ES, Carnevale AM. *Am Fam Physician.* 2025 Mar;111(3):218-229. PMID: 40106288.

Chronic pelvic pain affects up to 26% of individuals with female anatomy and is defined as at least 6 months of pain that is perceived to originate in the pelvis. Chronic pelvic pain is highly correlated with psychosocial comorbidities, including depression, anxiety, and history of abuse. Although common causes include irritable bowel syndrome, bladder pain syndrome (interstitial cystitis), pelvic floor dysfunction, and endometriosis, chronic pelvic pain is most often the result of multiple coexisting pain conditions and central nervous system hypersensitivity. Evaluation requires a biopsychosocial approach, beginning with a complete history and physical examination to ensure an accurate and

timely diagnosis. Diagnostic laboratory and imaging tests are of limited utility and should be tailored to investigate presenting symptoms and examination findings. When a single etiology is identified, treatment should follow disease-specific guidelines; otherwise, the management of undifferentiated chronic pelvic pain should follow an interdisciplinary approach to improve function and quality of life. Multimodal treatment includes pain education, self-care, behavioral therapy, physical therapy, and pharmacotherapy, with limited indications for surgical interventions. Regular follow-up to review progress is necessary. Clinicians should have a low threshold for referral to interdisciplinary pain management or other subspecialties when improvement is not seen.

USA

[PELVIC VENOUS DISORDERS ARE ASSOCIATED WITH AN EARLIER AGE-OF-ONSET IN FEMALES WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

El Haraki AS, Ritts R, Namugosa M, Regan J, Daniel B, Evans R, Walker SJ. Int Urogynecol J. 2025 Mar 1. doi: 10.1007/s00192-025-06088-z. Epub ahead of print. PMID: 40025237.

Pelvic venous disorders (PVDs) are a group of inter-related pathological diagnoses that can present with a range of symptoms including pelvic and urinary symptoms similar to those seen in interstitial cystitis/bladder pain syndrome (IC/BPS). The relationship between PVDs and IC/BPS in humans has yet to be evaluated. This study's objectives are to determine the prevalence of PVD in patients with IC/BPS and to identify associated characteristics. Charts from the authors' study on patients with IC/BPS undergoing hydrodistension (HOD) were screened for those with an MRI or CT scan of the abdomen/pelvis. Imaging findings suggestive of PVD were noted. Information regarding anesthetic bladder capacity (BC), Hunner lesion (HL) status, results for validated IC/BPS symptoms, and patient reports of comorbid non-urolological associated syndromes (NUAS) known to co-occur with IC/BPS were collected. A total of 133 patients with IC/BPS had the appropriate studies for a diagnosis of PVD, of which 64 (48.1%) were positive. PVD-positive patients were younger at IC/BPS diagnosis (35.36 ± 12.47 vs 42.32 ± 14.53 ; $p = 0.004$), younger at most recent HOD (45.59 ± 13.18 vs 53.32 ± 13.71 ; $p = 0.001$), and had a lower BMI (27.88 ± 7.35 vs 32.18 ± 9.29 ; $p = 0.004$). No significant differences were noted in age at earliest HOD, smoking status, average BC, HL status, total number of HOD, total NUAS, or any of multiple reported comorbidities. Additionally, none of the average IC/BPS symptom scores were significantly different. Imaging findings suggestive of PVD are common in patients with IC/BPS and may be associated with an earlier onset of disease.

Spain, USA

[DOES MUSCLE PAIN INDUCE ALTERATIONS IN THE PELVIC FLOOR MOTOR UNIT ACTIVITY PROPERTIES IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME? A HIGH-DENSITY SEMG-BASED STUDY.](#)

Albaladejo-Belmonte M, Houston M, Dias N, Spitznagle T, Lai H, Zhang Y, Garcia-Casado J. Sensors (Basel). 2024 Nov 21;24(23):7417. doi: 10.3390/s24237417. PMID: 39685954; PMCID: PMC11644557.

Open access

Several studies have shown interstitial cystitis/bladder pain syndrome (IC/BPS), a chronic condition that poses challenges in both diagnosis and treatment, is associated with painful pelvic floor muscles (PFM) and altered neural drive to these muscles. However, its pathophysiology could also involve other alterations in the electrical activity of PFM motor units (MUs). Studying these alterations could provide novel insights into IC/BPS and help its clinical management. This study aimed to characterize PFM activity at the MU level in women with IC/BPS and pelvic floor myalgia using high-density surface electromyography (HD-sEMG). Signals were recorded from 15 patients and 15 healthy controls and decomposed into MU action potential (MUAP) spike trains. MUAP amplitude, firing rate, and magnitude-squared coherence between spike trains were compared across groups. Results showed that MUAPs had significantly lower amplitudes during contractions on the patients' left PFM, and delta-band coherence was significantly higher at rest on their right PFM compared to controls. These findings suggest altered PFM tissue and neuromuscular control in women with IC/BPS and pelvic floor

myalgia. The authors conclude that their results demonstrate that HD-sEMG can provide novel insights into IC/BPS-related PFM dysfunction and biomarkers that help identify subgroups of IC/BPS patients, which may aid their diagnosis and treatment.

Taiwan

PELVIC FLOOR MUSCLE PAIN IS ASSOCIATED WITH HIGHER SYMPTOM SCORES AND BLADDER PAIN PERCEPTION IN WOMEN WITH INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME.

Yu WR, Jhang JF, Jiang YH, Kuo HC. *World J Urol.* 2024 Dec 3;43(1):9. doi: 10.1007/s00345-024-05366-7. PMID: 39625572.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous, multifactorial disease with a high prevalence of somatic symptoms. A high percentage of women with IC/BPS also experience pelvic floor muscle pain (PFMP). This study investigated the association between PFMP and clinical characteristics in patients with IC/BPS and the extent and severity of PFMP in women with IC and BPS. Demographics, sexual condition, IC symptom index (ICSI), IC problem index (ICPI), and Beck anxiety inventory and depression inventory were assessed. The objective assessment items included bladder wall thickness in computed tomography, urodynamic parameters, maximum bladder capacity (MBC) and glomerulation grade after cystoscopic hydrodistention, urine inflammatory proteins, and oxidative stress biomarkers. A total of 9 women with IC and 83 with BPS were enrolled. A total of 85.8% of patients had PFMP. Patients with PFMP had higher rates of dyspareunia ($p = 0.005$), lack of sexual activity ($p < 0.001$), more comorbidities ($p = 0.039$), pain-predominant IC/BPS phenotypes ($p = 0.04$), higher IC symptoms (ICSI, $p = 0.003$; ICPI, $p < 0.001$), and higher levels of urinary biomarker MIP-1 β ($p = 0.004$) than patients without PFMP. However, no significant correlation was found between PFMP and the bladder wall thickness, urodynamic parameters, MBC, or glomerulation grade. PFMP is present in a high percentage of patients with IC and BPS and associated with higher IC/BPS symptom score and dyspareunia, but not with MBC or glomerulation grade in patients with BPS.

VISCERAL HYPERSENSITIVITY

Preprint. USA

AN INTERORGAN NEUROIMMUNE CIRCUIT PROMOTES VISCERAL HYPERSENSITIVITY.

Kim B, Wang Z, Meng X, Xie Z, Hor CC, Zhang W, Li X, Song K, Auyeung K, Iriki H, Shibuya R, Zhang W, Major J, Zamidar L, Yassky D, Seker O, Wollam J, Villescay C, Vest A, Srinivasan S, Solomon M, Chang R, Naik S, Kubo M, Viswanath V, Xu S, Dong X, Artis D, Duan B, Hu H. *Res Sq [Preprint].* 2025 Mar 17;rs.3.rs-6221928. doi: 10.21203/rs.3.rs-6221928/v1. PMID: 40166016; PMCID: PMC11957215.

Open access

Visceral pain disorders such as interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS) often manifest concurrently in the bladder and colon. Yet, the mechanistic basis of such comorbidities and the transmission of neural hypersensitivity across organ systems has remained a mystery. Here, the authors identify a mast cell-sensory neuron circuit that initiates bladder inflammation and simultaneously propagates neural hypersensitivity to the colon in a murine model of IC/BPS. They unveil anatomic heterogeneity of mast cells in relation to nociceptors in the bladder and their critical dependence on Mas-related G protein-coupled receptor B2 (MrgprB2) to promote visceral hypersensitivity. Employing retrograde neuronal tracing, in vivo calcium imaging, and intersectional genetics, they uncover a population of polyorgan sensory neurons that simultaneously innervate multiple organs and exhibit functional convergence. Importantly, using humanized mice, they demonstrate that pharmacological blockade of mast cell-expressed MRGPRX2, the human ortholog of MrgprB2, attenuates both bladder pathology and colonic hypersensitivity. Their studies reveal evolutionarily conserved neuroimmune mechanisms by which immune cells can directly convey signals from one organ to another through sensory neurons, in the absence of physical proximity, representing a new therapeutic paradigm.

ASSOCIATED DISORDERS - ENDOMETRIOSIS

Systematic review. Italy

THE EVIL TWINS OF CHRONIC PELVIC PAIN SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS ON INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME AND ENDOMETRIOSIS.

Inzoli A, Barba M, Costa C, Carazita V, Cola A, Fantauzzi M, Passoni P, Polizzi S, Frigerio M. *Healthcare (Basel)*. 2024 Nov 29;12(23):2403. doi: 10.3390/healthcare12232403. PMID: 39685025; PMCID: PMC11641437.

Open access

Chronic pelvic pain is a debilitating condition affecting quality of life. Endometriosis is one of the leading causes of CPP, but recent studies highlighted the role of interstitial cystitis/bladder pain syndrome (IC/PBS) in causing CPP. Only some studies addressed the coexistence of these two conditions, which seems more frequent than what is supposed, leading to diagnostic delays and unnecessary surgeries. This systematic review aimed to evaluate the estimate of the prevalence of the comorbidity of endometriosis and IC/PBS. The authors performed a systematic review of the literature indexed on PubMed, Scopus, ISI Web of Science, and Cochrane using a combination of keywords and text words represented by “painful bladder syndrome”, “endometriosis”, “interstitial cystitis”, and “bladder pain syndrome”. They performed a meta-analysis of the results. Results: The meta-analysis shows that the coexistence of endometriosis and IC/PBS in women with CPP ranged from 15.5% to 78.3%, which is higher than the prevalence of IC/PBS in the general population. They found that prevalence data about the coexistence of endometriosis and IC/PBS are highly heterogeneous, probably due to the paucity of available data. However, in cases of endometriosis unresponsive to treatment, other reasons for CPP (such as IC/PBS) need to be ruled out.

ASSOCIATED DISORDERS – AUTOIMMUNE DISEASES

Mendelian randomization. China

CAUSAL ROLE OF COMMON AUTOIMMUNE DISEASES IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: MENDELIAN RANDOMIZATION (MR) STUDY.

Wu L, Wang T, Bai M, Chen J, Ning J, Jin Q, Ma Y, Xu X, Hao Z, Yang R. *Medicine (Baltimore)*. 2025 Feb 21;104(8):e41484. doi: 10.1097/MD.00000000000041484. PMID: 39993091; PMCID: PMC11857018.

Open access

Observational studies suggest that interstitial cystitis/bladder pain syndrome (IC/BPS) indices might be influenced by autoimmune diseases (AIDs), though it is difficult to infer causal relationships based on observational data due to risk of residual confounding. The authors from China utilized Mendelian randomization (MR) to explore causal relevance of multiple AIDs on IC/BPS. Their bidirectional two-sample MR analysis was based on summary statistics from the most recent and comprehensive genome-wide association studies. This particular approach was used to delve into the relationships of cause and effect between IC/BPS and a group of 14 AIDs. They examined a range of AIDs such as ulcerative colitis, Crohn disease, celiac disease, Sjogren syndrome, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, primary biliary cirrhosis, psoriasis, asthma, eczema, ankylosing spondylitis, type 1 diabetes, and primary sclerosing cholangitis. Their primary analytical approach involved using the inverse variance weighting method to establish causal relationships across various AIDs and IC/BPS conditions. Furthermore, they carried out additional examinations, such as utilizing the weighted median technique, MR-Egger regression, MR-PRESSO, and evaluating reverse causality, in order to strengthen the dependability of our results. Their findings indicate a strong association between genetically predicted asthma and the risk of developing IC/BPS with a weighted odds ratio of 1.692, a confidence interval of 1.147 to 2.496, and $P = .008$, while the Cochran Q test $P = .589$ and the MR-Egger intercept test $P = .554$, MR-PRESSO global test $P = .600$. No evidence was found for causal relationships between other AIDs and IC/BPS. Individuals with asthma show an increased vulnerability to IC/BPS according to our findings. More randomized controlled trials are

necessary to validate these results. These results underscore the importance for healthcare providers to assess the potential risk in asthma patients, offering a novel genetic perspective on studying interstitial cystitis.

ASSOCIATED DISORDERS – VULVODYNIA, UROGENITAL

Sweden, USA

THE ASSOCIATION BETWEEN UROLOGICAL CONDITIONS ACROSS THE LIFE COURSE AND PROVOKED VULVODYNIA.

Harlow BL, Mühlrad H, Yan J, Lu D, Bohm-Starke N. *J Womens Health (Larchmt)*. 2025 Feb 17. doi: 10.1089/jwh.2024.0933. Epub ahead of print. PMID: 39957362.

Vulvodynia is a condition characterized by chronic pain and discomfort in the vulvar region often accompanied with physical and psychological comorbidities. Interstitial cystitis (IC)/bladder pain syndrome (BPS), a chronic condition characterized by bladder pain and urinary urgency, has repeatedly been shown to comorbidly be present in a large proportion of women with vulvodynia. However, recent studies have shown that women with vulvodynia experienced additional bladder-related symptoms beyond that of just IC/BPS. Using Swedish National Registry data, the authors assessed the association between urological symptoms in the presence and absence of IC/BPS in women with vulvodynia/vaginismus relative to women with no vulvar pain history. After adjustment for birth year, parity, education, and residential location, women with vulvar pain had a 2.2-fold greater risk of cystitis or urethritis as expected (95% confidence interval [CI] 1.9-2.6). However, when women with cystitis codes were excluded, those with urethra disorders or other urinary symptoms codes were 1.9 times more likely to be vulvar pain cases (95% CI 1.7-2.1). These findings support the belief that vulvodynia is not limited to being comorbid with IC/BPS but may also likely be associated with a wide range of urological disorders.

Japan

COMORBID BLADDER PAIN SYNDROME AND VULVODYNIA - A CROSS-SECTIONAL ANALYSIS OF THE UNICORN-4 STUDY.

Okui N. *BMC Womens Health*. 2025 Feb 19;25(1):72. doi: 10.1186/s12905-025-03602-9. PMID: 39972456; PMCID: PMC11837444.

Open access

Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) and vulvodynia often coexist, exacerbating patient symptoms and complicating the diagnosis and treatment. This study from Japan aimed to identify distinct subtypes within a BPS/IC and vulvodynia cohort and evaluate their symptom profiles, psychological characteristics, and sexual function indicators. A cross-sectional analysis was conducted on 150 female patients diagnosed with BPS/IC and vulvodynia. The patients completed validated questionnaires assessing bladder symptoms, psychological distress (PHQ-9 and GAD-7), and sexual function (FSFI and FSDS-R). Hierarchical and K-means clustering were used to identify patient subgroups. Three distinct clusters were identified. Cluster 1 exhibited moderate bladder-specific symptoms and psychological distress. Cluster 2 had severe bladder symptoms and the highest psychological distress. Cluster 3, defined as the vulvodynia-predominant subtype, featured severe vulvodynia, significant psychological distress, and minimal bladder symptoms, aligning with a non-urologic pelvic pain phenotype. Sexual function was significantly impaired across all clusters, with Cluster 3 showing the most severe dysfunction. This study highlights the heterogeneity within BPS/IC and vulvodynia populations. The identification of a vulvodynia-predominant subtype and non-urologic pelvic pain phenotype emphasizes the need for personalized treatment strategies addressing both physical and psychological factors, particularly sexual dysfunction and psychological distress.

PATIENT EXPERIENCES SOCIAL MEDIA - UTI

USA

INTERSTITIAL CYSTITIS CHATTER: A QUALITATIVE EVALUATION OF BLADDER INSTILLATION ONLINE.

Wong R, Licari LC, Bologna E, Adelstein S. *Urology*. 2025 Jan;195:23-27. doi: 10.1016/j.urology.2024.10.051. Epub 2024 Oct 22. PMID: 39447878.

This study qualitatively assessed the perception and experiences of bladder instillation for interstitial cystitis among women on Reddit, a widely used anonymous social media platform. "r/interstitialcystitis," a Subreddit with >27,000 subscribers, was queried for bladder instillation among women with interstitial cystitis in November 2023. Posts were analyzed qualitatively by 3 independent researchers. Grounded theory principles were applied to derive preliminary themes. These themes were then used to develop emergent themes. Sixty-three posts with 637 responses published between 2022-2023 were analyzed. Qualitative analysis yielded 4 themes: (1) IC/BPS anxiety and depression, (2) limited treatment options for IC/BPS pain, (3) exhausting all IC/BPS treatment options before bladder instillation, (4) bladder instillation ineffectiveness for IC/BPS pain. Three emergent concepts were derived: (1) a prevailing sense of desperation for relief among women with IC/BPS, (2) women are fearful and apprehensive about bladder instillation, (3) a perception of bladder instillation as the final recourse for women suffering from IC/BPS. This study represents the first evaluation of bladder instillation as a therapeutic from a social media community focused exclusively on IC/BPS. These results capture patient's experiences with nonurological associated syndromes and indicate a role for physicians to address mental health concerns in patients with IC/BPS, in addition to opportunities to improve patient education on bladder instillations.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

Systematic review & meta-analysis. Korea

PENTOSAN POLYSULFATE SODIUM AND MACULOPATHY IN PATIENTS WITH INTERSTITIAL CYSTITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Lee J, Kim YJ, Lee K, Kim YK, Rhee TG, Shim SR, Kim JH. *World J Mens Health*. 2025 Feb 27. doi: 10.5534/wjmh.240295. Epub ahead of print. PMID: 40034025.

Open access

Pentosan polysulfate sodium (PPS) is the only pharmacological intervention approved by the US Food and Drug Administration for treating interstitial cystitis (IC) to date. However, PPS may induce an adverse event, maculopathy, which can be a significant challenge. The purpose of this study was to determine the risk of PPS-induced maculopathy in patients with IC. PubMed and Embase were systematically searched through July 2024. Two authors also independently and manually searched all relevant studies. The authors included national level cohort studies using healthcare claim big data or real-world data with the following criteria: (1) patients diagnosed with IC; (2) interventions included PPS as an active treatment; (3) comparisons were specified as non-PPS interventions; and (4) the primary outcome of interest was the risk of maculopathy. The pairwise meta-analysis was performed to compare the PPS treatment group with control used in IC. The primary outcome measure was the hazard ratio (HR), odds ratio (OR), and proportional report ratio (PRR) of maculopathy after receiving the PPS treatment, as compared to non-PPS interventions. A comprehensive literature search was conducted and identified 6 studies with 411,098 patients. The pooled risk for maculopathy due to PPS in patients with IC was significant (HR, 1.678; 95% confidence interval [95% CI], 1.066–2.642). The heterogeneity test produced a Higgins' *I*-squared statistic, which was 83.6%. In the subgroup analysis of follow-up period of less than 5 years (HR, 1.285; 95% CI, 1.139–1.449) and more (HR, 1.341; 95% CI, 1.307–1.375) were statistically significant, indicating that the patients with IC who had a long-term PPS treatment were more likely to have maculopathy than the control groups. This is the first study to investigate the relationship between PPS and its association with the risk of maculopathy in patients with IC through a systematic review and meta-analysis.

Infodemiology Study. USA

SENTIMENTS OF INDIVIDUALS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME TOWARD PENTOSAN POLYSULFATE SODIUM: INFODEMIOLOGY STUDY.

Hswen Y, Qin Q, Smith P, Swierczynski A, Bauer S, Ladson E, Garrett AL, Brownstein CA. *JMIR Form Res.* 2025 Jan 17;9:e54209. doi: 10.2196/54209. PMID: 39864816; PMCID: PMC11769693.

Open access

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a multifactorial, chronic syndrome involving urinary frequency, urgency, and bladder discomfort. These IC/BPS symptoms can significantly impact individuals' quality of life, affecting their mental, physical, sexual, and financial well-being. Individuals sometimes rely on peer-to-peer support to understand the disease and find methods of alleviating symptoms. The only US Food and Drug Administration–approved medication to treat IC/BPS is pentosan polysulfate sodium (PPS). However, ocular pigmentary maculopathy has been described in some individuals, with greater severity associated with prolonged PPS exposure. While prior research has separately assessed the benefits and side effects of PPS, this study sought to identify (1) sentiments of individuals with IC/BPS toward PPS and (2) topics discussed by individuals with IC/BPS in conjunction with PPS through use of an internet peer-to-peer forum. Data were collected from Inspire—an anonymous web-based health community where individuals gather by condition to find support and information. Sentiment analysis and percentages of negative, positive, and neutral sentiment for PPS discussions encompassing each topic was conducted using VADER (Valence Aware Dictionary for Sentiment Reasoning). Topic modeling was conducted using latent Dirichlet allocation. Words with the highest probability were ranked to categorize each topic, and authors manually investigated and labeled discussions. There were 354 forum posts related to PPS. Topic modeling with latent Dirichlet allocation revealed 5 topic categories: “ineffectiveness or discontinued use,” “alternative treatments,” “personal treatment suggestions based on experience,” “severe side effects,” and “risk of long-term use.” Topics related to “severe side effects” and “risk of long-term use” garnered less discussion, with the former also having the lowest positive sentiment (4.28, 14.29%). The topic “ineffectiveness or discontinued use” was most frequently discussed. This topic also had the highest percentage of negative posts (52/152, 34.21%). However, the average compound score was within the neutral compound score range (−0.094, SD 0.625). In addition, forum data highlighted individuals' acknowledgment of the efficacy of PPS in improving their quality of life, with statements such as “saved my sanity” being representative. The overall compound individuals' sentiment toward PPS was −0.083, split across 32.49% (115/354) negative, 22.03% (78/354) positive, and 45.48% (161/354) neutral sentiment categories. The overall authentic sentiment toward PPS is broad but balances to neutral. This neutral sentiment suggests that while some individuals express concerns about the side effects and long-term risks associated with PPS, others appreciate its positive impact on their quality of life. This research confirms that individuals with IC/BPS actively engage with health forums like Inspire to seek information, share their experiences, and explore different treatment options. As IC/BPS remains a complex syndrome, this study highlights the value of patient-led discussions in informing treatment decisions. Furthermore, these findings suggest that health care providers might benefit from considering the insights shared on peer-to-peer forums to better understand individual preferences, concerns, and expectations.

Retrospective study. USA

RETROSPECTIVE STUDY OF INCIDENCE/PREVALENCE OF PIGMENTARY MACULOPATHY AND RETINOPATHY IN PATIENTS RECEIVING PENTOSAN POLYSULFATE SODIUM.

Yuan Z, Vaughan S, Jeffcoat C, Hu P, Yuson R, Fife D, Borkar D. *PLoS One.* 2025 Jan 9;20(1):e0313497. doi: 10.1371/journal.pone.0313497. PMID: 39787060; PMCID: PMC11717312.

Open access

This study evaluated prevalence and incidence rates of pigmentary maculopathy and retinopathy (PM/PR), and visual acuity (VA) changes in patients exposed to pentosan polysulfate sodium (PPS) and in patients with interstitial cystitis (IC) not exposed to PPS. This is a retrospective cohort study (January 2015–March 2021) which included adult de-identified patients from the American Academy of

Ophthalmology IRIS® Registry (Intelligent Research in Sight) and Komodo Health database. Three patient cohorts were identified: two PPS-exposed patient cohorts, and Non-PPS-exposed IC patient cohort. Key study outcomes included PM/PR/Any (defined based on prior literature regardless of PPS exposure) and PM/PR/PPS (further defined by an algorithm that was based on clinical notes and other protocol-prespecified criteria in PPS-exposed patients), and VA changes in each respective cohort. Prevalence of PM/PR/Any was relatively common in patients prior to PPS exposure (4.16%–8.43%). Incidence rate of PM/PR/PPS was uncommon in both PPS-exposed cohorts (0.13–0.15 per 100 person-years). Crude incidence rates of PM/PR/Any (based on ITT analysis) varied slightly across 3 study cohorts (2.13–2.81 and 2.38 per 100-person-years for PPS-exposed cohorts and Non-PPS-exposed IC cohort, respectively). Across all 3 study cohorts, patients with PM/PR/Any appeared to have approximately 2-fold higher proportion of 3 lines of VA worsening than those without PM/PR/Any. It was concluded that prevalence of PM/PR was common in patients prior to PPS exposure. Incidence of PM/PR/PPS that may be associated with PPS exposure was relatively uncommon. Crude incidence rates of PM/PR appeared similar across all patient cohorts regardless of PPS exposure.

Review. USA

[PENTOSAN POLYSULFATE SODIUM MACULOPATHY: FINAL ANALYSIS OF A PROSPECTIVE COHORT, UPDATED REVIEW, AND ASSOCIATION WITH INFLAMMATORY BOWEL DISEASE.](#)

Santina A, Feo A, Bousquet E, Velaga SB, Abraham N, Fogel-Levin M, Romero-Morales V, Somisetty S, Wong A, Lu A, Nittala M, Chhablani J, Voichanski S, Au A, Sadda S, Sarraf D. Surv Ophthalmol. 2025 May-Jun;70(3):583-592. doi: 10.1016/j.survophthal.2024.12.002. Epub 2024 Dec 12. PMID: 39674406. Pentosan polysulfate sodium (PPS) maculopathy is a recently described condition of macular toxicity. The authors report the prevalence (15 %), the clinical characteristics, and the multimodal imaging (MMI) features of PPS maculopathy based on a final prospective analysis of a cohort of 154 subjects and highlight the association with inflammatory bowel disease (IBD). In addition, they summarize the most recent and relevant literature on PPS maculopathy. This study and other recent analyses provide solid evidence of the toxic effects of PPS on the retina and choroid and refute the concept that the maculopathy is an association of the underlying disease, interstitial cystitis. Moreover, this study and others raise a major concern that PPS may also be toxic to the bowel. Vigilant surveillance of patients receiving this potentially harmful drug is critical. They review the recommended screening guidelines, the pathophysiology and MMI spectrum of disease, the differential diagnosis including MMI clues to an accurate diagnosis, and the progression of retinopathy that can take place despite discontinuation of the drug, emphasizing the critical importance of early detection of toxicity.

Case Report. Israel, USA.

[POTENTIAL NEW PHENOTYPIC PRESENTATION OF PENTOSAN POLYSULFATE SODIUM MACULOPATHY.](#)

Ghiam S, Pirouz A, Adrean SD. J Vitreoretin Dis. 2024 Aug 22:24741264241271697. doi: 10.1177/24741264241271697. Epub ahead of print. PMID: 39554634; PMCID: PMC11562475.

Open access

The purpose of this study was to describe a potential new phenotypic presentation of pentosan polysulfate sodium maculopathy. An observational case was analyzed. A 55-year-old woman with interstitial cystitis who was treated with oral pentosan polysulfate sodium for 10 years presented with reports of decreased vision and metamorphopsia that had worsened over the past 3 months. On fundusoscopic examination, there were bilateral areas of retinal pigment epithelial hyperplasia inferior to the fovea with a surrounding halo of drusenoid material. Neurosensory retinal detachments with drusenoid deposition at the edges of the detachment were seen on spectral-domain optical coherence tomography. These findings could be mistaken for age-related macular degeneration, central serous retinopathy, Best disease, or adult vitelliform dystrophy. In this case, a review of pertinent medications assisted in making the diagnosis of toxic maculopathy. Proper diagnosis and prompt

discontinuation of the inciting medication are necessary to avoid the risk for potentially irreversible retinal damage and vision loss.

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