

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 - November 2023

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 These are preliminary reports of work that have not been certified by peer review.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

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

STATPEARLS (BOOKS) <https://www.ncbi.nlm.nih.gov/books/NBK430685/>

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME – latest update

Yizhe Lim, Stephen W. Leslie, Seanan O'Rourke.

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

2023 Nov 12. PMID: 34033350 Bookshelf ID: NBK570588

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complex and chronic medical condition that primarily affects the urinary bladder, leading to a range of distressing symptoms. This disorder is characterized by the inflammation of the bladder's lining, resulting in recurring and often severe discomfort, urgency, and frequency of urination. IC/BPS remains challenging to diagnose and manage, as its precise causes are not fully understood, and it can mimic other urinary tract disorders. Individuals living with IC/BPS face a significant impact on their quality of life, as the symptoms can be disruptive and emotionally taxing. Patients' responses to treatment are highly variable. This activity reviews the approach, investigation, and management of IC/BPS and highlights the role of the interprofessional team in evaluating and treating this challenging disorder.

Objectives:

- Identify the multifaceted etiology of interstitial cystitis/bladder pain syndrome.
- Implement evidence-based treatment plans, integrating the latest therapeutic options and guidelines, tailored to patients' specific needs and severity of interstitial cystitis/bladder pain syndrome.

- Apply a multidisciplinary approach to assessing the prognosis of interstitial cystitis/bladder pain syndrome.
- Collaborate with an interprofessional team to create a coordinated and comprehensive care plan for patients with interstitial cystitis/bladder pain syndrome.

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

CYSTOSCOPY, AN INDISPENSABLE TOOL FOR THE DIAGNOSIS AND PROGNOSIS OF BLADDER PAIN SYNDROME, TAKES NOMOGRAMS FOR PREDICTING RECURRENCE

Lin Zhu, Hanwei Ke, Qi Wang, Kexin Xu. World J Urol. 2023 Sep;41(9):2451-2458. doi: 10.1007/s00345-023-04517-6. Epub 2023 Jul 15. PMID: 37453960.

This study from Beijing, China aimed to illustrate the importance of cystoscopy for the diagnosis and prognosis of bladder pain syndrome (BPS) or interstitial cystitis (IC). The authors designed a 4-year prospective follow-up study. Patients who underwent cystoscopy between May 2011 and July 2021 with a diagnosis of BPS/IC before surgery or positive cystoscopic findings during initial surgery at Peking University People's Hospital were enrolled. Data related to symptom recurrence were obtained through clinic visits and telephone follow-up. They compared the differences in clinical features of BPS/IC subtypes differentiated by cystoscopy and first created clinical predictive nomograms for BPS/IC. A total of 141 patients were included. There was an 8.51% chance of BPS/IC being misdiagnosed as other diseases or other diseases being misdiagnosed as BPS/IC without cystoscopy. Patients with HIC had higher pain scores and ICPI, higher residual urine volume, lower first-sense-to-void, and maximum cystometric bladder capacities than NHIC. Nomogram Models showed that patients who with higher ICPI, ICSI and lower AMBC have a greater recurrence probability, and lesions in the trigone may indicate a greater likelihood of recurrence than lesions in other bladder walls. Timely detection of bladder cancer and other diseases using cystoscopy can avoid poor treatment effects. BPS/IC subtypes can be classified according to mucosal changes under cystoscopy. Lesions in the bladder triangle can indicate a higher recurrence risk, which is important in follow-up treatment. The authors strongly recommend that cystoscopy should be included in the international BPS/IC diagnostic criteria.

ROLE OF CYSTOSCOPY AS PRIMARY INITIAL INVESTIGATION IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Angadjot Singh, Shivam Priyadarshi, Somendra Bansal, Sanyam Nandwani. Urologia. 2023 Sep 29:3915603231203431. doi: 10.1177/03915603231203431. Online ahead of print. PMID: 37776017.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic painful bladder condition characterized by pelvic pain and urinary symptoms without another identifiable cause. Cystoscopy as primary initial investigation for IC/BPS has not been accepted yet and needs more studies to definitely conclude. The authors from India aimed to assess cystoscopy findings in patients of interstitial cystitis/bladder pain syndrome and to prove role of cystoscopy as primary initial investigation for interstitial cystitis/bladder pain syndrome. Their prospective observational study included 35 female patients aged 18-69 years presenting to the Urology OPD at SMS Hospital with suprapubic or pelvic pain for 6 months, bladder pain that worsens with bladder filling and reduced with voiding, dysuria, urinary frequency and urgency, nocturia, dyspareunia. Those with history of bladder capacity more than 350 ml, duration of symptoms less than 6 months, daytime frequency less than eight times per day, diagnosis of bacterial cystitis or prostatitis, bladder or ureteral calculi, active genital herpes, any existing urological malignancy, radiation cystitis were excluded from the study. They were then subjected to cystoscopy and the findings of the cystoscopy were analyzed. Out of the 35 patients, 11 (31.43%) had a normal cystoscopy. Of the 24 patients (68.57%) who had a positive cystoscopy, cystoscopy in seven patients (20.0%) revealed an ulcer. All these seven patients underwent fulguration. In the remaining 17 patients the abnormal findings were petechiae, large submucosal bleed. The sensitivity of cystoscopy in detecting the ulcerative type of Interstitial cystitis

was found to be 20.0%. The authors report that cystoscopy, if employed in initial investigation, can help early detection of ulcerative variety of IC/BPS and can act as therapeutic modality by using fulguration plus hydrodistension. Larger comparative studies are needed for diagnostic/therapeutic value of cystoscopy.

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Angadot Singh, Shivam Priyadarshi, Somendra Bansal, Sanyam Nandwani. Urologia. 2023 Sep 29:3915603231203431. doi: 10.1177/03915603231203431. Online ahead of print. PMID: 37776017.

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

Charlotte van Ginkel, Robert E Hurst, Dick Janssen. Curr Opin Urol. 2023 Nov 3. doi: 10.1097/MOU.0000000000001147. Online ahead of print. PMID: 37933666.

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

STUDY PROTOCOL OF A MULTICENTRE DOUBLE-BLIND RCT, COMPARING A TRADITIONAL RCT WITH AN AGGREGATED N-OF-1 TRIAL: GAG THERAPY EFFICACY TRIAL SOLUTION FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (GETSBI STUDY)

Charlotte van Ginkel, Cléo Baars, John Heesakkers, Frank Martens, Dick Janssen. *BMJ Open*. 2023 Apr 12;13(4):e068546. doi: 10.1136/bmjopen-2022-068546. PMID: 37045569.

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Obtaining level 1 evidence on efficacy of glycosaminoglycan (GAG) therapy is difficult, due to low incidence of bladder pain syndrome/interstitial cystitis (BPS/IC) and heterogeneous symptoms experienced by patients with BPS/IC. Currently, because of a lack of high-grade evidence, the recommendation for applying GAG therapy in most guidelines is 'low grade'. An aggregated N-of-1 trial is a multicrossover design that yields similar level 1 evidence as a traditional randomised controlled trial (RCT), while requiring far less patients. The goal of this study from the Netherlands is to investigate the efficacy of intravesical GAG therapy (Ialuril) for patients with BPS/IC with Hunner lesions using a dual RCT and aggregated N-of-1 trial design to obtain level 1 evidence. The GETSBI study is a double-blind multidesign multicentre randomised placebo-controlled study to assess the short-term and long-term efficacy of hyaluronic acid (1.6%) + chondroitin sulfate (2%) therapy (Ialuril Prefill, IBSA, Goodlife) in patients with symptomatic BPS/IC with Hunner lesions. It starts as a standard RCT (n=80) but continues as an aggregated N-of-1 trial. There are three parallel arms, receiving blinded treatment for three periods (1 x/week for 6 weeks, ratio placebo to intervention in periods of 2:1). Followed by an open prospective part for the long-term efficacy. The primary study outcome is the maximum bladder pain experienced in the last 3 days measured using the visual analogue pain scale (0-10). This study is a collaboration with the Dutch government and will deliver evidence for the decision to reimburse the therapy. Furthermore, this multidesign study will allow us to compare the two main methods to evaluate applicability for future study designs for BPS/IC research.

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

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

[Open Access](#)

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

[AUTONOMIC RESPONSES DURING BLADDER HYDRODISTENTION UNDER GENERAL VERSUS SPINAL ANAESTHESIA IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A RANDOMIZED CLINICAL TRIAL](#)

Yoon Jung Kim, Hyun-Kyu Yoon, Yu Jin Kang, Seung-June Oh, Min Hur, Hee-Pyoung Park, Hyung-Chul Lee. *Sci Rep*. 2023 Jun 7;13(1):9248. doi: 10.1038/s41598-023-36537-y. PMID: 37286619.

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Blocking the abrupt increase in systolic blood pressure associated with autonomic response during bladder hydrodistention in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) is essential for patient safety. In this study from Korea, the authors compared autonomic responses during bladder hydrodistention in patients with IC/BPS under general and spinal anaesthesia. Thirty-six patients were randomly allocated to a general anaesthesia (GA, n = 18) or a spinal anaesthesia (SA, n = 18) group. Blood pressure and heart rate were measured continuously and Δ SBP, defined as maximum increases in SBP during bladder hydrodistention from baseline, was compared between groups. Heart rate variability was analysed using electrocardiograms. The post-anaesthesia care unit assessed postoperative pain using a numeric (0-10) rating scale. Their analyses yield a significantly greater Δ SBP (73.0 [26.0-86.1] vs. 2.0 [- 4.0 to 6.0] mmHg), a significantly lower root-mean-square of successive differences in heart rate variability after bladder hydrodistention (10.8 [7.7-19.8] vs. 20.6 [15.1-44.7] ms), and significantly higher postoperative pain scores (3.5 [0.0-5.5] vs. 0.0 [0.0-0.0]) in the GA compared to the SA group. These findings suggest that SA has advantages over GA for bladder hydrodistention in preventing an abrupt increase in SBP and postoperative pain in IC/BPS patients.

TEMPORALLY COMPLEX INFLAMMATORY NETWORKS IN AN ANIMAL MODEL REVEAL SIGNATURES FOR INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME PHENOTYPE

Ashti M Shah, Yoram Vodovotz, Naoki Yoshimura, Christopher J Chermansky, Jocelyn Fitzgerald, Pradeep Tyagi. NeuroUrol Urodyn. 2023 Nov;42(8):1839-1848. doi: 10.1002/nau.25267. Epub 2023 Aug 17. PMID: 37587846.

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Introduction and objective: Interstitial cystitis and bladder pain syndrome (IC/BPS) presents with symptoms of debilitating bladder pain and is typically a diagnosis of exclusion. The cystoscopic detection of Hunner's lesions increases the likelihood of detecting tissue inflammation on bladder biopsy and increases the odds of therapeutic success with anti-inflammatory drugs. However, the identification of this subgroup remains challenging with the current lack of surrogate biomarkers of IC/BPS. On the path towards identifying biomarkers of IC/BPS, Shah and colleagues from the USA modelled the dynamic evolution of inflammation in an experimental IC/BPS rodent model using computational biological network analysis of inflammatory mediators (cytokines and chemokines) released into urine. The use of biological network analysis allows them to identify urinary proteins that could be drivers of inflammation and could therefore serve as therapeutic targets for the treatment of IC/BPS. Their analysis supports a complex evolution of inflammatory networks suggestive of the rise and fall of inflammation characteristic of IC/BPS flares.

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

Murat Demir, Fikret Altındağ. Environ Toxicol. 2023 Nov 13. doi: 10.1002/tox.24025. Online ahead of print. PMID: 37955270.

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

findings of the study reveal that BER and CUR treatments may reduce CYP-induced bladder damage by reducing apoptosis and inflammation and ameliorating histopathological changes.

EFFECTS OF LOW-INTENSITY EXTRACORPOREAL SHOCK WAVE THERAPY ON LIPOPOLYSACCHARIDE CYSTITIS IN A RAT MODEL OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Naohisa Kusakabe, Tadanobu Chuyo Kamijo, Naoki Wada, Hiroki Chiba, Nobuo Shinohara, Minoru Miyazato. Int Urol Nephrol. 2023 Sep 5. doi: 10.1007/s11255-023-03770-3. Online ahead of print. PMID: 37668867.

The purpose of this study from Japan was to investigate the effect of low-intensity extracorporeal shock wave therapy (LiESWT) on lipopolysaccharide (LPS)-induced cystitis in an animal model of interstitial cystitis/bladder pain syndrome (IC/BPS). Sprague-Dawley rats were divided into three groups: control, cystitis (LPS group, intravesical injection of LPS (1 mg) twice), and cystitis with LiESWT (LiESWT group). On the third and fourth days, LiESWT was administered (0.12 mJ/mm², 300 shots each time) on the lower abdomen toward the bladder. On the seventh day, the rats underwent pain assessment and a metabolic cage study. Subsequently, a continuous cystometrogram (CMG) was performed under urethane anaesthesia. Immunohistochemical studies were also performed, including S-100 staining, an immunohistochemical marker of Schwann cells in the bladder. In the LPS group, the pain threshold in the lower abdomen was significantly lower than that in the control group. In the metabolic cage study, the mean voided volume in the LPS group significantly increased. The CMG also revealed a significant decrease in bladder contraction amplitude, compatible with detrusor underactivity in the LPS group. Immunohistochemical studies showed inflammatory changes in the submucosa, increased fibrosis, and decreased S-100 stain-positive areas in the muscle layer of the LPS group. In the LiESWT group, tactile allodynia and bladder function were ameliorated, and S-100 stain-positive areas were increased. By restoring nerve damage, LiESWT improved lower abdominal pain sensitivity and bladder function in an LPS-induced cystitis rat model. This study suggests that LiESWT may be a new therapeutic modality for IC/BPS.

PIEZO2 CHANNEL UPREGULATION IS INVOLVED IN MECHANICAL ALLODYNIA IN CYP-INDUCED CYSTITIS RATS

Lei Liu, Yan Zhao, Wenhan An, Mengmeng Zhao, Ning Ding, Hanwen Liu, Nan Ge, Jiliang Wen, Xiulin Zhang, Shulu Zu, Wendong Sun. Mol Neurobiol. 2023 Sep;60(9):5000-5012. doi: 10.1007/s12035-023-03386-9. Epub 2023 May 25. PMID: 37227654.

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Mechanical sensing Piezo2 channel in primary sensory neurons has been shown contribute to mechanical allodynia in somatic chronic pain conditions. Interstitial cystitis (IC)-associated pain is often triggered by bladder filling, a presentation that mimics the mechanical allodynia. This study from China examined the involvement of sensory Piezo2 channel in IC-associated mechanical allodynia using a commonly employed cyclophosphamide (CYP)-induced IC model rat. Piezo2 channels in dorsal root ganglia (DRGs) was knocked down by intrathecal injections of Piezo2 anti-sense oligodeoxynucleotides (ODNs) in CYP-induced cystitis rats, and mechanical stimulation-evoked referred bladder pain was measured in the lower abdomen overlying the bladder using von Frey filaments. Piezo2 expression at the mRNA, protein, and functional levels in DRG neurons innervating the bladder was detected by RNA-fluorescence in situ hybridization, western blotting, immunofluorescence, and Ca²⁺ imaging, respectively. The authors found that Piezo2 channels were expressed on most (> 90%) of the bladder primary afferents, including afferents that express CGRP, TRPV1 and stained with isolectin B4. CYP-induced cystitis was associated with Piezo2 upregulation in bladder afferent neurons at the mRNA, protein, and functional levels. Knockdown of Piezo2 expression in DRG neurons significantly suppressed mechanical stimulation-evoked referred bladder pain as well as bladder hyperactivity in CYP rats compared to CYP rats treated with mismatched ODNs. Their results suggest upregulation of Piezo2 channels is involved in the development of

bladder mechanical allodynia and bladder hyperactivity in CYP-induced cystitis. Targeting Piezo2 might be an attractive therapeutic approach for IC-related bladder pain.

SI-NI-SAN AMELIORATES THE CLINICAL SYMPTOMS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN RATS BY DECREASING THE EXPRESSION OF INFLAMMATORY FACTORS

Yunjie Yang, Zhenduo Shi, Hui Yu, Mengzhen Liu, Tianhui Hu, Conghui Han. *Arch Esp Urol*. 2023 Jul;76(5):347-356. doi: 10.56434/j.arch.esp.urol.20237605.41. PMID: 37545154.

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The purpose of this study from China was to observe the therapeutic effect of Si-Ni-San (SNS) on interstitial cystitis/bladder pain syndrome (IC/BPS) in rats and explore the possible regulatory mechanism of SNS on IC/BPS combined with transcriptome analysis. An IC/BPS model of Sprague-Dawley (SD) rats was established with cyclophosphamide (CYP), and the SNS was extracted for treatment. The rats were divided into 4 groups (n = 10 in each group): Control group (blank), cyclophosphamide group (CYP group, CYP injection + normal saline gavage), lower-dose SNS group (LSNS group, CYP injection + 6 g/kg SNS gavage), and higher-dose SNS group (HSNS group, CYP injection + 12 g/kg SNS gavage). Urination, pain, and histological changes were observed in the rats after the experiment, and Western blotting (WB) and transcriptome analysis were performed on bladder tissues. Compared with the CYP group, the urination, pain and inflammation symptoms of the IC/BPS model rats in the SNS treatment groups (LSNS and HSNS) were significantly improved ($p < 0.05$). WB results showed that the expressions of inflammation-related proteins interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) in the SNS treatment groups were significantly decreased compared with those in the CYP group. Transcriptome results showed that SNS can affect the expression of inflammation-related genes and inflammatory signalling pathways. SNS can significantly alleviate the symptoms of inflammation and pain in IC/BPS rats, and its mechanism may be related to the down-regulation of inflammatory factors IL-6 and TNF- α through messenger RNA (mRNA) and long non-coding RNA (lncRNA) pathways.

THE EXPRESSION AND DISTRIBUTION OF TACAN IN HUMAN AND RAT BLADDERS

Qudong Lu, Qian Liu, Shiwei Chen, Jiaolian Wang, Yongjie Chen, Bishao Sun, Zhenxing Yang, Huan Feng, Shanhong Yi, Wei Chen, Jingzhen Zhu. *Low Urin Tract Symptoms*. 2023 Aug 31. doi: 10.1111/luts.12500. Online ahead of print. PMID: 37649457.

Many ion channels participate in the regulation of bladder function. TACAN, a new mechanosensitive ion channel, was first discovered in 2020. TACAN has been found to be expressed in many tissues, such as the dorsal root ganglia (DRG) and adipose tissue. However, it is unclear whether or not TACAN is expressed in the bladder. In this study from China, the authors decided to study the expression and distribution of TACAN in human and rat bladders. Meanwhile, the expression of TACAN in the rat model of interstitial cystitis/bladder pain syndrome (IC/BPS) was studied. Human bladder tissues were obtained from female patients. Cyclophosphamide (CYP) was used to build the rat model of IC/BPS. Real-time polymerase chain reaction, agarose gel electrophoresis, and western blotting were used to assess the expression of TACAN in human and rat bladders. Immunohistochemistry and immunofluorescence were used to observe the distribution of TACAN in human and rat bladders. Hematoxylin-eosin stain, withdrawal threshold, and micturition interval were used to evaluate animal models. The results of agarose gel electrophoresis and western blotting suggested that TACAN was expressed in human and rat bladders. Immunohistochemical results suggested that TACAN showed positive immunoreaction in the urothelial and detrusor layers. The immunofluorescence results indicated that TACAN was co-stained with UPKIII, α -SMA, and PGP9.5. The IC/BPS model was successfully established with CYP. The mRNA and protein expression of TACAN was upregulated in the CYP-induced rat model of IC/BPS. TACAN was found in human and rat bladders. TACAN was mainly distributed in the urothelial and detrusor layers and bladder nerves. The expression of TACAN was upregulated in the CYP-induced rat model

of IC/BPS. This new discovery will provide a theoretical basis for future research on the function of TACAN in the bladder and a potential therapeutic target for IC/BPS.

[SERPINA3N/SERPINA3 ALLEVIATES CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS BY ACTIVATING THE WNT/ \$\beta\$ -CATENIN SIGNAL](#)

Weilin Fang, Qixiang Song, Tingting Lv, Jianwei Lv, Zhikang Cai, Zhong Wang, Xin Song, Xiang Ji, Jin Huang. *Int Urol Nephrol.* 2023 Dec;55(12):3065-3075. doi: 10.1007/s11255-023-03726-7. Epub 2023 Aug 18. PMID: 37594700.

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Serpina3n/Serpina3 has been identified to be implicated in inflammatory diseases, but its role in interstitial cystitis/bladder pain syndrome (IC/BPS) remains unknown. In this study from China, the authors aimed to reveal serpina3n/serpina3 role in IC/BPS in vivo and in vitro. The IC/BPS model in mice was induced by intraperitoneal injection of 150 mg/kg of cyclophosphamide (CYP). HE and toluidine blue staining were used for histology assessment. Serpina3n/serpina3 expression in the bladder tissues from IC/BPS patients and mouse models were determined by qPCR, immunohistochemistry and western blotting. XAV-939 treatment was applied to inhibit β -catenin activation. Serpina3 role in modulating the growth and apoptosis of HBlEpCs, a human primary bladder epithelial cell line, was assessed by CCK-8 and flow cytometry assays. Serpina3n/serpina3 expression was decreased in both human and mice bladder tissues with IC/BPS. Upregulation of serpina3n significantly alleviated CYP-induced bladder injury, with decreased mast cells and pro-inflammatory factor levels, including IL-1 β , IL-6, and TNF- α , while increased IL-10 level. In addition, serpina3 overexpression inhibited the apoptosis of HBlEpCs, and increased cell growth. In mechanism, we found that serpina3 overexpression promoted the activation of wnt/ β -catenin signaling. Furthermore, the inhibition of wnt/ β -catenin signaling with XAV-939 abolished serpina3n/serpina3 role in protecting bladder tissues from CYP-induced cystitis, as well as inhibiting HBlEpC apoptosis. The authors concluded that Serpina3n/serpina3 expression was decreased in IC/BPS. Overexpression of serpina3n could alleviate CYP-induced IC/BPS by activating the Wnt/ β -catenin signal. This study may provide a new therapeutic strategy for IC/BPS.

[ANIMAL MODELS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Cindy Tay, Luke Grundy. *Front Physiol.* 2023 Sep 4:14:1232017. doi: 10.3389/fphys.2023.1232017. eCollection 2023. PMID: 37731545.

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The authors from Australia note that Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a chronic disorder characterized by pelvic and/or bladder pain, along with lower urinary tract symptoms that have a significant impact on an individual's quality of life. The diverse range of symptoms and underlying causes in IC/BPS patients pose a significant challenge for effective disease management and the development of new and effective treatments. To facilitate the development of innovative therapies for IC/BPS, numerous preclinical animal models have been developed, each focusing on distinct pathophysiological components such as localized urothelial permeability or inflammation, psychological stress, autoimmunity, and central sensitization. However, since the precise etiopathophysiology of IC/BPS remains undefined, these animal models have primarily aimed to replicate the key clinical symptoms of bladder hypersensitivity and pain to enhance the translatability of potential therapeutics. Several animal models have now been characterized to mimic the major symptoms of IC/BPS, and significant progress has been made in refining these models to induce chronic symptomatology that more closely resembles the IC/BPS phenotype. Nevertheless, it's important to note that no single model can fully replicate all aspects of the human disease. When selecting an appropriate model for preclinical therapeutic evaluation, consideration must be given to the specific pathology believed to underlie the development of IC/BPS symptoms in a particular patient group, as well as the type and severity of the model, its duration, and the proposed intervention's mechanism of action. Therefore, it is likely that different models will

continue to be necessary for preclinical drug development, depending on the unique etiology of IC/BPS being investigated.

CHANGES IN NERVE GROWTH FACTOR SIGNALING IN FEMALE MICE WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Harrison W Hsiang, Beatrice M Girard, Margaret A Vizzard. *Front Urol.* 2023;2:1089220. doi: 10.3389/fruro.2022.1089220. Epub 2023 Jan 26. PMID: 37701183.

Open Access

IC/BPS is a chronic inflammatory pelvic pain syndrome characterized by lower urinary tract symptoms including unpleasant sensation (pain, pressure, or discomfort) in the suprapubic or bladder area, as well as increased urinary frequency and urgency, and decreased bladder capacity. While its etiology remains unknown, increasing evidence suggests a role for changes in nerve growth factor (NGF) signalling. However, NGF signalling is complex and highly context dependent. NGF activates two receptors, TrkA and p75NTR, which activate distinct but overlapping signalling cascades. Dependent on their coexpression, p75NTR facilitates TrkA actions. Here, the authors show effects of CYP treatment and pharmacological inhibition of p75NTR (via LM11A-31) and TrkA (ARRY-954) on NGF signalling-related proteins: NGF, TrkA, phosphorylated (p)-TrkA, p75NTR, p-ERK1/2, and p-JNK. Cystitis conditions were associated with increased urothelial NGF expression and decreased TrkA and p75NTR expression as well as altering their co-expression ratio; phosphorylation of ERK1/2 and JNK were also altered. Both TrkA and p75NTR inhibition affected the activation of signalling pathways downstream of TrkA, supporting the hypothesis that NGF actions during cystitis are primarily TrkA-mediated. The authors from the USA report that their findings, in tandem with their recent companion paper demonstrating the effects of TrkA, TrkB, and p75NTR inhibition on bladder function in a mouse model of cystitis, highlight a variety of potent therapeutic targets and provide further insight into the involvement of NGF signalling in sustained conditions of bladder inflammation.

INTRATHECAL UMBILICAL CORD MESENCHYMAL STEM CELLS INJECTION ALLEVIATES NEUROINFLAMMATION AND OXIDATIVE STRESS IN THE CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS RATS THROUGH THE SIRT1/NRF2/HO-1 PATHWAY

Qiongqiong Gao, Yun Zhao, Ruixiang Luo, Minzhi Su, Chi Zhang, Cuiping Li, Bolong Liu, Xiangfu Zhou. *Life Sci.* 2023 Oct 15;331:122045. doi: 10.1016/j.lfs.2023.122045. Epub 2023 Aug 25. PMID: 37634813.

Neuroinflammation in the spinal dorsal horn (SDH) region plays an important role in the pathogenesis of interstitial cystitis (IC)/bladder pain syndrome (BPS). Oxidative stress is an important etiological factor for inflammatory diseases. This study from China aimed to investigate the therapeutic effects of umbilical cord mesenchymal stem cells UMSCs on neuroinflammation and oxidative stress in IC and the underlying mechanisms. Rats were intraperitoneally injected with cyclophosphamide (50 mg/kg bodyweight) to establish the IC animal model. Additionally, rats were intrathecally injected with a Sirt1-specific agonist (SRT1720; 8 µg/rat) or inhibitor (EX527; 8 µg/rat). Furthermore, rats were intrathecally injected with human UMSCs (hUMSCS; 8 × 10⁵ cells/rat). Rat behaviour was examined using the mechanical allodynia test, novel object recognition test, sucrose preference test, and urodynamics analysis. Neuroinflammation and oxidative stress the SDH region were examined using western blotting, immunofluorescence, enzyme-linked immunosorbent assay, and commercial kits. The Sirt1/Nrf2/HO-1 pathway was downregulated in IC rats. Sirt1 activation and inhibition differentially affected the behaviour of IC rats. hUMSCs effectively mitigated the upregulation of oxidative stress, proinflammatory cytokines, and glial activation in the SDH region. Additionally, hUMSCs suppressed mechanical allodynia, dysregulated urodynamics, memory deficits, and depressive-like behaviour in IC rats. hUMSCs exerted therapeutic effects through the Sirt1/Nrf2/HO-1 pathway. Intrathecal hUMSCs injection alleviated behavioural deficits of IC rats by

mitigating neuroinflammation and oxidative stress through the Sirt1/Nrf2/HO-1 pathway and can be potentially an effective therapeutic strategy for IC.

4-PBA INHIBITS ENDOPLASMIC RETICULUM STRESS TO IMPROVE AUTOPHAGIC FLUX IN THE TREATMENT OF PROTAMINE/LIPOPOLYSACCHARIDE-INDUCED INTERSTITIAL CYSTITIS IN RATS

Li Jia, Zhu Jingzhen, Yang Xinliang, Sun Bishao, Luo Xin, Zheng Ji, Fang Zhenqiang. Sci Rep. 2023 Aug 28;13(1):14057. doi: 10.1038/s41598-023-38584-x. PMID: 37640742.

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Interstitial cystitis (IC) has severe clinical symptoms with unclear mechanism. The continuous inflammatory response of the bladder is the basis of its pathogenesis. Endoplasmic reticulum stress (ERS) is involved in the regulation and development of various inflammatory diseases. And autophagy plays an important role in IC. In this study from China, the authors mainly focus on the therapeutic effect of endoplasmic reticulum stress and autophagy on protamine/lipopolysaccharide-induced interstitial cystitis. Female Sprague-Dawley rats were randomized into three experimental groups as follows: sham controls(N), IC alone, and IC+4-PBA. Rats in group IC received 10 mg/ml PS in the urinary bladder, followed by 2 mg/ml LPS instillation after 30 min, IC+4-PBA group SD rats received 4-PBA solution administered intragastrically once a day for 5 days. ERS biomarker (GRP78), autophagy-related proteins (LC3I/II, and Beclin1), autophagic flux biomarker (P62), inflammatory biomarkers (IL-6, TNF- α , NF- κ B), apoptotic biomarkers (Caspase 3, Bax) were highest in the IC group compared to IC+4-PBA group and N group and the biomarkers expression in IC+4-PBA group were lower than in the IC group, anti-apoptotic biomarker (Bcl-2) was highest in the N group compared to the IC group and IC+4-PBA group and lower in the IC group than in the IC+4-PBA group, oxidative stress biomarkers (HO-1, NQO-1) were remarkably lower in the control group than in the IC and IC+4-PBA groups and notably lower in the IC group than in the IC+4-PBA group. The histological score and mast cell count demonstrated most severe in the IC group than those in the IC+4-PBA group. TUNEL assay examined the level of apoptosis in IC group was higher than in the IC+4-PBA group. The bladder micturition function was significantly improved with 4-PBA treatment. 4-PBA inhibits ERS to recover autophagic flux, and then to suppress the bladder oxidative stress, the inflammatory reaction and apoptosis, finally improve the bladder urinary function in Protamine/Lipopolysaccharide (PS/LPS) induced IC.

INTRAVESICAL INJECTIONS OF AUTOLOGOUS PLATELET-RICH PLASMA FOR THE TREATMENT OF REFRACTORY INTERSTITIAL CYSTITIS

Hann-Chorng Kuo. Low Urin Tract Symptoms. 2023 Sep 13. doi: 10.1111/luts.12504. Online ahead of print. PMID: 37702275.

The urothelium acts as a barrier for the urinary bladder that prevents the influx of urinary toxic substances, electrolytes, urea nitrogen, and pathogens into the circulation. Acute or chronic inflammation of the urinary bladder may impair the regenerative function of urothelial cells and thus urothelial cell differentiation. In an inflamed bladder wall, mature apical cells are defective, resulting in impaired barrier function and thus increased urothelial permeability. This is considered to be the potential mechanism of the symptom trigger in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Previous studies have revealed that increased bladder inflammation, impaired urothelial cell maturation, a defective umbrella cell barrier, and defective junction proteins are prominent in IC/BPS bladders. Platelet-rich plasma (PRP) contains many growth factors and cytokines that are essential proteins for modulating inflammation and promoting tissue regeneration and thus wound healing. As such, PRP has been used as a regenerative therapy in many medical fields. Preliminary studies have demonstrated that multiple intravesical PRP injections could improve symptoms in 70% of IC/BPS patients. Repeated PRP treatments also improve junctional protein, increase cytoskeleton protein expression, and decrease urinary inflammatory proteins. These preliminary results suggest that PRP injections might reduce bladder inflammation and

improve urothelial cell regeneration in IC/BPS patients. This article from Taiwan reviews recently published clinical and basic research on the treatment potential of PRP for IC/BPS patients.

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

Erich Taubert, Frank van de Aa, John Heesakkers. Curr Opin Urol. 2023 Nov 20. doi: 10.1097/MOU.0000000000001150. Online ahead of print. PMID: 37975427.

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

GAMMA-BAND INTERMUSCULAR CONNECTIVITY IS ASSOCIATED WITH INCREASED NEURAL DRIVE TO PELVIC FLOOR MUSCLES IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Michael Houston, Nicholas Dias, Yun Peng, Theresa Spitznagle, Marcie Harris-Hayes, H Henry Lai, Yingchun Zhang. J Urol. 2023 Sep;210(3):465-471. doi: 10.1097/JU.0000000000003554. Epub 2023 Jul 7. PMID: 37285231.

Interstitial cystitis/bladder pain syndrome patients can experience overactive pelvic floor muscle activity at rest. While the frequency power spectrum of pelvic floor muscle has briefly been explored, intermuscular connectivity of the pelvic floor muscle has yet to be studied, which may provide useful insight into the neurological component, ie, neural drive to muscles, in interstitial cystitis/bladder pain syndrome. In this study from the USA, high-density surface electromyography was collected from 15 female interstitial cystitis/bladder pain syndrome patients with pelvic floor tenderness and 15 urologically healthy female controls. Intermuscular connectivity was calculated across the maximally active locations of the left and right sides of the pelvic floor muscle as identified from the root mean squared amplitude at rest and compared with Student t tests for common sensorimotor rhythms involved in motor control: alpha (8-12 Hz), beta (13-30 Hz), and gamma (31-70 Hz) frequency bands. The root mean squared amplitudes at rest were also compared across groups. The resting root mean squared amplitude of the pelvic floor muscle was significantly greater in female interstitial cystitis/bladder pain syndrome patients compared to healthy female controls ($P = .0046$). The gamma-band intermuscular connectivity was significantly different between rest and pelvic floor muscle contraction ($P = .0001$) for healthy female controls, but not for female patients with interstitial cystitis/bladder pain syndrome ($P = .1214$). Both results indicate an elevated neural drive to pelvic floor muscle at rest in female interstitial cystitis/bladder pain syndrome patients. Gamma-band pelvic floor muscle connectivity in female interstitial cystitis/bladder pain syndrome patients is increased at rest. The results of this study may provide insight into the impaired neural drive to pelvic floor muscle implicated with interstitial cystitis/bladder pain syndrome.

AMNIOTIC BLADDER THERAPY IN PATIENTS WITH RECALCITRANT INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME

Sophie Wittenberg, Raghav Madan, Aron Liaw, Steven Lucas, Alaa Hamada, Nivedita Dhar. Can Urol Assoc J. 2023 Aug 3. doi: 10.5489/cuaj.8441. Published online August 3, 2023. PMID: 37549350. Research Letter.

Open Access

This is the first clinical investigation regarding treatment of IC/BPS with micronized amniotic membrane intra-detrusor injection. The authors have demonstrated there is improved voiding symptoms and bladder pain in patients for at least three months following micronized amniotic membrane intra-detrusor injection. They plan to expand on this preliminary study and conduct further investigation to confirm the usefulness of amniotic bladder therapy in patients with IC/BPS.

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

Wei Guo, Haichao Liu, Jiaying Zhang, Jianzhong Zhang, Fei Wang, Peng Zhang, Yunbo Yang. J Biomed Mater Res A. 2023 Nov 16. doi: 10.1002/jbm.a.37643. Online ahead of print. PMID: 37975156.

Bladder mucosa damage that causes harm to the interstitium is a recognized pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS). The intravesical instillation of drugs is an important second-line therapy, but it is often necessary to use drugs repeatedly in the clinic because of their short residence time in the bladder cavity, which alters the therapeutic effect. To overcome this drawback, this study from China developed a novel composite acellular matrix/hyaluronic acid (HA) thermosensitive hydrogel (HA-Gel) using rabbit small intestinal submucosa extracellular matrix (ECM) as the thermosensitive material and HA as the drug component and examined its composition, microstructure, thermodynamic properties, temperature sensitivity, rheological properties, biocompatibility, drug release, hydrogel residue, and bacteriostatic properties. The study showed HA-Gel was liquid at temperatures of 15-37.5°C and solid at 37.5-50°C, its swelling rate decreased with increasing temperature, and its lower critical solution temperature occurred at approximately 37.5°C. This property made the hydrogel liquid at room temperature convenient for intravesical perfusion and turned into a solid about 1 min after entering the body and rising to body temperature to increase its residence time. Subsequent experiments also proved that the gel residue time of HA-Gel in vivo and the drug release time of HA in vivo could reach more than 5 days, which was significantly higher than that of HA alone, and it had good biocompatibility and antibacterial properties. Therefore, this hydrogel possesses the proper characteristics to possibly make it an ideal dosage form for IC/BPS intravesical instillation therapy.

CHEMICAL AND BIOLOGICAL DIFFERENCES BETWEEN ORIGINAL AND MIMETIC PENTOSAN POLYSULFATES

Dominik Lenhart, Marie-Theres Tischhöfer, Rudolf Gruber, Klaus Maag, Christian Reiter, Susanne Alban. Carbohydr Polym. 2023 Nov 1:319:121201. doi: 10.1016/j.carbpol.2023.121201. Epub 2023 Jul 15. PMID: 37567725.

Open Access

Pentosan polysulfate sodium (PPS) is a semi-synthetic, heparin-like polysaccharide with manifold therapeutic actions. It is approved for treatment of bladder pain syndrome / interstitial cystitis in humans and treatment of musculoskeletal diseases in animals. PPS is produced by a complex procedure using beech wood as starting material. It consists of a mixture of sulfated glucuronoxylans, whose structural composition cannot be fully characterized by physicochemical analysis. The question arises whether PPS follow-on products are identical with the original and thus meet the requirement for generic drug application. The aim of this study was to investigate whether commercially available PPS products differ in physicochemical characteristics and biological effects from the original. Ten PPS preparations from different manufactures were analyzed using orthogonal analytical techniques including, inter alia, size exclusion chromatography with triple detection, nuclear magnetic resonance spectroscopy, and high-resolution mid-infrared spectroscopy in aqueous solution with chemometric evaluation. For functional analysis, they measured the plasma kallikrein generation in human plasma and FXII activation. The study revealed significant structural and biological differences between PPS from different sources. Therefore, follow-on products cannot

be considered identical but at best similar to original PPS. However, their similar efficacy and safety have still to be proven by comprehensive studies.

[FURTHER ADVANCES IN IDENTIFICATION OF PENTOSAN POLYSULFATE MONOSACCHARIDE COMPOSITION BY NMR](#)

Giorgio Eisele, Anna Alekseeva, Sabrina Bertini, Cristina Gardini, Davide Paganini, Elizabeth Carolina Montatixe Fonseca, Marco Guerrini, Annamaria Naggi. J Pharm Biomed Anal. 2023 Oct 25;235:115672. doi: 10.1016/j.jpba.2023.115672. Epub 2023 Aug 19. PMID: 37619291.

Several publications have recently proposed NMR spectroscopy to evaluate the critical quality attributes (CQA) of pentosan polysulfate sodium (PPS), the active ingredient of Elmiron™ approved to treat interstitial cystitis. PPS is a polymer of sulfated $\beta(1-4)$ -d-xylopyranose residues randomly substituted by 4-O-methyl-glucopyranosyluronic acid, containing, beyond the main xylose-2,3-O-disulfate repetitive unit, some minor residues that can be marker of both the starting material and preparation process. In the present study, the authors from Italy assigned some previously unknown cross-peaks in 1H-13C HSQC NMR of PPS related to its minor sequences adding additional details to its CQA. Four anomeric cross-peaks related to glucuronate-branched xylose and different sulfation pattern as well as the preceding xyloses were identified. Two minor process-related signals of monosulfated xyloses (unsubstituted in position 2 or 3) were also assigned. The isolation of a disaccharide fraction allowed the assignment of the reducing end xylose- α/β as well as the preceding xylose residues to be corrected. Additionally, the oversulfation of PPS allowed detection of the reducing end xylose-tri-1,2,3-O-sulfate. The newly identified cross-peaks were integrated into an updated quantitative NMR method. Finally, it was demonstrated that an in-depth PPS analysis can be obtained using NMR instruments at medium magnetic fields (500 MHz/600 MHz), commonly available in pharmaceutical industries.

[\[TREATMENT OF INTRAVESICAL INSTILLATION WITH FULGURATION-HYDRODISTENSION ON FEMALE INTERSTITIAL CYSTITIS\]](#)

[Article in Chinese]

Peng Xin, Hao Zhang, Zhen Ming Jiang. Beijing Da Xue Xue Bao Yi Xue Ban. 2023 Oct 18;55(5):865-870. doi: 10.19723/j.issn.1671-167X.2023.05.014. PMID: 37807741.

[Open Access.](#)

Abstract in English, Chinese

The purpose of this study from China was to investigate the efficacy and safety of intravesical instillation of heparin/alkalized lidocaine (lidocaine mixed with sodium bicarbonate) combined with hydrodistension and transurethral fulguration in the treatment of female interstitial cystitis (IC). Female patients who attended the Department of Urology at the First Hospital of China Medical University between January 2012 and December 2020 and met the diagnostic criteria proposed in the guidelines of the American Urological Association with a new diagnosis of IC were selected for retrospective analysis. Cystoscopy and biopsy of suspicious lesions were performed at the time of diagnosis. All the patients were treated with an intravesical instillation regimen of 2% lidocaine 10 mL + 5% sodium bicarbonate 5 mL + heparin 25 000 IU for a continuous period of 12 months, with or without water dilatation and transurethral electrocautery according to the patient's preference, categorized as hydrodistension and transurethral fulguration (HD/TF) group and non-HD/TF group. The patients were evaluated before and 1, 6, and 12 months after treatment for O'Leary-Sant interstitial cystitis patient symptom index scores (ICSI), interstitial cystitis patient problem index scores (ICPI), visual analog scale (VAS) of suprapubic pain, and functional bladder capacity (FBC) changes. A total of 79 patients were collected in this study. Four (5.1%) of these patients underwent cystectomy due to pathological diagnosis of cancer or treatment failure. The remaining patients were followed up 1, 6 and 12 months after treatment. Repeated-measures ANOVA showed a significant decrease in ICPI, ICSI and VAS and an increase in FBC after treatment compared with before treatment ($P < 0.05$). FBC continued to decrease during the 1, 6 and 12 months' post-

treatment follow-ups, with statistically significant differences; ICSI continued to decrease during the 1 and 6 months post-treatment follow-ups, with statistically significant differences, while the difference between ICSI at 6 months post-treatment and at 12 months' post-treatment was not statistically significant. In the HD/TF group, ICPI continued to decrease in the follow-up from 1 and 6 months after treatment, and the difference was statistically significant, while the difference between ICPI 6 months after treatment and 12 months after treatment was not statistically significant. There was no statistically significant difference between the remaining indicators 1, 6 and 12 months after treatment. ICPI, ICSI, VAS and FBC improved earlier and the changes in VAS and FBC were more significant in the HD/TF group compared with the non-HD/TF group ($P < 0.05$). It was concluded that heparin/alkalized lidocaine combination of intravesical instillation with hydrodistension and transurethral fulguration for IC is an effective treatment option. Heparin/alkalized lidocaine combination of intravesical instillation may be the first choice of treatment, which can significantly reduce the economic burden of patients and medical insurance system. If patients can accept it, transurethral fulguration with hydrodistension may be considered.

URINARY ATP MAY BE A BIOMARKER OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND ITS SEVERITY

Yanyuan Wu, Yedie He, Jun Qi, Song Wang, Zongping Wang. *Biomol Biomed.* 2023 Oct 10. doi: 10.17305/bb.2023.9694. Online ahead of print. PMID: 37819233.

Open Access

Urinary tract cells respond to bladder distension by releasing adenosine triphosphate (ATP). Patients with interstitial cystitis/bladder pain syndrome (IC/BPS) exhibit elevated urinary ATP levels compared to asymptomatic controls. This study from China aimed to evaluate the potential of urinary ATP as a non-invasive biomarker for IC/BPS and its correlation with symptom severity. The authors included 56 patients diagnosed with IC/BPS and 50 asymptomatic controls. Urine samples were collected from both groups. Urinary ATP levels were quantified using the luciferin-luciferase bioluminescence method. The severity of IC/BPS symptoms was assessed using the visual analogue score (VAS), Interstitial Cystitis Symptom Index (ICSI), and Interstitial Cystitis Problem Index (ICPI) from the O'Leary-Sant score. The authors specifically examined the correlation between symptom scores and urinary ATP levels in IC/BPS patients. Urinary ATP levels were significantly higher in IC/BPS patients compared to the control group. There was a significant positive correlation between urinary ATP concentrations and VAS, ICPI, and ICSI scores among IC/BPS patients. The threshold value for ATP concentration was set at 56.6 nM, with an area under the receiver operating characteristic (ROC) curve of 0.811. Their findings indicate that IC/BPS patients excrete elevated amounts of ATP in their urine. This suggests that urinary ATP might serve as a non-invasive biomarker for IC/BPS, with a predictive potential in terms of symptom severity.

CUMINUM CYMINUM AMELIORATES UROTOXIC EFFECTS OF CYCLOPHOSPHAMIDE BY MODULATING ANTIOXIDANT, INFLAMMATORY CYTOKINES, AND URINARY BLADDER OVERACTIVITY: IN VIVO AND IN SILICO INVESTIGATIONS

Mohammed Bourhia, Irfan Anjum, Daanyaal Ali, Mueen Ahmad Chaudhry, Farhan Siddique, Mehvish Bibi, Abdel-Rhman Z Gaafar, Touriya Zair, Farid Khallouki. *Chem Biodivers.* 2023 Oct 16:e202301268. doi: 10.1002/cbdv.202301268. Online ahead of print. PMID: 37843082.

This study from Morocco, Pakistan and Saudi Arabia aimed to investigate the effect of aqueous ethanol extract of Cuminum cyminum (AEECC) on oxidative stress, inflammation and overactivity of the urinary bladder induced by cyclophosphamide (CYP). The enhanced nociception behavior, bladder weight, vascular permeability, edema, hemorrhage, nitric oxide, IL-6 and TNF- α levels by CYP administration were significantly reduced by AEECC (250 and 500 mg/kg). A significant increase in serum antioxidant systems such as CAT and GPx was also observed in AEECC-treated rats. The AEECC (3 mg/ml) significantly reduced urinary bladder tone in the strips pre-contracted with carbachol in both control and CYP-treated rats. This relaxation was demolished by atropine, nifedipine,

glibenclamide, and indomethacin but not with propranolol. The plant extract showed the presence of antioxidant and anti-inflammatory phytochemicals. These results suggest that *Cuminum cyminum* offers uroprotective activity and can ameliorate CYP-induced bladder toxicity by modulating antioxidant parameters, pro-inflammatory cytokine levels and bladder smooth muscle overactivity. The *in silico* binding interactions of anti-oxidant 2I3Y and anti-inflammatory protein 1TNF with various ligands from *Cuminum cyminum* seeds reveal potential bioactive compounds with promising anti-oxidant and anti-inflammatory properties, providing valuable insights for drug development and nutraceutical research.

[OPEN LABEL, PILOT EVALUATION OF THE SAFETY AND EFFICACY OF INTRAVESICAL SUSTAINED RELEASE SYSTEM OF LIDOCAINE AND OXYBUTYNIN \(TRG-100\) FOR PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME, OVERACTIVE BLADDER AND PATIENTS WITH RETAINED URETERAL STENTS FOLLOWING ENDOUROLOGICAL INTERVENTIONS](#)

Galiya Raisin, David Dothan, Dolev Perez, Natshe Ala-Adin, Ilan Kafka, Ofer Shenfeld, Shira Hatumi, Nadav Malchi, Avi Gordon, Dan Touitou, Robert Moldwin, Taher Nassar, Boris Chertin. Urology. 2023 Aug;178:42-47. doi: 10.1016/j.urology.2023.05.016. Epub 2023 Jun 1. PMID: 37268171.

Intravesical instillation of analgesic and anticholinergic drugs have shown efficacy in the treatment of pain and voiding symptoms. Unfortunately, drug loss with urination and dilution in the bladder limit their durability and clinical usefulness. The authors from the USA and Israel have recently developed and tested *in vitro*, a sustained delivery system (TRG-100) of fixed-dose combination of lidocaine and oxybutynin designed to allow for a longer exposure of the urinary bladder to the drugs. The purpose of this study was to assess the safety and efficacy of TRG-100 in Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS), overactive bladder (OAB), and endourological intervention stented (EUI) patients in an open-label, prospective study. Thirty-six patients were enrolled: 10 IC/BPS, 10 OAB, and 16 EUI. EUI patients received a once-weekly installation until stent removal, OAB and IC/BPS patient received weekly installations for 4 consecutive weeks. Treatment effect was assessed by visual analog scale (VAS) score for the EUI group, voiding diaries for OAB group and VAS score, voiding diaries and O'Leary Sant Questionnaires for the IC/BPS group. The EUI group showed a mean 4-point improvement in their VAS score. The OAB group showed 33.54% reduction in frequency of urination and IC/PBS group showed a mean of 3.2-point improvement in their VAS score, 25.43% reduction in frequency of urination, and a mean 8.1-point reduction in O'Leary Sant Questionnaires score. All changes were statistically significant. Intravesical instillation of TRG-100 was found to be safe and efficient in reducing pain and irritative bladder symptoms in this study population. TRG-100 efficacy and safety should be further assessed in a large, randomized control trial.

[LASER TREATMENT FOR PATIENTS WITH VULVODYNIA AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A CASE SERIES \(THE UNICORN-3 STUDY\)](#)

Nobuo Okui, Machiko Aurora Okui, Yuko Kouno, Kaori Nakano. Cureus. 2023 Jul 12;15(7):e41786. doi: 10.7759/cureus.41786. eCollection 2023 Jul. PMID: 37449291.

Open Access

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder characterized by urgency, frequency of urination, and pelvic pain. Women with IC/BPS often experience sexual dysfunction, vulvodynia, and vaginal health issues. Combined erbium and neodymium yttrium aluminum garnet (YAG) laser treatments targeting the vagina and vulva have shown promise in improving symptoms. This study from Japan investigated the effectiveness of these combined laser treatments in women with IC/BPS and vulvodynia. Women diagnosed with vulvodynia and IC/BPS underwent combined laser treatment using vaginal erbium:YAG laser (VEL) and neodymium:YAG laser (Nd:YAG). Various parameters were evaluated, including the vulvodynia test, numeric rating scale (NRS-11) for pain, interstitial cystitis symptom index and problem index (ICSI and ICPI), pelvic pain and urgency/frequency symptom score (PUF), and mean urination volume/daily urination

frequency in a three-day urination diary. Treatment was administered three times, with intervals of one month between each session, and follow-up evaluations were conducted at six and 12 months. All statistical analyses were designed and programmed by the AI chatbot GPT-4 (chatGPT-4). Fifteen female patients diagnosed with vulvodynia and IC/BPS were treated with three sessions of VEL + Nd:YAG. Significant improvements were observed in the vulvodynia test, NRS-11 scores, PUF, ICSI scores, ICPI scores, mean urination volume, and daily urination frequency at six and 12 months ($p < 0.01$). Short-term improvements in IC/BPS pain scores correlated with improvements in the vulvodynia test ($p = 0.007$), suggesting a synergistic effect. However, no significant correlations were found at 12 months. Combined laser treatments targeting the vagina and vulva showed significant therapeutic effects in women with IC/BPS and vulvodynia. The addition of Nd:YAG to the VEL treatment enhanced outcomes. Short-term improvements in IC/BPS pain scores correlated with improvements in the vulvodynia test, indicating a synergistic effect. Long-term improvements in both vulvodynia and IC/BPS symptoms may occur independently. These findings highlight the importance of comprehensive approaches for treating coexisting vulvodynia and IC/BPS.

INTRAVESICAL INJECTION OF ABOBOTULINUMTOXIN-A IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Mohammad-Sajjad Rahnema'i, Hanieh Salehi-Pourmehr, Sana Saeedi, Sona Tayebi, Sakineh Hajebrahimi. Urol Res Pract. 2023 May;49(3):205-210. doi: 10.5152/tud.2023.22243. PMID: 37877871.

Open Access

This study from Iran and the Netherlands aimed to evaluate retrospectively the outcomes of Abobotulinumtoxin-A (Dysport®) intravesical injection in refractory bladder pain syndrome/interstitial cystitis patients to first- and second-line treatment. From March 2016 to 2021, 44 adult patients with bladder pain syndrome who were refractory to first- and second-line treatment were enrolled in our study. The Bladder Pain/Interstitial Cystitis Symptom Score questionnaire was filled out for every patient before and 1-3 months after intervention in addition to urodynamic evaluation. Patient satisfaction was evaluated using a scoring system that was defined as high or >80% improvement (highly satisfied), intermediate 40%-79% (intermediate satisfaction), and poor 0%-39% improvement. The mean age of our study population was 57 years, including 41 females and 3 males. The mean follow-up time was 9 months. According to the results of urodynamics, 68% of cases had low capacity, and detrusor overactivity, while 18% had only low capacity. In terms of the endpoint outcome, half of the patients (52%) had intermediate satisfaction, whereas 41% reported a good response. Only 3 cases had no response or felt (7%) any improvement after the intervention (poor response). The paired t-test analysis revealed that the mean Bladder Pain/Interstitial Cystitis Symptom Score was reduced after injection. The authors report that their results showed the efficacy and safety of intravesical injections with Abobotulinumtoxin-A (Dysport®) in patients with bladder pain syndrome/interstitial cystitis. Further randomized controlled trials are recommended to investigate its superiority over placebo considering the need for anaesthesia, the occurrence of local complications, risks of urinary retention, and a large post-void residual (PVR) volume.

CENTERING GROUP TREATMENT FOR WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PROSPECTIVE, PARALLEL-GROUP COHORT STUDY

Kate V Meriwether, Niharika Ravichandran, Cassandra J Darley, Virginia Panter, Yuko M Komesu. Urogynecology (Phila). 2023 Apr 1;29(4):410-421. doi: 10.1097/SPV.0000000000001271. Epub 2022 Oct 21. PMID: 37695251.

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Women with interstitial cystitis/bladder pain syndrome (ICBPS) face isolation and treatment challenges. Group medical visits using Centering models have successfully treated other conditions but have not been explored in ICBPS. This study from the USA aimed to describe ICBPS pain and

symptom control comparing standard treatment alone versus standard treatment augmented with Centering visits. This prospective cohort study recruited women with ICBPS receiving standard care (control) or standard care augmented with group Centering. They administered validated questionnaires at baseline and monthly for 12 months. The primary outcome was change in the pain numerical rating scale, with Patient-Reported Outcomes Measurement Information System Pain Interference Scale and Bladder Pain/Interstitial Cystitis Symptom Score change as secondary measures. They enrolled 45 women (20 Centering, 25 controls). Centering had significantly better numerical rating scale pain scores at 1 month (mean difference [diff], -3.45) and 2 months (mean diff, -3.58), better Patient-Reported Outcomes Measurement Information System Pain Interference Scale scores at 1 month (mean diff, -10.62) and 2 months (mean diff, -9.63), and better Bladder Pain/Interstitial Cystitis Symptom Score scores at 2 months (mean diff, -13.19), and 3 months (mean diff, -12.3) compared with controls. In modelling, treatment group (Centering or control) and educational levels were both associated with all the outcomes of interest. Beyond 6 months, there were too few participants for meaningful analyses. Women with ICBPS participating in a Centering group have, in the short term, less pain, pain interference, and ICBPS-specific symptoms than patients with usual care alone. Larger studies with more follow-up are needed to determine if this treatment effect extends over time.

ROLE OF INTRAVESICAL OZONE IN THE MANAGEMENT OF BPS/INTERSTITIAL CYSTITIS

Maria Verônica Pires, Henrique Cunha Carvalho, Livia Helena Moreira, Adriana Barrinha Fernandes, Carlos José de Lima. Published: 13 October 2023. Current Bladder Dysfunction Reports (2023)

In this review from Brazil, studies and mechanisms of action relative to intravesical ozone in Bladder Pain Syndrome/Interstitial Cystitis (IC/BPS) are summarized and correlated with pathologies of chronic pelvic pain in animal models and clinical trials. Some studies have investigated intravesical ozone therapy in view of the disadvantages of conventional interventions and the extensive popularization of ozone in healthcare. Despite the small number of specific studies, many recent, results postulate ozone as a promising alternative for the management of IC/BPS given its antioxidant, anti-inflammatory, and immunomodulatory effect.

OUR 11-YEAR EXPERIENCE WITH PERCUTANEOUS TIBIAL NERVE STIMULATION IN MEN AND WOMEN FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Abdelrahman S Abdalla, Sean W Berquist, Ashu Mohammad, Amy D Dobberfuhr. Urology. 2023 Sep 9:S0090-4295(23)00744-6. doi: 10.1016/j.urology.2023.08.025. Online ahead of print. PMID: 37690542.

The purpose of this study from the USA was to evaluate the effect of percutaneous tibial nerve stimulation (PTNS) in interstitial cystitis/bladder pain syndrome (IC/BPS). Retrospective chart review was completed for patients with at least 10 weekly treatments of PTNS from January 2010 to October 2021. PTNS success was defined as conversion to PTNS maintenance therapy following 12weeks of PTNS induction therapy. Data were analyzed using GraphPad. Over the 11-year study period, 27 out of 34 patients (mean age 52.9 ± 16.8 years; 25 females, 9 males) completed 12weeks of PTNS induction therapy, and 48.1% (13/27) successfully converted to PTNS maintenance therapy. Following 12weeks of PTNS induction therapy, significant improvements were noted in the urgency severity scale (range 0-4: 2.9 ± 1.2 before vs 1.1 ± 1.1 after PTNS, $P = .001$) and nocturnal urinary frequency (number of voids: 3.3 ± 1.9 before vs 2.2 ± 1.6 after PTNS, $P = .041$); and nonsignificant improvements were noted in daytime void frequency (hours: 1.5 ± 0.7 before vs 2.0 ± 0.9 after PTNS, $P = .090$) and the pain domain of the interstitial cystitis symptoms index (question 4, range 0-4: 2.5 ± 1.4 before vs 1.3 ± 1.8 after PTNS, $P = .082$). According to the authors, this sample size is among the largest sample of PTNS in IC/BPS from a single center. While PTNS achieved nonsignificant improvements in pain and daytime void frequency, significant improvements were observed in urinary urgency and nocturia. PTNS appears to be a plausible option in the multimodal approach to managing IC/BPS.

CONTINENT DIVERSION IS LOSING ITS MOMENTUM: A NATIONWIDE TREND ANALYSIS FROM GERMANY 2005–2021

Jakob Klemm, Margit Fisch, Ekaterina Laukhtina, Roland Dahlem, Shahrokh F. Shariat, Malte W. Vetterlein. First published: 29 October 2023 <https://doi.org/10.1111/bju.16215>. Research Letter

Open Access

Continent (CUDs) and incontinent urinary diversions (IUDs) are widely established methods used to restore urinary flow following extirpative procedures for benign or malign bladder conditions. Decision making between use of CUD vs IUD is multifactorial and relies on patient education, preference, and informed consent. In this context, most international contemporary data indicate a notable decline in CUD use. Intriguingly, nationally representative evidence from developed countries is lacking. Furthermore, as robotic surgery continues to gain momentum in the field of cystectomy and urinary diversion (UD), the relatively low prevalence of CUDs in large-scale randomized studies remains a topic of debate, although the superiority of CUDs over IUDs in terms of functional patient-reported outcomes is questionable. Against this backdrop, the aim was to present evidence from the most populated country in the European Union, and to test the hypothesis that the declining trend in CUD use would be observed on a nationwide level in Germany.

BLADDER PAIN SYNDROME AND SEXUAL FUNCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

A Sobti, S Shower, P Ballard, A Khunda. Int Urogynecol J. 2023 Oct;34(10):2359-2371. doi: 10.1007/s00192-023-05633-y. Epub 2023 Aug 22. PMID: 37608090.

Bladder pain syndrome (BPS)/interstitial cystitis can adversely affect physical, mental, and sexual health. The aim of this systematic review from the United Kingdom was to compare sexual function between patients with BPS and healthy controls and to examine whether or not treatment of BPS improves sexual function. A literature search was conducted on Embase, Medline, and other databases. Studies comparing sexual function in BPS patients with healthy controls and before/after treatment were included. Where appropriate, data were pooled in a meta-analysis, using a random effects model and the standardised mean difference (SMD) was used for comparison. Out of 384 studies initially identified, 26 studies met the inclusion criteria for the systematic review and 11 for the meta-analysis. Six studies compared sexual function in BPS cases with healthy controls. All studies found that the Female Sexual Function Index (FSFI) was worse in BPS cases than in controls. Pooled data from 5 studies showed that the SMD was -1.02 (CI -1.64, -0.4) in total FSFI scores between the cases and controls, $p=0.001$. Further analysis showed better sexual function in all FSFI subdomains in healthy controls. Five studies compared sexual function in BPS patients before treatment with after treatment. Pooled data from 3 studies showed an overall improvement in total FSFI score after intravesical treatment: SMD=0.69 (CI 0.23, 1.14), $p=0.003$. Further analysis showed improvement in all subdomains. The authors believe that their review suggests that sexual function might be worse in BPS patients than in the general population, but it seems to improve with intravesical BPS treatment.

BLADDER PAIN SYNDROME AND PREGNANCY

Amy M Ivare, Aneta Obloza, Jonathan C Goddard. Eur J Obstet Gynecol Reprod Biol. 2023 Sep;288:29-35. doi: 10.1016/j.ejogrb.2023.06.017. Epub 2023 Jun 22. PMID: 37421744.

Bladder pain syndrome (BPS) is a poorly understood condition. In pregnancy, lower urinary tract symptoms and pain are common, but the possibility of BPS is rarely considered and almost never explored. The consequences of BPS on pregnancy and vice versa are poorly understood, and management options appear to be limited. This article from Leicester, United Kingdom reviews the current evidence to allow us to better counsel, investigate, diagnose and manage patients with suspected or known BPS who fall pregnant or who are considering pregnancy. MEDLINE, EMBASE and PubMed were searched for a combination of mesh terms of keywords: 'cystitis', 'interstitial', 'bladder', 'pain' and 'pregnancy'. Relevant articles were identified, reviewed and further relevant

articles identified from the references. BPS symptoms are very common in pregnancy, with limited data suggesting significant negative effects on the woman and pregnancy. There are safe options for investigation, diagnosis and management in pregnancy. There is a need to raise awareness of the impact of BPS symptoms in pregnancy and the available options for diagnoses and management, improving patient experience and outcomes.

PATIENT SUMMARY: Patients with BPS or symptoms akin to BPS need not be abandoned in pregnancy. There is data to support them in making decisions around investigation and management in pregnancy.

CURRENT POSITION OF NEUROMODULATION FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Harry J Kendall, Julia Schrijvers, John P F A Heesakkers. Curr Opin Urol. 2023 Nov 7. doi: 10.1097/MOU.0000000000001148. Online ahead of print. PMID: 37933670.

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

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

Lei Pang, Zijun Ding, Xiaodong Bian, Weibing Shuang. IET Syst Biol. 2023 Nov 13. doi: 10.1049/syb2.12083. Online ahead of print. PMID: 37957441

Open Access

Lei Pang and colleagues from China analyzed the symptoms composition of Interstitial Cystitis (IC), the regularity of the evolution of symptoms before and after treatment, and the visualization of the community network, to provide a reference for clinical diagnosis and treatment of Interstitial Cystitis. Based on the outpatient electronic case data of 552 patients with Interstitial Cystitis, they used a complex network community discovery algorithm, directed weighted complex network, and Sankey map to mine the data of the symptoms composition of Interstitial Cystitis, the evolution of symptoms before and after treatment and the visualization of the community network, to analyze the epidemiological characteristics of interstitial cystitis symptoms in the real world. By the community division of the complex network of interstitial cystitis symptoms, they finally obtained three core symptom communities. Among them, symptom community A (bladder-related symptoms) is the symptom community with the highest proportion of nodes (60.00%) in the complex network of Interstitial Cystitis, symptom community B (non-bladder-related symptoms 1) ranks second (32.00%) in a complex network of Interstitial Cystitis, and symptom community C (non-bladder-related symptoms 2) has the lowest proportion (8.00%). There is a complex evolutionary relationship between the symptoms of Interstitial Cystitis before and after treatment. Among the single symptoms before and after treatment, the decreased rate in Day frequency is 93.22%, and the

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

VALIDATION STUDY OF NEW CLINICAL SCORING - "APOLLO CLINICAL SCORING SYSTEM" FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS AND COMPARISON OF OUTCOME WITH STANDARD "O'LEARY-SANT SCORE"

Rajesh Taneja, Ashutosh Kumar Singh, Ankur Sharma, Nilesh Taneja, Apeksha Raheja. Int Urogynecol J. 2023 Aug 29. doi: 10.1007/s00192-023-05641-y. Online ahead of print. PMID: 37642668 DOI: 10.1007/s00192-023-05641-y

The aim of this study from India was to validate the recently published newer clinical scoring system for bladder pain syndrome/interstitial cystitis and comparison of the results with the pre-existing standard O'Leary-Sant score. The symptoms are our primary guide to disease severity analysis, treatment, and response monitoring. The combined ICSI/ICPI (O'Leary-Sant Interstitial Cystitis Symptom and Problem Index) consist of a four-item symptom and problem index focusing on urgency, frequency, nocturia, and pain. A new scale, assigning more weight to pain and nocturia and adding the domains of sexual dysfunction and psychological impact, has been published by one of the authors (El Khoudary et al. J Women's Health 2002. 18:1361-1368; 7). This is a prospective study conducted to validate a newer clinical scoring system, named the 'Apollo Clinical Scoring' (ACS) system for patients with bladder pain syndrome/ interstitial cystitis (BPS/IC), and to compare its outcome with the simultaneously applied standard O'Leary-Sant (OLS) score. Thirty-five patients of BPS/IC diagnosed using the ESSIC definition were enrolled in the study and followed for 6 months. Intraclass correlation coefficient (ICC) for test-retest reliability, and Cronbach's α for measure of internal consistency, were applied to both scoring systems. Intraclass correlation coefficient for ACS was 0.715 and for OLS was 0.689. Cronbach's α for ACS was 0.736 and for OLS was 0.698. The present study suggests that the recently devised Apollo Clinical Scoring (ACS) system for patients of BPS/IC is internally consistent and a reliable scoring system. When compared with OLS in parallel setting, the newer ACS appeared to be marginally better.

NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A PROMISING NON-INVASIVE BIOMARKER FOR SYMPTOM ASSESSMENT AND DIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Hanwei Ke, Lin Zhu, Qi Wang, Kexin Xu. BMC Urol. 2023 Nov 8;23(1):180. doi: 10.1186/s12894-023-01353-z. PMID: 37940904.

Open Access

The aim of this study from China was to investigate the association between the serum neutrophil-to-lymphocyte ratio (NLR) and interstitial cystitis (IC), as well as to explore whether NLR can serve as a diagnostic marker to distinguish IC from overactive bladder (OAB). The authors postulates that elevated NLR levels are intricately linked to the onset and clinical presentation of IC, and that the NLR profiles in OAB patients exhibit discernible disparities from those of IC patients. In a retrospective analysis, they scrutinized the medical records of 70 women diagnosed with IC/BPS, 20 women diagnosed with OAB, and a randomly selected cohort of 150 healthy women who underwent physical examinations during the same temporal frame. A comprehensive panel of blood tests was

administered to all participants, and NLR was determined through the calculation of the neutrophil-to-lymphocyte proportion. Additionally, symptom assessment questionnaires and urination diaries were collected from IC/BPS patients. Their study unveils the prospective utility of serum NLR as a promising biomarker for both diagnostic and symptom evaluation purposes in IC/BPS patients. It effectively demarcates this condition from OAB, which presents with similar clinical features. Consequently, NLR demonstrates potential as a non-invasive diagnostic instrument to distinguish between the subtypes of IC, particularly HIC and NHIC, which manifest similar symptoms within the IC/BPS spectrum.

POSTSURGERY OPIATE USE IS SIGNIFICANTLY LOWER IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME FOLLOWING CYSTECTOMY WITH URINARY DIVERSION

Maxwell Sandberg, Wyatt Whitman, Anita Rong, Brian Andres-Robusto, Gopal Badlani, Robert Evans, Stephen J Walker. Urology. 2023 Oct;180:86-92. doi: 10.1016/j.urology.2023.07.013. Epub 2023 Jul 22. PMID: 37482104.

The purpose of this study from the USA was to compare pre-and post-operative opiate use in a large cohort of interstitial cystitis/bladder pain syndrome (IC/BPS) patients who underwent cystectomy with urinary diversion (CWUD). A retrospective analysis was completed using a database of IC/BPS patients who underwent CWUD at a single institution from 2014 to 2022. In addition to demographic information, bladder capacity and Hunner lesion status were documented for each patient. Opiate use (milligram morphine equivalents [MME]) was calculated for each patient and change in MME (Δ MME) was calculated by subtracting pre-CWUD MME from post-CWUD MME. Paired t test was used to compare Δ MME for all parameters except age, where a Pearson's correlation was used. The analysis included 82 patients (17 M; 65 F) that underwent CWUD as follows: 53 ileal conduit diversions, 11 neobladders, and 18 Indiana Pouches. Mean pre-CWUD MME use was 4509.57 and mean post-CWUD MME was 1788.48 with a Δ MME of - 2721.09 ($P < .001$). Δ MME was not significantly different based on gender ($P = .597$), bladder capacity ($P = .754$), age ($P = .561$), or Hunner lesion status ($P = .085$). IC/BPS patients using opiates primarily for relief of pain directly related to their condition show a significant decrease in opiate use following CWUD, which likely represents significant pain reduction and implicates the bladder as the primary source of that pain.

[INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)]

[Article in German]

Winfried Vahlensieck. Urologie. 2023 Jun;62(6):582-589. doi: 10.1007/s00120-023-02080-x. Epub 2023 Apr 28. PMID: 37115301. Abstract in English, German

In this review from Germany, aspects of interstitial cystitis/bladder pain syndrome (IC/BPS) are presented against the background of the German S2k guideline on this disease. Quite often this disease, characterized by bladder or lower abdominal pain (permanent or intermittent) and pollakisuria without pathogenic bacteria in the urine culture, is diagnosed much too late. The debate on disease definition, aspects on pathophysiology and epidemiology are presented. For diagnosis, disease severity must be determined and relevant differential diagnoses like bladder cancer must be excluded. Conservative measures (clothing, food, sexuality, sport, bladder training, sufficient fluid intake, prevention of hypothermia) are effective especially in early stages of the disease. Combination drug therapy with mucosa stabilizing, anti-inflammatory, psychotropic, and pain-reducing drugs should be adjusted individually. Inpatient rehabilitation, hydrodistension, laser- and electrocoagulation, neuromodulation (sacral or pudendal) or hyperbaric oxygen therapy may help after pharmacotherapy failure. Cystectomy and urinary diversion are used in irreversible shrunken urinary bladder. If all treatment modalities are consequently used, many patients may reach a state that is more bearable. With a high level of suffering in many patients with IC/BPS, all available treatment modalities should be known and used.

HUNNER LESION

[DEEP LEARNING MODELS FOR CYSTOSCOPIC RECOGNITION OF HUNNER LESION IN INTERSTITIAL CYSTITIS](#)

Takuya Iwaki, Yoshiyuki Akiyama, Hirokazu Nosato, Manami Kinjo, Aya Niimi, Satoru Taguchi, Yuta Yamada, Yusuke Sato, Taketo Kawai, Daisuke Yamada, Hidenori Sakanashi, Haruki Kume, Yukio Homma, Hiroshi Fukuhara. Eur Urol Open Sci. 2023 Jan 26:49:44-50. doi: 10.1016/j.euros.2022.12.012. eCollection 2023 Mar. PMID: 36874607.

Open Access

Accurate cystoscopic recognition of Hunner lesions (HLs) is indispensable for better treatment prognosis in managing patients with Hunner-type interstitial cystitis (HIC), but frequently challenging due to its varying appearance. The purpose of this study from Japan was to develop a deep learning (DL) system for cystoscopic recognition of a HL using artificial intelligence (AI). A total of 626 cystoscopic images collected from January 8, 2019 to December 24, 2020, consisting of 360 images of HLs from 41 patients with HIC and 266 images of flat reddish mucosal lesions resembling HLs from 41 control patients including those with bladder cancer and other chronic cystitis, were used to create a dataset with an 8:2 ratio of training images and test images for transfer learning and external validation, respectively. AI-based five DL models were constructed, using a pretrained convolutional neural network model that was retrained to output 1 for a HL and 0 for control. A five-fold cross-validation method was applied for internal validation. True- and false-positive rates were plotted as a receiver operating curve when the threshold changed from 0 to 1. Accuracy, sensitivity, and specificity were evaluated at a threshold of 0.5. Diagnostic performance of the models was compared with that of urologists as a reader study. The mean area under the curve of the models reached 0.919, with mean sensitivity of 81.9% and specificity of 85.2% in the test dataset. In the reader study, the mean accuracy, sensitivity, and specificity were, respectively, 83.0%, 80.4%, and 85.6% for the models, and 62.4%, 79.6%, and 45.2% for expert urologists. Limitations include the diagnostic nature of a HL as warranted assertibility. The authors report that they have constructed the first DL system that recognizes HLs with accuracy exceeding that of humans. This AI-driven system assists physicians with proper cystoscopic recognition of an HL.

Patient summary: In this diagnostic study, we developed a deep learning system for cystoscopic recognition of Hunner lesions in patients with interstitial cystitis. The mean area under the curve of the constructed system reached 0.919 with mean sensitivity of 81.9% and specificity of 85.2%, demonstrating diagnostic accuracy exceeding that of human expert urologists in detecting Hunner lesions. This deep learning system assists physicians with proper diagnosis of a Hunner lesion.

[GENOME-WIDE ASSOCIATION STUDY IDENTIFIES RISK LOCI WITHIN THE MAJOR HISTOCOMPATIBILITY COMPLEX REGION FOR HUNNER-TYPE INTERSTITIAL CYSTITIS](#)

Yoshiyuki Akiyama, Kyuto Sonehara, Daichi Maeda, Hiroto Katoh, Tatsuhiko Naito, Kenichi Yamamoto, Biobank Japan Project, Takayuki Morisaki, Shumpei Ishikawa, Tetsuo Ushiku, Haruki Kume, Yukio Homma, Yukinori Okada. Cell Rep Med. 2023 Jul 18;4(7):101114. doi: 10.1016/j.xcrm.2023.101114. PMID: 37467720.

Open Access

Hunner-type interstitial cystitis (HIC) is a rare, chronic inflammatory disease of the urinary bladder with unknown etiology and genetic background. Here, the authors from Japan conduct a genome-wide association study of 144 patients with HIC and 41,516 controls of Japanese ancestry. The genetic variant, rs1794275, in the major histocompatibility complex (MHC) region (chromosome 6p21.3) is associated with HIC risk (odds ratio [OR] = 2.32; $p = 3.4 \times 10^{-9}$). The association is confirmed in a replication set of 26 cases and 1,026 controls ($p = 0.014$). Fine mapping demonstrates the contribution to the disease risk of a completely linked haplotype of three human leukocyte antigen HLA-DQ β 1 amino acid positions, 71, 74, and 75 (OR = 1.94; $p = 5 \times 10^{-8}$) and of HLA-DP β 1 amino acid position 178, which tags HLA-DP β 1*04:02 (OR = 2.35; $p = 7.5 \times 10^{-8}$). The three HLA-DQ β 1 amino acid positions are located together at the peptide binding groove, suggesting their

functional importance in antigen presentation. This study reveals genetic contributions to HIC risk that may be associated with class II MHC molecule antigen presentation.

[EFFICACY AND SAFETY OF INTRAVESICAL DIMETHYL SULFOXIDE TREATMENT FOR PATIENTS WITH REFRACTORY HUNNER-TYPE INTERSTITIAL CYSTITIS: REAL-WORLD DATA POSTOFFICIAL APPROVAL IN JAPAN](#)

Yoshiyuki Akiyama, Aya Niimi, Akira Nomiya, Satoru Taguchi, Yuta Yamada, Yusuke Sato, Taketo Kawai, Daisuke Yamada, Haruki Kume, Yukio Homma. Int J Urol. 2023 Oct 11. doi: 10.1111/iju.15320. Online ahead of print. PMID: 37817647.

The purpose of this Japanese study was to examine real-world data regarding intravesical dimethyl sulfoxide (DMSO) therapy after official approval as a treatment for Hunner-type interstitial cystitis (HIC) in Japan. This single institution, retrospective observational study was conducted between 2021 and 2022 to evaluate the outcomes of 30 patients with refractory HIC who received intravesical DMSO therapy according to the approved standardized regimen: administration of DMSO every 2 weeks for a total of 12 weeks. Treatment outcomes were evaluated using a 7-graded global response assessment scale, O'Leary and Sant's symptom and problem indices (OSSI/OSPI), the overactive bladder symptom score (OABSS), an 11-point pain intensity numerical rating scale, quality of life (QOL) score, and frequency volume chart variables. Related complications were also documented. The response rates at 2, 4, 6, 8, 10, and 12 weeks were 36.7%, 43.3%, 53.3%, 60.0%, 70.0%, and 70.0%, respectively. Compared with baseline, OSSI/OSPI, pain intensity, urinary frequency, and the QOL score improved significantly from 4 weeks of treatment. The OABSS score and functional bladder capacity also showed a tendency toward moderate improvement, but the difference was not significant. The mean duration of symptom relapse after termination of treatment was 6.4 ± 3.9 months. No patients discontinued treatment due to adverse events, although acute bladder irritation during infusion was noted in 21 patients (70%), which disappeared within 3 days. This study verifies the safety, moderately durable efficacy, and tolerability of the standard intravesical treatment with DMSO for HIC in Japan.

[RECURRENCE AFTER POSTOPERATIVE INTRAVESICAL INSTILLATION THERAPY IN HUNNER TYPE INTERSTITIAL CYSTITIS](#)

Kwang Jin Ko, Michael Jakun Koo, Seokhwan Bang, Hye Jin Byun, Min-Ji Kim, Kyunga Kim, Kyu-Sung Lee. Sci Rep. 2023 Oct 25;13(1):18256. doi: 10.1038/s41598-023-44894-x. PMID: 37880250.

Open Access

The authors from Korea performed a prospective, single-arm study comparing outcomes between transurethral ablation plus postoperative instillation of hyaluronic acid and chondroitin sulfate (HACS group) and transurethral ablation only in patients with Hunner type interstitial cystitis (historical control group). A total of 78 patients were enrolled, and 51 were included in the per-protocol analysis set. The 2-year recurrence rate was 47.1% in the HACS group, which was significantly lower than that in the control group (86.2%). After instillation therapy, the hazard ratio for recurrence was 0.38. The HACS group had an increased recurrence-free survival with the median interval not being reached, while it was 11.4 months in the control group. Regardless of the instillation treatment, there were significant improvements in all symptom questionnaire scores and pain compared to the baseline. However, in the instillation group improvement was stable even after 12 months. In patients with Hunner type interstitial cystitis, intravesical instillation of hyaluronic acid and chondroitin sulfate after transurethral ablation significantly reduced the recurrence rate and maintained symptom improvement for more than 1 year.

[EFFICACY AND SAFETY OF LOW-DOSE ORAL PREDNISOLONE FOR PATIENTS WITH REFRACTORY HUNNER-TYPE INTERSTITIAL CYSTITIS](#)

Yoshiyuki Akiyama, Aya Niimi, Akira Nomiya, Satoru Taguchi, Yuta Yamada, Yusuke Sato, Daisuke Yamada, Daichi Maeda, Tetsuo Ushiku, Haruki Kume, Yukio Homma. *Eur Urol Open Sci.* 2023 Aug 26;56:1-8. doi: 10.1016/j.euros.2023.07.006. eCollection 2023 Oct. PMID: 37822513

Open Access

Hunner-type interstitial cystitis (HIC) is an immunological, chronic inflammatory disease. The efficacy of corticosteroid as a treatment for HIC is unclear. The aim of this study from Japan was to assess the efficacy and safety of low-dose oral prednisolone (PSL) treatment for patients with refractory HIC. This retrospective observational study reviewed the clinical outcomes of 31 patients with refractory HIC who received oral PSL daily (initial dose, 5.0 or 7.5 mg) for at least 12 mo between 2016 and 2023. The dose was tapered to the minimum that maintained symptom relief during follow-up. Treatment outcomes were evaluated using a seven-graded global response assessment (scores $\geq +2$, moderately or markedly improved, were defined as treatment response), O'Leary and Sant symptom and problem indices (OSSI/OSPI), overactive bladder symptom score (OABSS), an 11-point pain intensity numerical rating scale, a quality of life (QOL) score, and frequency-volume chart variables. Related complications were also documented. No patients discontinued treatment due to adverse events, although hypertension and glucose intolerance occurred in two patients, but these were resolved by temporal medications. This study showed that low-dose oral PSL significantly improves bladder pain, urinary symptoms, and QOL in patients with HIC, without serious adverse events. Further prospective evaluation is warranted to verify the potential efficacy and safety of low-dose PSL for HIC.

Patient summary: *This retrospective observational study reviewed the clinical outcomes of 31 patients suffering from refractory Hunner-type interstitial cystitis treated with low-dose oral prednisolone. Low-dose prednisolone improved bladder pain, urinary symptoms, and quality of life significantly, without serious adverse events. The response rate of 64.5% at 12 mo was comparable with the rates reported in previous studies that used higher doses of prednisolone. This study provides a rationale for further prospective evaluation of low-dose prednisolone for this intractable disease.*

OPTIMAL ENDOSCOPIC TREATMENT AND PARTIAL CYSTECTOMY WITH OR WITHOUT BLADDER AUGMENTATION FOR HUNNER-TYPE INTERSTITIAL CYSTITIS

Jiwoong Yu, Chung Un Lee, Kyu-Sung Lee, Kwang Jin Ko. *Low Urin Tract Symptoms.* 2023 Sep 26. doi: 10.1111/luts.12505. Online ahead of print. PMID: 37750459

The authors from Korea note that interstitial cystitis/bladder pain syndrome (IC/BPS) presents a significant challenge for urologists in terms of management, owing to its chronic nature and adverse impact on patient quality of life. Given the potential distinction between two disease entities within IC/BPS, namely Hunner-type IC and BPS without Hunner lesion, there is a need for an optimal therapeutic approach that focuses on the bladder lesions in Hunner-type IC. In cases where Hunner lesions are observed, complete transurethral ablation of these lesions should be prioritized as the initial intervention, as it has demonstrated effectiveness in symptom control. However, recurrence remains a limitation of this intervention. The techniques of resection and coagulation are equally effective in terms of symptom relief and recurrence prevention. Reconstructive surgery becomes necessary in cases of end-stage IC/BPS where various therapeutic approaches have failed. Patient selection is crucial in reconstructive surgery, particularly for patients with clear Hunner lesions and small bladder capacity who have not responded to previous treatments. Furthermore, it is vital to consider the patients' expectations and preferences adequately. Based on a comprehensive review of the literature and our own clinical experiences, subtotal cystectomy followed by bladder augmentation is considered a safe and effective surgical option. This stepwise and tailored therapeutic approach aims to optimize patients' quality of life by specifically targeting Hunner-type IC.

IC/BPS VERSUS OAB

SERUM ANANDAMIDE AND LIPIDS ASSOCIATED WITH LINOLEIC ACID CAN DISTINGUISH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME FROM OVERACTIVE BLADDER: AN EXPLORATORY STUDY

Kazumasa Torimoto, Tomohiro Ueda, Daisuke Gotoh, Kuniyuki Kano, Makito Miyake, Yasushi Nakai, Shunta Hori, Yosuke Morizawa, Kenta Onishi, Takuto Shimizu, Mitsuru Tomizawa, Junken Aoki, Kiyohide Fujimoto. *Low Urin Tract Symptoms*. 2023 Sep 8. doi: 10.1111/luts.12501. Online ahead of print. PMID: 37688290.

Diagnosing interstitial cystitis/bladder pain syndrome presents a major challenge because it relies on subjective symptoms and empirical cystoscopic findings. A practical biomarker should discriminate diseases that cause increased urinary frequency, particularly overactive bladder. Therefore, the authors from Japan aimed to identify blood biomarkers that can discriminate between interstitial cystitis/bladder pain syndrome and overactive bladder. They enrolled patients with Hunner-type interstitial cystitis (n = 20), bladder pain syndrome (n = 20), and overactive bladder (n = 20) and without lower urinary tract symptoms (controls, n = 15) at Ueda Clinic and Nara Medical University Hospital from February 2020 to August 2021. The degree of interstitial cystitis/bladder pain syndrome symptoms was evaluated using the interstitial cystitis symptom and problem indices. Metabolomics analysis was performed on 323 serum metabolites using liquid chromatography time-of-flight mass spectrometry. In the Hunner-type interstitial cystitis or bladder pain syndrome group, they observed smaller relative areas, including anandamide, acylcarnitine (18:2), linoleoyl ethanolamide, and arachidonic acid, compared to those in the overactive bladder or control group. Notably, the differences in the relative areas of anandamide were statistically significant (median: 3.950e-005 and 4.150e-005 vs. 8.300e-005 and 9.800e-005), with an area under the curve of 0.9321, demonstrating its ability to discriminate interstitial cystitis/bladder pain syndrome. Serum anandamide may be a feasible diagnostic biomarker for interstitial cystitis/bladder pain syndrome. Reduced serum anandamide levels may be associated with pain and inflammation initiation, reflecting the pathology of interstitial cystitis/bladder pain syndrome. Furthermore, the authors believe that their findings suggest that abnormal linoleic acid metabolism may be involved in the pathogenesis of interstitial cystitis/bladder pain syndrome.

IC/BPS VERSUS MALE LUT DYSFUNCTION

USE OF URINARY BIOMARKERS IN DISCRIMINATING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME FROM MALE LOWER URINARY TRACT DYSFUNCTIONS

Wan-Ru Yu, Yuan-Hong Jiang, Jia-Fong Jhang, Hann-Chorng Kuo. *Int J Mol Sci*. 2023 Jul 27;24(15):12055. doi: 10.3390/ijms241512055. PMID: 37569430.

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The aim of this article from Taiwan was to analyze the urinary biomarkers in men with lower urinary-tract symptoms (LUTS) and identify interstitial cystitis/bladder pain syndrome (IC/BPS) from the other lower urinary-tract dysfunctions (LUTDs) by the levels of characteristic urinary biomarkers. In total, 198 men with LUTS were prospectively enrolled and urine samples were collected before intervention or medical treatment. Videourodynamic studies were routinely performed and the LUTDs were diagnosed as having bladder-outlet obstruction (BOO) such as bladder-neck dysfunction, benign prostatic obstruction, or poor relaxation of external sphincter (PRES); and bladder dysfunction such as detrusor overactivity (DO), hypersensitive bladder (HSB), and IC/BPS. Patients suspicious of IC/BPS were further confirmed by cystoscopic hydrodistention under anesthesia. The urine samples were investigated for 11 urinary inflammatory biomarkers including eotaxin, IL-6, IL-8, CXCL10, MCP-1, MIP-1 β , RANTES, TNF- α , NGF, BDNF, and PGE2; and 3 oxidative stress biomarkers 8-OHdG, 8-isoprostane, and TAC. The urinary biomarker levels were analyzed between LUTD subgroups and IC/BPS patients. The results of this study revealed that among the patients, IC/BPS was diagnosed in 48, BOO in 66, DO in 25, HSB in 27, PRES in 15, and normal in 17. Patients with BOO had a higher detrusor pressure and BOO index than IC/BPS, whereas patients with IC/BPS, BOO,

and DO had a smaller cystometric bladder capacity than the PRES and normal subgroups. Among the urinary biomarkers, patients with IC/BPS had significantly higher levels of eotaxin, MCP-1, TNF- α , 8-OHdG, and TAC than all other LUTD subgroups. By a combination of different characteristic urinary biomarkers, TNF- α , and eotaxin, either alone or in combination, had the highest sensitivity, specificity, positive predictive value, and negative predictive value to discriminate IC/BPS from patients of all other LUTD subgroups, BOO, DO, or HSB subgroups. Inflammatory biomarker MCP-1 and oxidative stress biomarkers 8-OHdG and TAC, although significantly higher in IC/BPS than normal and PRES subgroups, did not have a diagnostic value between male patients with IC/BPS and the BOO, DO, or HSB subgroups. The study concluded that using urinary TNF- α and eotaxin levels, either alone or in combination, can be used as biomarkers to discriminate patients with IC/BPS from the other LUTD subgroups in men with LUTS.

IC/BPS AND UTI

THE BURDEN OF URINARY TRACT INFECTIONS ON QUALITY OF LIFE AND HEALTHCARE IN PATIENTS WITH INTERSTITIAL CYSTITIS

Cléo Baars, Charlotte van Ginkel, John Heesakkers, Mathilde Scholtes, Frank Martens, Dick Janssen. Healthcare (Basel). 2023 Oct 18;11(20):2761. doi: 10.3390/healthcare11202761. PMID: 37893834.

Open Access

Interstitial cystitis/bladder pain syndrome (IC/BPS) patients are more susceptible to urinary tract infections (UTIs), likely worsening pre-existing symptoms. However, this receives limited attention in guidelines. This study from the Netherlands aimed to explore the burden of UTIs on IC/BPS patients' quality of life and their healthcare. Two quantitative retrospective database studies were conducted in cystoscopically proven IC/BPS patients: one compiled existing patient survey data (n = 217) from July 2021 to examine physical and emotional UTI burden, and the other used a patient file database (n = 100) from January 2020 to May 2022, focusing on UTI prevalence, healthcare use, urine cultures and antibiotic resistance. A delay in diagnosis was seen in 70% of patients, due to doctors confusing IC/BPS symptoms with UTIs. The UTI prevalence was over 50%; these patients also report anxiety for new UTIs (70%) and worsening of IC/BPS symptoms (60%). Additionally, for UTI+ patients, healthcare consumption was significantly increased in both studies. Antibiotic resistance (80% of cultures) and prophylactic antibiotic use were common. These findings highlight the burden of UTIs on quality of life in IC/BPS patients and the healthcare system. These results emphasize the need for improved UTI guidelines concerning diagnosis, management and prevention for IC/BPS patients to improve quality of life and care.

URINARY TRACT INFECTIONS: A REVIEW OF THE CURRENT DIAGNOSTICS LANDSCAPE

Braith Grey, Mathew Upton, Lovleen Tina Joshi. J Med Microbiol. 2023 Nov;72(11). doi: 10.1099/jmm.0.001780. PMID: 37966174.

Urinary tract infections are the most common bacterial infections worldwide. Infections can range from mild, recurrent (rUTI) to complicated (cUTIs), and are predominantly caused by uropathogenic *Escherichia coli* (UPEC). Antibiotic therapy is important to tackle infection; however, with the continued emergence of antibiotic resistance there is an urgent need to monitor the use of effective antibiotics through better stewardship measures. Currently, clinical diagnosis of UTIs relies on empiric methods supported by laboratory testing including cellular analysis (of both human and bacterial cells), dipstick analysis and phenotypic culture. Therefore, development of novel, sensitive and specific diagnostics is an important means to rationalise antibiotic therapy in patients. This review from the United Kingdom discusses the current diagnostic landscape and highlights promising novel diagnostic technologies in development that could aid in treatment and management of antibiotic-resistant UTIs.

THE ROLE OF VIRAL INFECTION IN THE PATHOGENESIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Jhang, JF., Kuo, HC. Curr Bladder Dysfunct Rep (2023). <https://doi.org/10.1007/s11884-023-00713-7>

The pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS) is still unclear. The diagnosis of IC/BPS is made after ruling out bacterial cystitis. However, viral infection in the bladder might be a pathogenic factor for IC/BPS. The purpose of this review from Taiwan is to demonstrate the association between viral infection and IC/BPS. The presence of urinary tract viruses in patients with IC/BPS has been sporadically investigated since the 1970s. Early studies used viral culture to investigate urine and bladder tissue samples from patients with IC/BPS, but viruses were rarely detected. With polymerase chain reaction, several studies have reported increased papillomavirus, BK virus, and John Cunningham virus viral load in urine samples from patients with IC/BPS. The presence of urinary papillomavirus was associated with more severe IC/BPS symptoms. Recent studies have used transcriptomic RNA sequencing to investigate gene expression in bladder tissue samples from patients with IC/BPS. Enriched viral infection-associated gene pathways in patients with IC/BPS were noted in the studies, including cytomegalovirus infection, Kaposi sarcoma-associated herpesvirus infection, human papillomavirus infection, and Epstein–Barr virus (EBV) infection. Recent studies reported the presence of EBV in IC/BPS bladders, especially in patients with IC/BPS with Hunner’s lesion (HIC). EBV latency and lytic infection were observed in HIC bladders, indicating EBV infection persistence and reactivation. EBV latency infection in B cells could induce brain-derived neurotrophic factor overexpression and might cause nerve hyperplasia in IC/BPS bladders. The presence of urinary virus in the patients with IC/BPS suggested that viral infection might be a pathogenic factor in patients with IC/BPS. Molecular evidence from IC/BPS bladder tissue also showed that viral infection may involve the pathogenesis of IC/BPS. Further studies are needed to clarify the mechanism.

IC/BPS AND QUALITY OF LIFE

THE LIFE EXPERIENCES OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A QUALITATIVE PHENOMENOLOGICAL STUDY

Min-Ju Chien, Ching-Hui Chien, Xuan-Yi Huang, Yueh-Tao Chiang. J Adv Nurs. 2023 Jun 23. doi: 10.1111/jan.15754. Online ahead of print. PMID: 37350439.

The purpose of this study from Taiwan was to explore the life experiences of women with interstitial cystitis in a qualitative phenomenological study. Fifteen women with interstitial cystitis were recruited from a regional hospital in Taiwan using purposive sampling. Data were collected via one-on-one semistructured interviews and analysed using the Colaizzi's method. Rigorous testing was conducted to identify the themes and subthemes. Four major themes were identified: torment, restriction, acceptance and empowerment. These themes reflect the life experiences of women with interstitial cystitis. They endured unrelenting physical and psychological distress and loneliness, experienced obstacles and limitations in daily living because of their symptoms, accepted reality and considered their symptoms as a part of everyday life and developed coping skills for the disease. Medical care, psychological support and emotional venting are crucial for women with interstitial cystitis. Despite living a life full of frustrations and suffering caused by the unpredictable and unrelenting nature of interstitial cystitis, through external support and intrinsic positive cognitive reconstruction, women with interstitial cystitis gradually accepted that they were ill. They adapted to their situation, developed a suitable lifestyle and pace and ultimately achieved stable coexistence with the disease. Although women with interstitial cystitis are affected by an incurable disease, through adequate assistance and reconstruction of perception, they can develop coping skills and stably coexist with their disease. There is a delicate dynamic balance between their lives and disease. This study may help clinicians to understand patients' life experiences and provide suitable care. This may improve the quality of care provided to women with interstitial cystitis and help them adapt to their disease, thereby improving their life satisfaction.

[QUALITY OF LIFE ANALYSIS IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: IMPLICATIONS FOR A MULTIMODAL INTEGRATED TREATMENT](#)

Daniele Porru, Daniela Anselmo, Amanda Magliano, Serena Scalmati, Annalisa DE Silvestri, Marcella Ilardi, Barbara Gardella, Arsenio Spinillo, Pierluigi Politi, Richard Naspro. Minerva Urol Nephrol. 2023 Oct;75(5):634-641. doi: 10.23736/S2724-6051.23.05292-8. PMID: 37728498.

The aim of this study from Italy was to evaluate whether there is a higher prevalence of anxiety-depressive disorders in women with BPS/IC (bladder pain syndrome/interstitial cystitis) than in women with chronic non-neoplastic pain with or without fibromyalgia, to examine possible correlations between urological and psychiatric symptoms. The patients included in the study were divided into two groups: 1) group 0: patients with an existing diagnosis of BPS/IC. BPS/IC was confirmed by reviewing medical record; group 1+2: patients with chronic non-neoplastic pain, suffering from fibromyalgia or other types of chronic pain (chronic arthralgia or lower back pain). Three questionnaires were administered: PHQ-9 to investigate psychological symptoms, O'Leary Saint (ICSI-ICPI) to investigate urological symptoms in women with BPS/IC and BPI to investigate specifically pain. The survey included 69 patients, 42 patients had a diagnosis of BPS/IC while 27 of them had chronic non-neoplastic pain. The average PHQ-9 Score was 10.3 in BPS/IC group, considered as major depression (score between 10 and 14); the average score of PHQ-9 was 6.9 in group 1+2, as in sub-threshold depression (between 5-9). The chronic pain of BPS/IC can affect mood more than in other painful conditions, as more than half of this population has a score that identifies depression with the PHQ-9 questionnaire, confirming the hypothesis that the syndrome is associated with a higher prevalence of an anxious-depressive condition.

IMPACT OF COVID PANDEMIC

[NUMBER OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SEEN BEFORE VERSUS DURING THE COVID-19 PANDEMIC AT AN ACADEMIC, URBAN, MULTISITE UROGYNECOLOGY PRACTICE](#)

Tahireh Markert, Alexa Courtepatte, Subrina Farah, Jeannine M Miranne. Low Urin Tract Symptoms. 2023 Sep 12. doi: 10.1111/luts.12502. Online ahead of print. PMID: 37700527.

Little is known about the impact of the COVID-19 pandemic on interstitial cystitis/bladder pain syndrome (IC/BPS). The authors compared the number of newly diagnosed IC/BPS cases and number of patients with flares prior to and during the pandemic. They conducted a retrospective cohort study of women ≥ 18 years who were diagnosed with or treated for IC/BPS between March 2019 and March 2021 at an academic, urban, multisite urogynecology practice in the USA. The primary outcome was the number of IC/BPS cases from March 1, 2019 to February 29, 2020 (pre-pandemic) compared with March 1, 2020 to February 28, 2021 (during pandemic). The secondary outcome was the number of patients with flares during those same two time periods. Demographic and clinical characteristics were compared using nonparametric tests and interrupted time series (ITS) was used to evaluate their outcomes of interest. p -Value $< .05$ was considered significant. Fifty-four women (4.87% of new patients) were diagnosed with IC/BPS during the pandemic compared with 40 women pre-pandemic (4.05% of new patients). The median age was 35.0. Seventy-two percent were premenopausal, 75% sexually active, and 31% had anxiety, and there were no significant differences between groups. Although the number of patients newly diagnosed with IC/BPS was higher during the pandemic, the diagnosis rates between time periods were not statistically different. Thirty-five patients experienced flares during the pandemic compared with 49 patients the year prior ($p = .43$). This difference was also not statistically significant on ITS analysis. Although more patients were diagnosed with IC/BPS during versus before the pandemic, the difference in diagnosis rates was not different between these periods.

[THE EFFECT OF THE PANDEMIC PERIOD ON BLADDER PAIN SYNDROME PATIENTS UNDER AMITRIPTYLINE TREATMENT](#)

Mehmet Fatih Şahin, Rıdvan Özcan, Arzu Malak, Çağrı Doğan, Cenk Murat Yazıcı, Müge Özcan, Murat Akgül. Neurourol Urodyn. 2023 Aug;42(6):1188-1193. doi: 10.1002/nau.25199. Epub 2023 May 8. PMID: 37155258.

COVID-19 is a disease that may cause anxiety, depression, and stress. Bladder pain syndrome (BPS) is a disease in which stress and psychological factors might negatively affect its course. In this study from Turkey, the authors examined the possible clinical aggregation of the pandemic period on BPS patients. A total of 35 BPS patients diagnosed between 2010 and 2018 were included. All patients were using medical treatment, and the follow-up period was at least 6 months. According to their clinical follow-up protocol, the BPS patients were given the King's Health Questionnaire (KHQ), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Overactive Bladder Form V8 (OAB-V8), and Visual Analog Score (VAS) in every visit. In the sixth month of the pandemic, the clinical course of the patients was questioned by telephone or video interview, and their treatment continuities were questioned. Information was received about the delays in their follow-up and the difficulties in accessing healthcare opportunities. The same questionnaires were filled out and compared with pre-pandemic scores. The mean age of the patients included in the study was 50.2 ± 13.32 (min:20, max:74), 11 were males and 24 were females. The mean follow-up periods were 71.8 ± 35.6 months. All questionnaire scores showed an increase compared to the pre-pandemic period. A statistically significant increase was detected during the pandemic in all sub-units of the KHQ. The VAS and OAB-V8 scores of 16 patients who requested hospital admission were significantly higher than before the pandemic. However, there was no statistically significant difference in the increase in VAS and OAB-V8 scores of the 19 patients who refused to come to the hospital. BPS patients have been negatively affected by the emotional effects of the COVID-19 pandemic. Due to the fear, stress, anxiety, and depression, the symptoms of BPS patients exacerbated, and the patients could not receive the necessary support due to a lack of regular follow-ups.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

PENTOSAN POLYSULFATE MACULOPATHY

J Ben Margines, Samuel D. Hobbs. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. 2023 Jul 4. PMID: 36944010 Bookshelf ID: NBK589706. Free Books & Documents.

Open Access

Pentosan polysulfate (PPS) is a semisynthetic pentasaccharide heparinoid with anticoagulant properties and was initially used in the 1950s as a thrombolytic due to the ability of the molecule to bind the glycocalyx of circulating red blood cells. It is the only medication approved by the United States Food and Drug Administration to treat interstitial cystitis (IC). Interstitial cystitis is characterized by bladder pain (suprapubic, pelvic, urethral, vaginal, or perineal) caused by filling and relieved by emptying with petechial bladder mucosal hemorrhages on endoscopy and decreased bladder compliance on urodynamics. This disease is very common: it affects over one million Americans, the vast majority female. In the bladder, PPS is postulated to bind to the urothelium and replace disrupted glycosaminoglycans to protect the urothelium. Less frequently, PPS is used for other indications, including irritable bowel syndrome, pelvic pain syndrome, and inner bladder wall cracks. The recommended dosage for PPS is 100 mg three times a day. Twenty-two years after its approval as a second-line agent for interstitial cystitis, a six-patient case series described a progressive maculopathy associated with long-term use of the drug, an association that researchers have demonstrated and characterized multiple times. "Pentosan polysulfate (PPS) is a commonly used medication to treat interstitial cystitis, also known as bladder pain syndrome. In 2018 it was first associated with a progressive retinal pigmentary maculopathy, a finding which was later corroborated by several other large studies. PPS maculopathy (PPSM) can cause severe visual impairment by decreasing visual acuity and causing nyctalopia. PPSM is generally not reversible and can be progressive even once discontinued. This activity reviews the evaluation and etiology of

PPSM and highlights techniques to help diagnose the condition earlier with specific imaging modalities.

MACULAR HOLE IN A PATIENT WITH PENTOSAN POLYSULFATE MACULOPATHY

Neha Arora, Sandra Hoyek, Nimesh A Patel. Retin Cases Brief Rep. 2023 Jun 14. doi: 10.1097/ICB.0000000000001444. Online ahead of print. PMID: 37321232.

Pentosan polysulfate (PPS), a drug used for interstitial cystitis, has recently been detected to cause maculopathy in a dose-dependent manner. Outer retinal atrophy is the hallmark of this condition. In this study from Boston, USA, history, examination and multimodal imaging were used to guide diagnosis and management. The authors report a case of PPS-related maculopathy in a 77-year-old lady, who presented with florid retinal atrophy at the posterior pole in both eyes, and a concurrent macular hole in the left eye. She had been diagnosed with interstitial cystitis several years prior for which she was prescribed PPS (Elmiron). She had noticed a drop in vision 5 years following initiation of PPS and self-discontinued the drug after 24 years of use. A diagnosis of PPS-related maculopathy with a macular hole was made. She was counselled regarding the prognosis and was advised to avoid PPS. Surgery for macular hole was deferred in view of the severe retinal atrophy. PPS-related maculopathy can lead to severe retinal atrophy and a subsequent degenerative macular hole. A high index of suspicion is required for early detection and cessation of drug to prevent this irreversible vision loss.

INCIDENCE AND RISK OF RETINOPATHY IN PATIENTS WITH AND WITHOUT INTERSTITIAL CYSTITIS AND PENTOSAN POLYSULFATE SODIUM USE

Eric B Desjarlais, Velinka Medic, Judy E Kim. J Vitreoretin Dis. 2023 Aug 7;7(5):412-419. doi: 10.1177/24741264231190978. eCollection 2023 Sep-Oct. PMID: 37706083

This study from the USA investigated the potential for indication bias to be present in previous studies of pentosan polysulfate sodium (PPS) pigmentary retinopathy by comparing the incidence and risk of retinopathy in patients with interstitial cystitis (IC) to matched controls. Adult women with IC from a multicenter database of electronic medical record data were matched to non-IC controls at a 1:4 ratio. The IC cohort was subdivided according to duration of PPS use: never, <5 years, and ≥5 years. Incidence and risk (estimated by Cox proportional hazards models) of retinopathy (defined by 6 International Classification of Diseases, Ninth and Tenth Revision codes) were compared between groups. There were 22 060 women with IC and 88 240 women without IC. Average age was 53.92 years (SD, 16.22 years), and 96 110 (87.14%) patients were non-Hispanic White. Incidence of retinopathy per 100 000 person-years was 173.88 (95% CI, 162.78-185.53) for patients without IC, 226.63 (95% CI, 197.73-258.56) for IC without PPS use, 293.02 (95% CI 230.86-366.75) for IC with <5 years of PPS use, and 558.91 (95% CI, 399.29-761.07) for IC with ≥5 years of PPS use. Adjusted hazard ratios were 1.31 (95% CI, 1.13-1.51, P < .001) for IC without PPS use, 1.70 (95% CI, 1.35-2.15, P < .001) for IC with <5 years of PPS use, and 3.10 (95% CI, 2.26-4.27, P < .001) for IC with ≥5 years of PPS use. It was concluded that patients with IC had greater incidence and risk of retinopathy. PPS use further increased the incidence and risk of retinopathy.

INFLAMMATORY BLADDER DISORDERS

RESTORING THE BARRIER OF CHRONICALLY DAMAGED UROTHELIUM USING CHONDROITIN SULFATE GLYCOSAMINOGLYCAN-REPLENISHMENT THERAPY: A PRECLINICAL STUDY USING A CHRONIC EXPERIMENTAL MODEL FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS AND REFLECTIONS ON LATELY PUBLISHED SIMILAR MODELS

Boy B Rozenberg 1, Charlotte J van Ginkel, Dick A W Janssen. Curr Opin Urol. 2023 Nov 14. doi: 10.1097/MOU.0000000000001149. Online ahead of print. PMID: 37962190.

This study from the Netherlands aims to further understand the physiological mechanism of chondroitin sulfate treatment on the urinary bladder in cases of inflammation, by investigating the

effect of chondroitin sulfate therapy on recovery of urothelial barrier in an in-vitro chronic injury model. With inflammatory bladder conditions, the urothelial barrier seems decreased. Glycosaminoglycan (GAG) replacement therapy is supposed to help restore this barrier. Clinical studies on inflammatory bladder conditions are complicated because of the heterogeneous patient population, hence the need for preclinical models. In a model using porcine urothelial cells, functional barrier (TEER) and barrier markers were assessed. Chronic urothelial damage was simulated through protamine sulfate instillations with and without subsequent chondroitin sulfate instillations during 3 days. Chondroitin sulfate instillations significantly improved TEER compared to protamine sulfate treatment only (TEER difference $310 \Omega \cdot \text{cm}^2$, $P < 0.001$). This consistent effect over 3 days resulted in a significant higher mean TEER value in the chondroitin sulfate treated group (difference $1855 \Omega \cdot \text{cm}^2$, $P < 0.001$). Enhanced recovery of chondroitin sulfate and other barrier markers was observed. Chondroitin sulfate therapy shows promise in facilitating the recovery of the urothelial barrier in cases of chronic damage. This preclinical study lends support to the use of clinical GAG replenishment therapy for patients with a chronically impaired urothelium.

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

Sławomir Poletajew, Magdalena M Brzózka, Wojciech Krajewski, Hubert Kamecki, Łukasz Nyk, Piotr Kryst. Pain Ther. 2023 Nov 2. doi: 10.1007/s40122-023-00559-1. Online ahead of print. PMID: 37917298

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

AUTONOMIC NERVOUS SYSTEM AND BLADDER INFLAMMATION

BEYOND THE UROTHELIUM: INTERPLAY BETWEEN AUTONOMIC NERVOUS SYSTEM AND BLADDER INFLAMMATION IN URINARY TRACT INFECTION, BLADDER PAIN SYNDROME WITH INTERSTITIAL CYSTITIS AND NEUROGENIC LOWER URINARY TRACT DYSFUNCTION IN SPINAL CORD INJURY-ICI-RS 2023

Michel Wyndaele, Ana Charrua, François Hervé, Patrik Aronsson, Luke Grundy, Vik Khullar, Alan Wein, Paul Abrams, Francisco Cruz, Célia Duarte Cruz. Neurourol Urodyn. 2023 Oct 25. doi: 10.1002/nau.25310. Online ahead of print. PMID: 37876314.

Inflammation and neuronal hypersensitivity are reactive protective mechanisms after urothelial injury. In lower urinary tract dysfunctions (LUTD), such as urinary tract infection (UTI), bladder pain syndrome with interstitial cystitis (BPS/IC) and neurogenic LUTD after spinal cord injury (SCI), chronic inflammation can develop. It is unclear how the protective reactionary inflammation escalates into chronic disease in some patients. During its 2023 meeting in Bristol, the International Consultation on Incontinence-Research Society (ICI-RS) reviewed the urothelial and inflammatory changes after UTI, BPS/IC and SCI. Potential factors contributing to the evolution into chronic disease were explored in a think-tank. Five topics were discussed. (1) Visceral fat metabolism participates in the

systemic pro-inflammatory effect of noradrenalin in BPS/IC and SCI. Sympathetic nervous system-adipocyte-bladder crosstalk needs further investigation. (2) Sympathetic hyperactivity also potentiates immune depression in SCI and needs to be investigated in BPS/IC. Gabapentin and tumour necrosis factor- α are promising research targets. (3) The exact peripheral neurons involved in the integrative protective unit formed by nervous and immune systems need to be further identified. (4) Neurotransmitter changes in SCI and BPS/IC: Neurotransmitter crosstalk needs to be considered in identifying new therapeutic targets. (5) The change from eubiosis to dysbiosis in SCI can contribute to UTI susceptibility and needs to be unravelled. The think-tank discussed whether visceral fat metabolism, immune depression through sympathetic hyperactivity, peripheral nerves and neurotransmitter crosstalk, and the change in microbiome could provide explanations in the heterogenic development of chronic inflammation in LUTD. High-priority research questions were identified.

LOWER URINARY TRACT

[HOW DOES THE LOWER URINARY TRACT CONTRIBUTE TO BLADDER SENSATION? ICI-RS 2023](#)

Luke Grundy, Jean J Wyndaele, Hikaru Hashitani, Bahareh Vahabi, Alan Wein, Paul Abrams, Basu Chakrabarty, Christopher H Fry. Neurourol Urodyn. 2023 Oct 30. doi: 10.1002/nau.25316. Online ahead of print. PMID: 37902296.

Bladder sensation is critical for coordinating voluntary micturition to maintain healthy bladder function. Sensations are initiated by the activation of sensory afferents that innervate throughout the bladder wall. However, the physiological complexity that underlies the initiation of bladder sensory signalling in health and disease remains poorly understood. This review summarises the latest knowledge of the mechanisms underlying the generation of bladder sensation and identifies key areas for future research. Experts in bladder sensory signalling reviewed the literature on how the lower urinary tract contributes to bladder sensation and identified key research areas for discussion at the 10th International Consultation on Incontinence-Research Society. The importance of bladder sensory signals in maintaining healthy bladder function is well established. However, better therapeutic management of bladder disorders with exaggerated bladder sensation, including overactive bladder syndrome (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS) is limited by a lack of knowledge in a number of key research areas including; the contribution of different nerves (pudendal, pelvic, hypogastric) to filling sensations in health and disease; the relative contribution of stretch sensitive (muscular) and stretch-insensitive (mucosal) afferents to bladder sensation in health and disease; the direct and indirect contributions of the muscularis mucosae to bladder contraction and sensation; and the impact of manipulating urothelial release factors on bladder sensation. Disturbances in bladder sensory signalling can have severe consequences for bladder sensation and function including the development of OAB and IC/BPS. Advancing therapeutic treatments for OAB and IC/BPS requires a deeper understanding of the mechanisms underlying the generation of bladder sensation, and key areas for future research have been identified.

[NUTRITIONAL CONSIDERATIONS FOR BLADDER STORAGE CONDITIONS IN ADULT FEMALES](#)

Barbara Gordon. Int J Environ Res Public Health. 2023 Oct 3;20(19):6879. doi: 10.3390/ijerph20196879. PMID: 37835149.

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Clinical guidelines developed by urologic, urogynecologic, and gynecologic associations around the globe include recommendations on nutrition-related lifestyle and behavioral change for bladder storage conditions. This study from the USA identified and compared clinical guidelines on three urological conditions (interstitial cystitis/bladder pain syndrome (IC/BPS), overactive bladder, and stress urinary incontinence) affecting adult women. It was concluded that clinical guidelines for IC/BPS, overactive bladder, and stress urinary incontinence include nutrition recommendations;

however, the extent of dietary manipulation varied by condition. The need to ensure that clinicians are informing patients of the limitations of the evidence supporting those recommendations emerged. Furthermore, given the need to treat nutrition-related comorbid conditions as a strategy to help mitigate these three urological disorders, the value of referral to a dietitian for medical nutrition therapy is apparent.

STRESS-INDUCED SYMPTOM EXACERBATION: STRESS INCREASES VOIDING FREQUENCY, SOMATIC SENSITIVITY, AND URINARY BLADDER NGF AND BDNF EXPRESSION IN MICE WITH SUBTHRESHOLD CYCLOPHOSPHAMIDE (CYP)

Beatrice M Girard, Susan E Campbell, Margaret A Vizzard. *Front Urol.* 2023;3:1079790. doi: 10.3389/fruro.2023.1079790. Epub 2023 Mar 22. PMID: 37811396.

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Symptom exacerbation due to stress is prevalent in many disease states, including functional disorders of the urinary bladder (e.g., overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS)); however, the mechanisms underlying the effects of stress on micturition reflex function are unclear. In this study from the USA, the authors designed and evaluated a stress-induced symptom exacerbation (SISE) mouse model that demonstrates increased urinary frequency and somatic (pelvic and hindpaw) sensitivity. Cyclophosphamide (CYP) (35 mg/kg; i.p., every 48 hours for a total of 4 doses) or 7 days of repeated variate stress (RVS) did not alter urinary bladder function or somatic sensitivity; however, both CYP alone and RVS alone significantly ($p \leq 0.01$) decreased weight gain and increased serum corticosterone. CYP treatment when combined with RVS for 7 days (CYP+RVS) significantly ($p \leq 0.01$) increased serum corticosterone, urinary frequency and somatic sensitivity and decreased weight gain. CYP+RVS exposure in mice significantly ($p \leq 0.01$) increased (2.6-fold) voiding frequency as they determined using conscious, open-outlet cystometry. CYP+RVS significantly ($p \leq 0.05$) increased baseline, threshold, and peak micturition pressures. They also evaluated the expression of NGF, BDNF, CXC chemokines and IL-6 in urinary bladder in CYP alone, RVS alone and CYP+RVS mouse cohorts. Although all treatments or exposures increased urinary bladder NGF, BDNF, CXC and IL-6 content, CYP+RVS produced the largest increase in all inflammatory mediators examined. These results demonstrated that CYP alone or RVS alone creates a change in the inflammatory environment of the urinary bladder but does not result in a change in bladder function or somatic sensitivity until CYP is combined with RVS (CYP+RVS). The SISE model of CYP+RVS will be useful to develop testable hypotheses addressing underlying mechanisms where psychological stress exacerbates symptoms in functional bladder disorders leading to identification of targets and potential treatments.

CHRONIC PELVIC PAIN, PELVIC FLOOR

ENDOMETRIOSIS-RELATED CHRONIC PELVIC PAIN

Soo Youn Song, Ye Won Jung, WonKyo Shin, Mia Park, Geon Woo Lee, Soohwa Jeong, Sukjeong An, Kyoungmin Kim, Young Bok Ko, Ki Hwan Lee, Byung Hun Kang, Mina Lee, Heon Jong Yoo. *Biomedicines.* 2023 Oct 23;11(10):2868. doi: 10.3390/biomedicines11102868. PMID: 37893241.

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The authors from Korea report that endometriosis, which is the presence of endometrial stroma and glands outside the uterus, is one of the most frequently diagnosed gynecologic diseases in reproductive women. Patients with endometriosis suffer from various pain symptoms such as dysmenorrhea, dyspareunia, and chronic pelvic pain. The pathophysiology for chronic pain in patients with endometriosis has not been fully understood. Altered inflammatory responses have been shown to contribute to pain symptoms. Increased secretion of cytokines, angiogenic factors, and nerve growth factors has been suggested to increase pain. Also, altered distribution of nerve fibers may also contribute to chronic pain. Aside from local contributing factors, sensitization of the nervous system is also important in understanding persistent pain in endometriosis. Peripheral

sensitization as well as central sensitization have been identified in patients with endometriosis. These sensitizations of the nervous system can also explain increased incidence of comorbidities related to pain such as irritable bowel disease, bladder pain syndrome, and vulvodynia in patients with endometriosis. In conclusion, there are various possible mechanisms behind pain in patients with endometriosis, and understanding these mechanisms can help clinicians understand the nature of the pain symptoms and decide on treatments for endometriosis-related pain symptoms.

INTEGRATED TOTAL PELVIC FLOOR ULTRASOUND IN PELVIC FLOOR DYSFUNCTION

A.J. Hainsworth, T. Gala, L. Johnston, D. Solanki, L. Ferrari, A.M.P. Schizas, G. Santoro. Continence, Volume 8, 2023, 101045, ISSN 2772-9737, <https://doi.org/10.1016/j.cont.2023.101045>.

(<https://www.sciencedirect.com/science/article/pii/S2772973723009037>)

Integrated total pelvic floor ultrasound is a combination of endoanal, transperineal, and endovaginal ultrasound used for the static and dynamic assessment of the entire pelvic floor. It can be used as a screening investigation for defaecatory dysfunction so that defaecatory radiological imaging may be avoided. It enables assessment of concomitant pelvic floor disorders such as anterior and middle compartment dysfunctions. Other advantages include the ability to perform in the outpatient rooms in a one stop clinic, alongside clinical assessment, and anorectal physiology, whilst avoiding separate radiology appointments and radiation exposure. Moreover, it has the potential to be used as a visual biofeedback tool. Integrated total pelvic floor ultrasound is user dependent and currently there are no fixed protocols for performance or reporting protocols. As integrated total pelvic floor ultrasound becomes more commonplace this is something which should be addressed. This article from the United Kingdom and Italy outlines the clinical utility, practicalities, and guidance for the interpretation of imaging which may be used. It is the basis for integrated total pelvic floor ultrasound workshops which have been held at the International Continence Society conference over the last 5 years.

MTHFR MUTATION ANOTHER UNIFYING ETIOLOGY OF CHRONIC OVERLAPPING PAIN CONDITIONS

Joseph Visingardi, Jan A. Paredes Mogica, Padma Sundaram, Talia Denis, Courtney Bellomo, Artem Loktev, Charles Argoff, Elise J.B. De. Continence, 2023, 101052, ISSN 2772-9737, <https://doi.org/10.1016/j.cont.2023.101052>.

(<https://www.sciencedirect.com/science/article/pii/S2772973723009104>)

Chronic pelvic pain (CPP) is a heterogeneous condition with multiple etiologies. Better characterization and understanding of CPP will lead to new therapeutic options and individualization of care, especially in patients with chronic overlapping pain syndromes (COPCs), which increase complexity of diagnosis. In this study from the USA and Russia, the authors present 6 patients with COPC and complex CPP, non-focal exam, who tested negative for small fiber neuropathy but who reported a history of methylenetetrahydrofolate reductase (MTHFR) mutations, and retrospective review of 76 patients with MTHFR mutation. This study explores through literature review whether MTHFR mutations play a role in the pathogenesis of chronic pelvic pain and overlapping pain conditions in a subset of patients with COPCs. Study design included an observational study of 6 patients, a retrospective cross-sectional study of 76 patients, and a literature review. The etiology of chronic pelvic pain is complex. Multisystem pain extending beyond the pelvis complicates the differential diagnosis but suggests a systemic cause. MTHFR mutations may play a unifying role in a subset of chronic pelvic pain patients with concomitant chronic overlapping pain syndromes. The mutations may affect folate metabolism pathways in these patients and hinder the ability to maintain nerve fibers over time, leading to dereliction of pain signal conduction. Disturbance of these pathways may have a role in chronic overlapping pain syndromes and complex pelvic pain.

APPROACH OF CHRONIC PELVIC PAIN WITH TOP FLAT MAGNETIC STIMULATION

Benedetta Salsi, Giulia Ganassi, Graziella Lopopolo, Silvia Callarelli, Alessandra Comito, Irene Fusco, Pablo González Isaza. Adv Urol. 2023 Sep 16:2023:9983301. doi: 10.1155/2023/9983301. eCollection 2023. PMID: 37745206 PMCID.

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In this study from Italy, vulvar Functional Status Questionnaire (VQ) was used for the evaluation of patient's chronic pelvic pain and muscle hypertone improvements. The interstitial cystitis was assessed by the Leary-Sant symptom and problem indexes (ICSI and ICPI). The scores resulting from the sum of the two indexes were evaluated as OSS (ICSI + ICPI). Women with chronic pelvic pain and muscle hypertone showed VQ mean values significantly lower than the controls ($p < 0.005$) from the second treatment up to the sixth one. In 6 patients affected by interstitial cystitis, the mean score of OSS was significantly lower than the controls ($p < 0.005$) from the second treatment up to 2 months follow-up after the last treatment session. No side effects were observed. Based on these results, this technology may successfully manage muscle hypertonicity condition, the chronic pelvic pain, and interstitial cystitis.

THE PERSISTENCY INDEX: A NOVEL SCREENING TOOL FOR IDENTIFYING MYOFASCIAL PELVIC FLOOR DYSFUNCTION IN PATIENTS SEEKING CARE FOR LOWER URINARY TRACT SYMPTOMS

A Lenore Ackerman, Michele Torosis, Nicholas J Jackson, Ashley T Caron, Melissa R Kaufman, Jerry L Lowder, Jonathan C Routh. Am J Obstet Gynecol. 2023 Aug 24:S0002-9378(23)00587-2. doi: 10.1016/j.ajog.2023.08.017. Online ahead of print. PMID: 37633575.

Open Access

Patients with myofascial pelvic floor dysfunction often present with lower urinary tract symptoms, such as urinary frequency, urgency, and bladder pressure. Often confused with other lower urinary tract disorders, this constellation of symptoms, recently termed myofascial urinary frequency syndrome, is distinct from other lower urinary tract symptoms and optimally responds to pelvic floor physical therapy. A detailed pelvic floor myofascial examination performed by a skilled provider is currently the only method to identify myofascial urinary frequency syndrome. Despite a high influence on quality of life, low awareness of this condition combined with no objective diagnostic testing leads to the frequent misdiagnosis or underdiagnosis of myofascial urinary frequency syndrome. This study from the USA aimed to develop a screening measure to identify patients with myofascial urinary frequency syndrome (bothersome lower urinary tract symptoms secondary to myofascial pelvic floor dysfunction) from patient-reported symptoms. A population of patients with isolated myofascial urinary frequency syndrome was identified by provider diagnosis from a tertiary urology practice and verified by standardized pelvic floor myofascial examination and perineal surface pelvic floor electromyography. This study recommends a novel screening method for patients presenting with lower urinary tract symptoms to identify patients with myofascial urinary frequency syndrome. As telemedicine becomes more common, this index provides a way of screening for myofascial urinary frequency syndrome and initiating pelvic floor physical therapy even before a confirmatory pelvic examination.

NEUROMODULATION FOR THE MANAGEMENT OF CHRONIC PELVIC PAIN SYNDROMES: A SYSTEMATIC REVIEW

Brandon Gish, Brendan Langford, Christopher Sobey, Chahait Singh, Newaj Abdullah, Jeremy Walker, Hannah Gray, Jon Hagedorn, Priyanka Ghosh, Kiran Patel, Timothy Deer. Pain Pract. 2023 Sep 19. doi: 10.1111/papr.13295. Online ahead of print. PMID: 37726930.

Chronic pelvic pain is a burdensome condition that involves multiple medical sub-specialties and is often difficult to treat. Sacral stimulation for functional bladder disease has been well established, but little large-scale evidence exists regarding utilization of other neuromodulation techniques to treat chronic pelvic pain. Emerging evidence does suggest that neuromodulation is a promising treatment, and we aim to characterize the use and efficacy of such techniques for treating chronic pelvic pain syndromes. In this study from the USA, a systematic review of the literature was carried

out demonstrating the treatment of chronic pelvic pain syndromes with neuromodulation. Abstracts were reviewed and selected for inclusion, including case series, prospective studies, and randomized controlled trials (RCTs). Case studies and publications in abstract only were not included. The reporting for this systematic review follows Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The literature search was performed using MEDLINE, Embase, Cochrane Library, PubMed, CINAHL, and Scopus. A total of 50 studies were included in this review, three of which were randomized controlled trials, and the remaining were prospective and retrospective case series. The range of pelvic pain conditions treated included interstitial cystitis, peripheral neuralgia, pudendal neuralgia, gastrointestinal pain, urogenital pain, sacroiliac joint pain, and visceral chronic pelvic pain. The authors reported on outcomes involving pain, functionality, psychosocial improvement, and medication reduction. It was concluded that neuromodulation is a growing treatment for various chronic pain syndromes. Peripheral nerve stimulation was the least studied form of stimulation. Posterior tibial nerve stimulation appears to offer short-term benefit, but long-term results are challenging. Sacral nerve stimulation is established for use in functional bladder syndromes and appears to offer pain improvement in these patients as well. Dorsal root ganglion stimulation and spinal cord stimulation have been used for a variety of conditions with promising results. Further studies of homogeneous patient populations are necessary before strong recommendations can be made at this time, although pooled analysis may also be impactful.

IMPACT OF CHRONIC PELVIC PAIN AND PAINFUL BLADDER SYNDROME ON THE PITTSBURGH SLEEP QUALITY INDEX ON WOMEN WITH DEEP ENDOMETRIOSIS: A CROSS-SECTIONAL STUDY

Ricardo José de Souza, Nivaldo Ribeiro Villela, Leila Cristina Soares Brollo, Marco Aurelio Pinho Oliveira. *Int Urogynecol J.* 2023 Oct;34(10):2487-2493. doi: 10.1007/s00192-023-05560-y. Epub 2023 May 20. PMID: 37209169.

Painful bladder syndrome (PBS) is frequently associated with deep endometriosis (DE), and both conditions cause chronic pelvic pain (CPP), which often impairs sleep quality. This study from Brazil was aimed at analyzing the impact of CPP plus PBS in women with DE on the global sleep quality index using the Pittsburgh Sleep Quality Index (PSQI) and subsequently examine each sleep dimension. One hundred and forty women with DE were included and answered the PSQI and the O'Leary-Sant Interstitial Cystitis Symptoms and Problem Index questionnaires with or without CPP. Women were categorized into good or poor sleepers using the PSQI cutoff; subsequently, a linear regression model was used to analyze the PSQI score and a logistic regression model for each questionnaire's sleep component. Only 13% of women with DE had a good sleep. Approximately 20% of those with DE but no/mild pain were good sleepers; 138 women with DE (88.5%), 94% with PBS, and 90.5% with moderate/severe pain were poor sleepers. For PSQI components, CPP worsened the subjective sleep quality by more than threefold ($p = 0.019$), increased sleep disturbances by nearly sixfold ($p = 0.03$) and decreased the sleep duration by practically sevenfold ($p = 0.019$). Furthermore, PBS increased sleep disturbances by nearly fivefold ($p < 0.01$). The addition of PBS to CPP in women with DE is devastating for overall sleep quality, probably because it impacts some sleep dimensions unaffected by CPP and amplifies the problem in those already affected by pain.

AUTOPHAGY AND UROLOGICAL DISEASE

THE MOLECULAR MECHANISM AND THERAPEUTIC APPLICATION OF AUTOPHAGY FOR UROLOGICAL DISEASE

Kuang-Shun Chueh, Jian-He Lu, Tai-Jui Juan, Shu-Mien Chuang, Yung-Shun Juan. *Int J Mol Sci.* 2023 Oct 4;24(19):14887. doi: 10.3390/ijms241914887. PMID: 37834333.

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Autophagy is a lysosomal degradation process known as autophagic flux, involving the engulfment of damaged proteins and organelles by double-membrane autophagosomes. It comprises microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy. Macroautophagy

consists of three stages: induction, autophagosome formation, and autolysosome formation. Atg8-family proteins are valuable for tracking autophagic structures and have been widely utilized for monitoring autophagy. The conversion of LC3 to its lipidated form, LC3-II, served as an indicator of autophagy. Autophagy is implicated in human pathophysiology, such as neurodegeneration, cancer, and immune disorders. Moreover, autophagy impacts urological diseases, such as interstitial cystitis/bladder pain syndrome (IC/BPS), ketamine-induced ulcerative cystitis (KIC), chemotherapy-induced cystitis (CIC), radiation cystitis (RC), erectile dysfunction (ED), bladder outlet obstruction (BOO), prostate cancer, bladder cancer, renal cancer, testicular cancer, and penile cancer. Autophagy plays a dual role in the management of urologic diseases, and the identification of potential biomarkers associated with autophagy is a crucial step towards a deeper understanding of its role in these diseases. Methods for monitoring autophagy include TEM, Western blot, immunofluorescence, flow cytometry, and genetic tools. Autophagosome and autolysosome structures are discerned via TEM. Western blot, immunofluorescence, northern blot, and RT-PCR assess protein/mRNA levels. Luciferase assay tracks flux; GFP-LC3 transgenic mice aid study. Knockdown methods (miRNA and RNAi) offer insights. This article from Taiwan extensively examines autophagy's molecular mechanism, pharmacological regulation, and therapeutic application involvement in urological diseases.

ARTIFICIAL INTELLIGENCE (AI)

OVERVIEW OF CURRENT APPLICATIONS AND TRENDS IN ARTIFICIAL INTELLIGENCE FOR CYSTOSCOPY AND TRANSURETHRAL RESECTION OF BLADDER TUMOURS

Atsushi Ikeda, Hirokazu Nosato. *Curr Opin Urol.* 2023 Oct 31. doi: 10.1097/MOU.0000000000001135. Online ahead of print. PMID: 37902120

The authors from Japan note that accurate preoperative and intraoperative identification and complete resection of bladder cancer is essential. Adequate postoperative follow-up and observation are important to identify early intravesical recurrence or progression. However, the accuracy of diagnosis and treatment is dependent on the knowledge and experience of the physicians. Artificial intelligence (AI) can be an important tool for physicians performing cystoscopies. Reports published over the past year and a half have identified an adequate amount of cystoscopy datasets for deep learning, with rich datasets of multiple tumour types including images of flat, carcinoma-in-situ, and elevated lesions, and more diverse applications. In addition to detecting bladder tumours, AI can assist in diagnosing interstitial cystitis. Applications of AI using conventional white-light and also to bladder endoscopy with different image enhancement techniques and manufacturers is underway. A framework has also been proposed to standardise the management of clinical data from cystoscopy to aid education and AI development and to compare with gastrointestinal endoscopic AI. Although real-world clinical applications have lagged, technological developments are progressing. AI-based cystoscopy is likely to become an important tool and is expected to have real-world clinical applications comprehensively linking AI and imaging, data management systems, and clinicians.

PATIENTS & SOCIAL MEDIA

THE ROLE OF FACEBOOK SUPPORT GROUPS FOR WOMEN WITH BENIGN UROLOGIC CONDITIONS

Omar K Farah, Connie N Wang, Doreen E Chung. *Neurourol Urodyn.* 2023 Nov;42(8):1795-1801. doi: 10.1002/nau.25283. Epub 2023 Sep 13. PMID: 37705338 DOI: 10.1002/nau.25283

The purpose of this study from the USA was to understand the availability and content of patient support groups on social media platforms. Five prevalent benign, urologic conditions affecting adult women were selected for analysis. Facebook support groups for these conditions were identified. Groups specific to one urologic condition and with at least 400 members were included, and groups for pediatric and malignant conditions were excluded. Each support group was analyzed for member count, posts per month, and period of activity. The 100 most recent posts in the largest support

groups were manually reviewed and further categorized into content subsections. A total number of 56 Facebook support groups were identified that satisfied the inclusion/exclusion criteria. Interstitial cystitis (IC) had 25 groups (68 466 members; 4825 posts), pelvic organ prolapse (POP) had 14 groups (72 342; 3067), UTI had nine groups (36 414; 3204), overactive bladder and/or urinary incontinence (OAB/UI) had seven groups (8246; 306), urinary retention had one group (1168; 118). Across all groups, post content was predominantly informational support (77.6%). Remaining post content was both informational and emotional support (10.0%), emotional support only (7.6%), or unrelated to either informational or emotional support (4.8%). Individuals with benign urologic conditions are utilizing social media support groups predominantly to seek and share informational support from patient peers. The number of existing groups as well as the level of activity and number of members within individual support groups varies significantly between different urologic conditions. This suggests that there is an unmet need for accessible informational content for patients who suffer with benign urological conditions.

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