International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization focused on interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
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RESEARCH UPDATE – October 2024

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

Most of these have a direct link to the PubMed abstract if you click on the title. An increasing number of scientific articles "In Press" or "Early View" are being published early online (on the Journal website) as "Epub ahead of print" sometimes long before they are published in the journals. While abstracts are usually available on PubMed, the pre-publication articles can only be read online if you have online access to that specific journal. However, in some cases there may be open access to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of open access.
We also include so-called "Preprints". These are preliminary reports of work that have not been certified by peer review. They should therefore not be relied on to guide clinical practice or health-related behaviour. (See https://www.medrxiv.org/content/about-medrxiv for further information).

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

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

QUALITY OF LIFE AND TREATMENT MODALITIES IN PATIENTS WITH INTERSTITIAL CYSTITIS: THE PATIENTS' PERSPECTIVE

Ginkel CV, Martens F, Scholtes M, Heesakkers J, Janssen DAW. Healthcare (Basel). 2024 Feb 13;12(4):466. doi: 10.3390/healthcare12040466. PMID: 38391841; PMCID: PMC10887755.
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Quality of life (QoL)-based outcomes are scarcely incorporated into interstitial cystitis/bladder pain syndrome (IC/BPS) guidelines because studies are limited and outdated. Therefore, guidelines might not reflect the current clinical situation accurately. Secondly, guidelines suggest using a multimodal approach for BPS/IC management, but data on the patient-perceived efficacy of these therapies are limited. The aim of this study from the Netherlands was to investigate the perception of IC/BPS patients of their QoL, to determine which treatments they have received, and to examine how they evaluate the efficacy of these various (alternative) therapies. A quantitative retrospective database evaluation was performed, with data from an existing IC/BPS patient survey (n = 217) conducted in 2021. This survey contained QoL data based on validated questionnaires such as EQ-5D 5L. The QoL of patients is affected significantly by IC/BPS. This is evident from the various affected domains on the EQ-5D 5L. The symptom severity was negatively affected by a delay in diagnosis, and there were clear differences in QoL domains between females and males. Secondly, coagulation therapy and intravesical glycosaminoglycan (GAG) therapy were most appreciated by patients. Other (alternative) treatments were commonly utilized, although some had doubtful results and high

discontinuation rates. The authors concluded that QoL is considerably impaired in IC/BPS patients. The diverse responses and adherence to various treatments warrant a personalized approach (phenotype-oriented therapy). To achieve QoL improvement, it is important to incorporate the patient's perspective in treatment guidelines.

COPING WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Sutherland S, Grace Kelly A, McKernan LC, Dmochowski RR, Reynolds WS, Sebesta EM. Neurourol Urodyn. 2024 Sep 16. doi: 10.1002/nau.25579. Epub ahead of print. PMID: 39282858.

Compensatory coping, or maladaptive alterations in behavior with the intention of preventing or managing symptoms, is increasingly being explored as a key factor in how people respond to bladder conditions. Preliminary investigations have identified relations between coping behaviors and psychological distress in urologic conditions, including interstitial cystitis/bladder pain syndrome (IC/BPS). However, previous explorations of coping have not accounted for heterogeneity in coping behaviors or addressed the likelihood that some coping behaviors may be more adaptive than others. This study from the USA sought to examine how two specific types of coping behaviors, primary control coping and disengaged coping, are related to distress and symptoms in IC/BPS, and to explore the potential role of pain phenotype in this relationship. A secondary data analysis was conducted with a large community data set (N = 677 women with IC/BPS) and employed descriptive and inferential statistics to characterize coping patterns and explore novel predictors of distress. Results indicated that almost all participants engaged in at least one compensatory coping behavior within the last week. Both types of coping behaviors correlated with psychological symptoms, and when controlling for relevant clinical variables (i.e., age and severity of urinary symptoms), disengaged coping behaviors were significantly associated with psychological distress. Further, the addition of pain phenotype to multiple regression models resulted in a more effective predictive model when considering the relation between coping behaviors and depression. By investigating more deeply the relationship between coping and distress, understanding of potential risk factors and mechanisms is increased, offering valuable insights for intervention strategies for IC/BPS patients.

CURRENT CLINICAL STATUS OF IC/BPS AND WHAT THE FUTURE HOLDS IN BASIC & TRANSLATIONAL SCIENCE

Guldal Inal , Dick Janssen, Naside Mangir, Francisco Cruz, Ana Charrua. Continence Vol 11. September 2024. 101338

This review from Turkey, Netherlands and Portugal summarizes the scientific content in the workshop “Current clinical status of IC/BPS and what the future holds in basic & translational science” at the International Continence Society (ICS) 2023, Toronto. In the workshop, clinicians and scientists from different disciplines and nationalities discussed the current clinical status of IC/BPS diagnostic and treatment. They defined the available trends in biomarker search and translational medicine. The recent contribution of computational science and bioinformatics, together with artificial intelligence and the recent improvements in the use of animal models were also explored.

The search for diagnostic and predictive biomarkers for IC/BPS patients is important. The use of well-refined and characterized animal models and the use of bioinformatics and artificial intelligence will be useful in this search.

RISK CLASSIFICATION FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME USING MACHINE LEARNING BASED PREDICTIONS.

Lamb LE, Janicki JJ, Bartolone SN, Ward EP, Abraham N, Laudano M, Smith CP, Peters KM, Zwaans BMM, Chancellor MB. Urology. 2024 Jul;189:19-26. doi: 10.1016/j.urology.2024.03.043. Epub 2024 Apr 25. PMID: 38677373.

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The purpose of this study was to improve diagnosis of IC/BPS, Lamb and colleagues from the USA developed an improved IC risk classification using machine learning algorithms. National crowdsourcing resulted in 1264 urine samples consisting of 536 IC (513 female, 21 male, 2 unspecified), and 728 age-matched controls (318 female, 402 male, 8 unspecified) with corresponding patient-reported outcome (PRO) pain and symptom scores. In addition, 296 urine samples were collected at three academic centers: 78 IC (71 female, 7 male) and 218 controls (148 female, 68 male, 2 unspecified). Urinary cytokine biomarker levels were determined using Luminex assay. A machine learning predictive classification model, termed the Interstitial Cystitis Personalized Inflammation Symptom (IC-PIS) Score, that utilizes PRO and cytokine levels, was generated and compared to a challenger model. The top-performing model using biomarker measurements and PROs (area under the curve [AUC]=0.87) was a support vector classifier, which scored better at predicting IC than PROs alone (AUC=0.83). While biomarkers alone (AUC=0.58) did not exhibit strong predictive performance, their combination with PROs produced an improved predictive effect. It was concluded that IC-PIS represents a novel classification model designed to enhance the diagnostic accuracy of IC/bladder pain syndrome by integrating PROs and urine biomarkers. According to the authors, the innovative approach to sample collection logistics, coupled with one of the largest crowdsourced biomarker development studies utilizing ambient shipping methods across the US, underscores the robustness and scalability of their findings.

URINARY SPHINGOSINE-1-PHOSPHATE AS A BIOMARKER FOR BLADDER PAIN SYNDROME.

Eggers E, Crouss T, Lipetskaia L, DiSanto M. Urogynecology (Phila). 2024 Mar 1;30(3):374-380. doi: 10.1097/SPV.0000000000001473. PMID: 38484256.

Sphingosine-1-phosphate (S1P) is a signalling molecule involved in inflammation and bladder contraction. The aims of this case-control pilot study from the USA were to compare urinary S1P concentrations in bladder pain syndrome (BPS) participants to controls and determine whether these concentrations correlate with disease severity and duration. Adult females with BPS and controls were enrolled. Bladder pain syndrome participants completed an O'Leary-Sant questionnaire. Information on duration of symptoms and treatment history was obtained. Urinary S1P and creatinine concentrations were determined. Mann-Whitney U tests were used to compare groups, and Spearman correlation was used to test for associations between concentrations and duration and severity of symptoms. Twenty-five participants were in each group. Median S1P concentration was 1,225 ng/dL in the BPS group and 2,183 ng/dL in the control group, which was significantly different ($P < 0.0001$). This difference did not persist when normalized to urinary creatinine ($P = 0.58$). No differences were noted in urinary S1P concentrations between treated and untreated participants ($P = 0.53$) or with symptom scores of 13 or greater and less than 13 ($P = 0.69$). Sphingosine-1-phosphate levels did not correlate with O'Leary-Sant scores ($P = 0.08$) or duration of symptoms ($P = 0.67$). Results did not change when using S1P concentrations normalized to creatinine. This study demonstrated successful quantification of human urinary S1P concentrations. A difference in urinary S1P was found between BPS participants and controls but not when normalized to creatinine. While this is the first study to investigate urinary S1P as a biomarker for BPS, results suggest that it may have a potential role as a biomarker requiring further research.

POTENTIAL URINE AND SERUM BIOMARKERS IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Wang L, Gao J, Zheng S, Wang Z, Zheng S, Luo Z. Arch Esp Urol. 2024 May;77(4):353-358. doi: 10.56434/j.arch.esp.urol.20247704.48. PMID: 38840277.

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IC/BPS is a common chronic disease, and its aetiology and pathogenesis remain unclear. This study from China aimed to identify potential urine and serum biomarkers in patients with IC/BPS to further understand the pathogenesis and diagnosis of the disease. Patients with IC/BPS diagnosed and treated in the First Hospital of Hebei Medical University from 1 July 2021 to 30 July 2023 were

selected. The urine and serum biomarkers of 50 patients with IC/BPS were investigated and compared with the urine and serum samples of 50 healthy controls. IBM SPSS Statistics 26.0 was used for statistical analysis of the recorded data by using chi-square test, *T*-test and logistic regression analysis. Overall, 50 patients with IC/BPS (mean age, 54.20 ± 8.15 years) were included in the study. Those with history of urinary diseases, anxiety or depression were susceptible to IC/BPS. Levels of interleukin (IL)-6, tumor necrosis factor-α (TNF-α), nerve growth factor, and prostaglandin E2 (PGE2) in urine, as well as IL-8, TNF-α, and PGE2 in serum, were found to significantly increase in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). These differences were statistically significant ($p < 0.05$). Multifactor analysis showed that anxiety, depression, IL-6, IL-8, TNF-α and PEG2 are risk factors for patients with IC/BPS. Multiple biomarkers were identified in the urine and serum of patients with IC/BPS, suggesting a potential close relationship to the pathogenesis of IC/BPS.

IDENTIFICATION OF PLAC8 AS A POTENTIAL BIOMARKER FOR THE DIAGNOSIS OF INTERSTITIAL CYSTITIS.

Li P, Xu M, Zhang Z, Zhang X, Xie F, Zhang X. Comb Chem High Throughput Screen. 2024;27(13):1938-1947. doi: 10.2174/0113862073273817231107050852. PMID: 38441011.

Interstitial cystitis is a diagnosis of exclusion due to the complexity of its etiology and pathology, which is a chronic disease with an unknown etiology. The authors from China note that, to their knowledge, few studies have been performed to identify predictive biomarkers for interstitial cystitis. The interstitial cystitis datasets were retrieved from the Gene Expression Omnibus (GEO) database. Differentially expressed genes (DEGs) were identified by using the R package and were subjected to functional and pathway enrichment analysis. Key biomarkers of interstitial cystitis were identified by using Lasso regression analysis and the SVM-RFE algorithm. The diagnostic value of key biomarkers was validated in internal and external datasets, and pathways that relate to biomarkers of interstitial cystitis were screened. The ssGSEA was employed to identify the immune cells closely related to biomarkers. The expression of PLAC8 in patients with interstitial cystitis was detected by Immune-Histochemistry (IHC). Sixteen differentially expressed genes associated with interstitial cystitis were identified, which were primarily linked to the biological process of the chemokine signalling pathway. PLAC8, identified as a biomarker for interstitial cystitis, was validated to express a significantly different between IC and normal bladder tissues. PLAC8-related pathways were analyzed, with a focus on NF-κB, TNF, Toll-like receptor, chemokine, IL-17, and JAK-STAT signalling pathways. PLAC8 was proved to be closely related to immune activations, which is similar to the pathogenesis of IC, which is a chronic dysregulated immune disease. The authors also observed a higher level of PLAC8 in IC tissues. It was concluded that PLAC8 has promising application prospects as a biomarker for interstitial cystitis diagnosis. These findings could aid in the diagnosis and treatment of interstitial cystitis.

EXCLUDING CONFUSABLE DISEASES IN PATIENTS WITH PRESUMPTIVE DIAGNOSIS OF INTERSTITIAL CYSTITIS: A LARGE PATIENT COHORT STUDY.

Jeong HJ, Kang YJ, Choo MS, Jeong SJ, Oh SJ. Int J Gynaecol Obstet. 2024 Aug 11. doi: 10.1002/ijgo.15856. Epub ahead of print. PMID: 39127911.

The purpose of this study from South Korea was to analyze the results of excluding confusable diseases in patients with a presumptive diagnosis of interstitial cystitis (IC). The authors retrospectively reviewed the electronic medical records of consecutive patients with IC between October 2005 and December 2019. Patients with pelvic pain underwent an initial workup. Of these, 646 patients (164 men, 25.4%; 482 women, 74.6%) underwent observational cystoscopy under the suspicion of IC. Fourteen patients had genitourinary tract malignancies (2.2%) (bladder cancer, n = 13; prostate cancer, n = 1). Of the 13 patients with bladder cancer, three were diagnosed during initial observation cystoscopy. The remaining 10 patients were diagnosed during subsequent follow-up cystoscopic surgery. Urinary tuberculosis was identified in seven (1.1%) of 646 patients during the

examination. Five (0.8%) of the six patients with suspected urinary tuberculosis at baseline imaging were positive for tuberculosis in the acid-fast bacillus test. One patient developed tuberculous granulomas in the bladder tissue after a cystectomy for intractable pelvic pain. The authors concluded that their results show that continuous efforts to rule out bladder tumors or tuberculosis are still essential in the follow up of patients with suspected IC, even if these diseases are not excluded at the initial examination. Imaging studies are necessary to rule out tuberculosis.

EVALUATING SYMPTOM SEVERITY AND URINARY CYTOKINE LEVELS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS, WITH AND WITHOUT HUNNER'S LESIONS.

Zwaans BM, Mota S, Bartolone SN, Ward EP, Peters KM, Chancellor MB. Am J Clin Exp Urol. 2024 Apr 15;12(2):110-118. doi: 10.62347/BLED2401. PMID: 38736620; PMCID: PMC11087211.

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IC/BPS is a condition characterized in part by urinary urgency, frequency, and pain. There is a strong interest in gathering more data to compare and assess the differences in characteristics based on the presence of Hunner's lesions in patients with IC/BPS. Using a nationwide crowdsource effort, the authors collected surveys and urine samples from patients with a history of IC/BPS. Participants completed the Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI), Overactive Bladder questionnaire (OABq SF), and pain scores. In addition, participants reported any co-morbidities and lifestyle modifications. Urinary cytokine levels were measured and compared to symptom severity. 491 participants enrolled: 119 with history of ulcerative Hunner's lesions (UIC), 372 reported no lesions (NHIC), and 2 unknowns. 96.3% were female, and prevalence of UIC was equal for both genders. Average age was higher for UIC vs. NHIC group ($P = 0.011$), as was the duration since diagnosis ($P < 0.001$). Symptom scores were elevated in UIC patients ($P < 0.001$). Both groups widely implemented lifestyle modifications, with dietary changes being most prevalent (70.1%), followed by prescription medication usage (63.1%). More UIC compared to NHIC participants experienced co-morbidities ($P = 0.010$). Urine samples were analyzed for GRO, IL-6, IL-8, and MCP-1. MCP-1 levels were significantly higher in UIC patients ($P = 0.044$). Weak positive correlation was found between cytokines and symptom scores. Patients with UIC and NHIC from across the United States displayed distinct phenotypic and urine biological characteristics. These findings contribute to increased understanding of IC/BPS and may aid in improving our knowledge of the condition.

SECONDARY ANALYSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS ENROLLED IN A RECURRENT URINARY TRACT INFECTION PREVENTION STUDY PROVIDES A NOVEL PARADIGM FOR ETIO-PATHOGENESIS AND PRACTICAL MANAGEMENT OF THIS INFECTION PHENOTYPE.

Nickel JC, Cotechini T, Doiron RC. Pathogens. 2024 May 9;13(5):396. doi: 10.3390/pathogens13050396. PMID: 38787248; PMCID: PMC11123849.

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A subset of IC/BPS patients experience recurrent urinary tract infection (rUTI) associated with symptom flares. In this Canadian study, recurrent UTI subjects with associated IC/BPS were enrolled in the first North American early clinical experience trial evaluating a new sublingual UTI preventative vaccine, MV140. It has been shown that women with rUTI develop an imbalance in the T helper 1 and 2 (Th2 over-expression) in the bladder mucosa. The hypothesis-generating secondary analysis will suggest that this infection subcategory of IC/BPS patients develop a similar imbalance of Th1-Th2 response type to bacteria present in their urinary microbiome, leading to a bladder hypersensitivity that responds to mucosal immune modulation. Female participants with ≥3 documented UTI/year underwent a 3-month vaccination treatment period with a 9-month efficacy period after completion of vaccine treatment (total 12 months). There were no exclusion criteria for subjects in relation to baseline urinary symptoms and/or discomfort/pain. Primary outcome was no UTI following vaccination. Secondary outcomes included change in UTI incidence, overall patient-reported subjective global assessment (SGA responder defined as moderately or markedly improved on 7-point scale), and safety. Sixteen subjects with IC/BPS-related symptoms and rUTI (mean age 47;

range 23-74 years; mean number of UTI episodes in previous year 6.1 +/- 4.2) were eligible to be included in the Health Canada-approved MV140 vaccine study for prevention of rUTI. All subjects completed the 3-month vaccination period. One subject was lost to follow-up after their 6-month visit. Six subjects were UTI-free, while all 16 subjects had a reduction in UTI episodes compared to the year pre-vaccination. The total post-vaccination reduction in UTI episodes compared to pre-vaccination was 80% (0.1 UTI/subject/month from 0.5 UTI/subject/month, respectively). At 12 months, 13 subjects (81%) were SGA responders (moderately or markedly improved), and the responders reported a reduction in IC/BPS symptoms, with 8 subjects reporting significant or almost complete resolution of their specific long-term bladder discomfort/pain and bothersome urinary frequency or urgency. Four subjects reported mild and self-limited adverse events during vaccination period, but none were related to MV140 vaccine. Sublingual MV140 vaccine in IC/BPS patients with rUTI not only achieved UTI-free or reduced UTI incidence status but also, after approximately 9 months post vaccination, resolution of patients' long-term treatment-refractory IC/BPS symptoms. This suggests some cases of IC/BPS may be etiologically based on Th2-driven hypersensitivity to bacteria within or entering the urinary microbiome that responds to a vaccine whose mechanism of action is to normalize or balance the bladder Th1/Th2 mucosal immune system.

USING URINE BIOMARKERS TO DIFFERENTIATE BLADDER DYSFUNCTIONS IN WOMEN WITH SENSORY BLADDER DISORDERS.

Chen YC, Jiang YH, Jhang JF, Kuo HC. Int J Mol Sci. 2024 Aug 29;25(17):9359. doi: 10.3390/ijms25179359. PMID: 39273307; PMCID: PMC11395209.

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Sensory bladder disorders encompass several distinct conditions with overlapping symptoms, which pose diagnostic challenges. This study from Taiwan aimed to evaluate urine biomarkers for differentiating between various sensory bladder disorders, including non-Hunner's interstitial cystitis (NHIC), detrusor overactivity (DO), hypersensitive bladder (HSB), and urodynamically normal women. A retrospective analysis of 191 women who underwent a videourodynamic study (VUDS) was conducted, with some also receiving cystoscopic hydrodistention to confirm the presence of NHIC. Participants were categorized into four groups: DO (n = 51), HSB (n = 29), NHIC (n = 81), and normal controls (n = 30). The urine levels of inflammatory and oxidative stress biomarkers were measured. The DO patients exhibited elevated IP-10 levels, while the HSB patients had decreased TAC and 8-OHdG levels. The NHIC patients showed lower IL-2 and higher TNF-α levels. A TNF-α ≥ 1.05 effectively identified NHIC, with an AUROC of 0.889, a sensitivity of 98.8%, and a specificity of 81.3%. An IP-10 ≥ 6.31 differentiated DO with an AUROC of 0.695, a sensitivity of 56.8%, and a specificity of 72.3%. An 8-OHdG ≤ 14.705 and a TAC ≤ 528.7 identified HSB with AUROCs of 0.754 and 0.844, respectively. The combination of 8-OHdG and TAC provided an AUROC of 0.853 for HSB. These findings suggest that TNF-α, IP-10, TAC, 8-OHdG, and IL-2 are promising non-invasive biomarkers for distinguishing between these conditions, which may improve diagnosis and management.

CHARACTERIZATION AND THERAPEUTIC POTENTIAL OF CURCUMIN-LOADED CERIUM OXIDE NANOPARTICLES FOR INTERSTITIAL CYSTITIS MANAGEMENT.

Lin YC, Liang YJ, Zhang CH, Liu LJ, Lin FH. Antioxidants (Basel). 2024 Jul 10;13(7):826. doi: 10.3390/antiox13070826. PMID: 39061895; PMCID: PMC11273629.

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Oxidative stress resulting from reactive oxygen species (ROS) is often considered to be the leading cause of interstitial cystitis (IC), which is a chronic inflammatory disease. Antioxidants have been proven to have promising therapeutic effects on IC. In this study from Taiwan and China, the authors present an antioxidant intervention for IC by introducing curcumin-loaded cerium oxide nanoparticles (Cur-CONPs). Recognizing oxidative stress as the primary contributor to IC, this research builds on previous work utilizing cerium oxide nanoparticles (CONPs) for their outstanding

antioxidant and anti-inflammatory properties. However, given the need to effectively relieve acute inflammation, they engineered Cur-CONPs to harness the short-term radical-scavenging antioxidant prowess of curcumin. Through in vitro studies, they demonstrate that the Cur-CONPs exhibit not only robust antioxidant capabilities but also superior anti-inflammatory properties over CONPs alone. Furthermore, in vivo studies validate the therapeutic effects of Cur-CONPs on IC. Mice with IC subjected to the Cur-CONP treatment exhibited improved micturition behaviors, relief from pelvic pain sensitivity, and reduced expression of inflammatory proteins (*IL-6*, *IL-1β*, *TNF-α*, *Cox2*). These findings suggest that the synergistic antioxidant properties of the Cur-CONPs that combine the sustained antioxidant properties of CONPs and acute anti-inflammatory capabilities of curcumin hold promise as a novel treatment strategy for IC.

MECHANISMS OF OXIDATIVE STRESS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Mohammad A, Laboulaye MA, Shenhar C, Dobberfuhl AD. Nat Rev Urol. 2024 Jul;21(7):433-449. doi: 10.1038/s41585-023-00850-y. Epub 2024 Feb 7. PMID: 38326514.

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

CDK1/P53/P21 FEEDBACK LOOP MECHANISMS IN THE PATHOGENESIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Wang K, Shi J, Chen Z, Xue D, He X.Biochim Biophys Acta Mol Basis Dis. 2024 Oct;1870(7):167305. doi: 10.1016/j.bbadis.2024.167305. Epub 2024 Jun 14. PMID: 38880159.

This study from China aimed to elucidate the role of the Cdk1/p53/p21 feedback loop in the pathogenesis of IC/BPS. An IC/BPS cell model was established. Cell viability was determined using the CCK-8 assay. Flow cytometry was adopted to assess cell apoptosis rates. ELISA was employed to measure secretion levels of inflammatory factors (IL-6, IL-8, and TNF-α). Gene expressions were assessed using PCR, while protein expressions were analyzed through Western blotting analysis. Epithelial permeability was demonstrated using the phenol red leakage experiment and FITC-dextran permeability assay. The interaction between proteins was determined using co-immunoprecipitation, and protein localization was investigated using immunofluorescence. The CCK-8 assay revealed a significantly reduced viability of IC/BPS cells compared to normal epithelial cells ($p < 0.05$). Elevated levels of IL-6, IL-8, and TNF-α were detected in IC/BPS cells. Changes in the expressions of E-cadherin and ZO-1 were evident, leading to increased epithelial permeability in IC/BPS cells. Furthermore, within IC/BPS cells, Cdk1 phosphorylated p53 in the nucleus. The Cdk1/p53/p21 feedback loop was established to influence urothelial permeability. Both p21 and Cdk1 inhibitors notably reduced the epithelial permeability in IC/BPS cells. The Cdk1/p53/p21 feedback loop was instrumental in IC/BPS, acting as a regulator of urothelial permeability. This discovery offered a novel therapeutic approach for IC/BPS management.

IDENTIFICATION OF KEY PATHWAYS AND MRNAS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME TREATMENT WITH QUERCETIN THROUGH BIOINFORMATICS ANALYSIS OF MRNA-SEQUENCE DATA.

Wang G, Li P, Su SW, Xu R, Huang ZY, Yang TX, Li JM. Aging (Albany NY). 2024 Mar 22;16(7):5949-5966. doi: 10.18632/aging.205682. Epub 2024 Mar 22. PMID: 38526326; PMCID: PMC11042929.

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IC/BPS is a chronic condition with a painful bladder. At present, the pathogenesis of IC/BPS is still unknown. Quercetin (QCT) is a kind of natural flavonoid with wide sources and multiple biological activities. The purpose of this study from China was to explore the effects of QCT on mRNA expression and related regulatory signal pathways in IC model rats. LL-37 was used to induce the IC/BPS model rats. 20 mg/kg QCT was injected intraperitoneally into IC/BPS rats. ELISA, HE, Masson and TB staining were used to evaluate the level of inflammation and pathology. The concentration of QCT in rats was detected by HPLC. The mRNA sequencing was used to detect the differentially expressed (DE) mRNA in each group. The over-expression experiment of Lpl was carried out in IC/BPS model rats. QCT treatment significantly decreased the level of MPO, IL-1β, IL-6 and TNF-α induced by LL-37 in rats, and alleviated bladder injury and mast cell degranulation. There were significant differences in mRNA sequencing data between groups, and the hub gene Lpl were screened by Cytohubba. The expression of Lpl was downregulated in IC/BPS rats. QCT intervention promoted Lpl expression. Overexpression of Lpl reduced the bladder injury induced by LL-37, increased GAG level and decreased the expression of MPO, IL-1β, IL-6 and TNF-α. In this study, the authors provided the DE mRNA in IC/BPS rats treated with QCT, the signaling pathways for DE enrichment, screened out the hub genes, and revealed that Lpl overexpression alleviated IC/BPS model rats.

EXPERIMENTAL ANIMAL MODELS FOR IC/BPS.

*Tetsuichi Saito, Teruyuki Ogawa, Pradeep Tyagi & Naoki Yoshimura. Curr Bladder Dysfunct Rep **19**, 119–126 (2024). https://doi.org/10.1007/s11884-024-00753-7*

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a disease that causes bladder symptoms such as pelvic pain and frequent urination and is often an intractable disease affecting a patient's quality of life. Saito and colleagues from Japan and the USA report that the etiology of IC/BPS remains elusive, and treatment strategies are still not fully established. To better understand the underlying pathophysiology, many studies have strived to recreate an animal model of IC/BPS to help further expand the treatment options of this difficult disease. Basic animal studies of IC/BPS have often been conducted by provoking inflammation in the bladder, which is useful at least in part due to the similarity of the pathophysiology to profound inflammatory responses in IC/BPS, especially in the Hunner lesion subtype. Also, other animal models such as bladder stimulation models, pelvic organ cross-sensitization models, autoimmune models, and psychological stress models have been explored and shown various new outsights. However, the predicted underlying etiology of IC/BPS is complex often with a combination of inflammation, ischemia, and neurogenic changes, which makes it challenging for researchers to translate the results in animal models to clinical applications. Each animal model that is containing a piece of the underlying etiology of IC/BPS cannot be obtained alone, but by forming a picture by using each piece adequately will enable us to expand the horizon of the unexplored pathophysiology, which will lead us to identify novel therapeutic targets.

A HUMAN STAT3 GAIN-OF-FUNCTION VARIANT DRIVES LOCAL TH17 DYSREGULATION AND SKIN INFLAMMATION IN MICE.

Toth KA, Schmitt EG, Kolicheski A, Greenberg ZJ, Levendosky E, Saucier N, Trammel K, Oikonomou V, Lionakis MS, Klechevsky E, Kim BS, Schuettpelz LG, Saligrama N, Cooper MA. J Exp Med. 2024 Aug 5;221(8):e20232091. doi: 10.1084/jem.20232091. Epub 2024 Jun 11. PMID: 38861030; PMCID: PMC11167377.

Germline gain-of-function (GOF) variants in STAT3 cause an inborn error of immunity associated with early-onset poly-autoimmunity and immune dysregulation. To study tissue-specific immune dysregulation, the authors from the USA used a mouse model carrying a missense variant (p.G421R) that causes human disease. They observed spontaneous and imiquimod (IMQ)-induced skin inflammation associated with cell-intrinsic local Th17 responses in STAT3 GOF mice. CD4+ T cells were sufficient to drive skin inflammation and showed increased Il22 expression in expanded clones. Certain aspects of disease, including increased epidermal thickness, also required the presence of STAT3 GOF in epithelial cells. Treatment with a JAK inhibitor improved skin disease without affecting local Th17 recruitment and cytokine production. These findings collectively support the involvement of Th17 responses in the development of organ-specific immune dysregulation in STAT3 GOF and suggest that the presence of STAT3 GOF in tissues is important for disease and can be targeted with JAK inhibition.

MIF-MODULATED SPINAL PROTEINS ASSOCIATED WITH PERSISTENT BLADDER PAIN: A PROTEOMICS STUDY.

Ye S, Agalave NM, Ma F, Mahmood DFD, Al-Grety A, Khoonsari PE, Leng L, Svensson CI, Bucala R, Kultima K, Vera PL. Int J Mol Sci. 2024 Apr 19;25(8):4484. doi: 10.3390/ijms25084484. PMID: 38674069; PMCID: PMC11050327.

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Bladder pain is a prominent symptom in IC/BPS. Ye and colleagues from Sweden and the USA studied spinal mechanisms of bladder pain in mice using a model where repeated activation of intravesical Protease Activated Receptor-4 (PAR4) results in persistent bladder hyperalgesia (BHA) with little or no bladder inflammation. Persistent BHA is mediated by spinal macrophage migration inhibitory factor (MIF), and is associated with changes in lumbosacral proteomics. They investigated the contribution of individual spinal MIF receptors to persistent bladder pain as well as the spinal proteomics changes associated with relief of persistent BHA by spinal MIF antagonism. Female mice with persistent BHA received either intrathecal (i.t.) MIF monoclonal antibodies (mAb) or mouse IgG1 (isotype control antibody). MIF antagonism temporarily reversed persistent BHA (peak effect: 2 h), while control IgG1 had no effect. Moreover, i.t. antagonism of the MIF receptors CD74 and C-X-C chemokine receptor type 4 (CXCR4) partially reversed persistent BHA. For proteomics experiments, four separate groups of mice received either repeated intravesical scrambled peptide and sham i.t. injection (control, no pain group) or repeated intravesical PAR4 and: sham i.t.; isotype IgG1 i.t. (15 µg); or MIF mAb (15 µg). L6-S1 spinal segments were excised 2 h post-injection and examined for proteomics changes using LC-MS/MS. Unbiased proteomics analysis identified and relatively quantified 6739 proteins. They selected proteins that showed significant changes compared to control (no pain group) after intravesical PAR4 (sham or IgG i.t. treatment) and showed no significant change after i.t. MIF antagonism. Six proteins decreased during persistent BHA (V-set transmembrane domain-containing protein 2-like confirmed by immunohistochemistry), while two proteins increased. Spinal MIF antagonism reversed protein changes. Therefore, spinal MIF and MIF receptors mediate persistent BHA and changes in specific spinal proteins. These novel MIF-modulated spinal proteins represent possible new targets to disrupt spinal mechanisms that mediate persistent bladder pain.

THE SEROTONIN(5-HT)2A RECEPTOR IS INVOLVED IN THE HYPERSENSITIVITY OF BLADDER AFFERENT NEURONS IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS.

Chen X, Lv R, Li M, Zhang L, Sun Y, Cao N, Gu B. Eur J Pharmacol. 2024 Aug 21;982:176909. doi: 10.1016/j.ejphar.2024.176909. Epub ahead of print. PMID: 39154826.

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic bladder inflammation characterized by the main symptoms of urinary frequency, urgency, and pelvic pain. The authors from Shanghai, China note that hypersensitivity of bladder afferent neurons is considered a significant

pathophysiologic mechanism in IC/PBS. Serotonin (5-HT, 5-hydroxytryptamine) receptors are known to be involved in the regulation of the micturition reflex and hyperalgesia, but the effect of 5-HT receptors on cystitis remains unknown. In this study, a rat model of interstitial cystitis induced by intraperitoneal injection of cyclophosphamide (CYP) was used to investigate the role of 5-HT receptors on cystitis. The histology and urodynamics exhibited chronic cystitis and overactive bladder in CYP-treated rats. Notably, among 5-HT1A, 5-HT2A and 5-HT7 receptors, the expression of 5-HT2A receptor was significantly increased in bladder afferent neurons in CYP-treated rats. Intrathecal administration of the 5-HT2A receptor antagonist M100907 could alleviate bladder overactivity and hyperalgesia in CYP-induced cystitis rats. Neuronal calcium imaging of bladder afferent neurons revealed increased calcium influx induced by the 5-HT2A receptor agonist or capsaicin in cystitis rats, which could be inhibited by M100907. Moreover, RNA sequencing indicated that differentially expressed genes were enriched in inflammation-related pathways and cellular calcium homeostasis. These findings suggest that the 5-HT2A receptor is involved in the hypersensitivity of bladder afferent neurons in CYP-induced cystitis, and M100907 could alleviate bladder overactivity and hyperalgesia in CYP-induced cystitis by inhibiting neuronal hypersensitivity in the afferent pathways. The 5-HT2A receptor may be a potential therapeutic target for the treatment of IC/BPS.

MIR-9-ENRICHED MESENCHYMAL STEM CELLS DERIVED EXOSOMES PREVENT CYSTITIS-INDUCED BLADDER PAIN VIA SUPPRESSING TLR4/NLRP3 PATHWAY IN INTERSTITIAL CYSTITIS MICE.

Cui X, Bi X, Zhang X, Zhang Z, Yan Q, Wang Y, Huang X, Wu X, Jing X, Wang H. Immun Inflamm Dis. 2024 Feb;12(2):e1140. doi: 10.1002/iid3.1140. PMID: 38415918; PMCID: PMC10836038.

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The inflammatory response of the central nervous system is an important component mechanism in the bladder pain of IC/BPS. Exosomes transfer with microRNAs (miRNA) from mesenchymal stem cell (MSCs) might inhibit inflammatory injury of the central nervous system. The purpose of this study from China was to explore the therapeutic effects by which extracellular vesicles （EVs） derived from miR-9-edreched MSCs in IC/BPS and further investigate the potential mechanism to attenuate neuroinflammation. On the basis of IC/BPS model, Cui and colleagues used various techniques including bioinformatics, cell and molecular biology, and experimental zoology, to elucidate the role and molecular mechanism of TLR4 in regulating the activation of NLRP3 inflammasome in bladder pain of IC/BPS and investigate the mechanism and feasibility of MSC-EVs enriched with miR-9 in the treatment of bladder pain of IC/BPS. The inflammatory responses in systemic and central derived by TLR4 activation were closely related to the cystitis-induced pelvic/bladder nociception in IC/BPS model. Intrathecal injection of miR-9-enreched MSCs derived exosomes were effective in the treatment of cystitis-induced pelvic/bladder nociception by inhibiting TLR4/NF-κb/NLRP3 signal pathway in central nervous system of IC/BPS mice. This study demonstrated that miR-9-enreched MSCs derived exosomes alleviate neuroinflammaiton and cystitis-induced bladder pain by inhibiting TLR4/NF-κb/NLRP3 signal pathway in interstitial cystitis mice, which is a promising strategy against cystitis-induced bladder pain.

ELUCIDATION OF THE PATHOPHYSIOLOGY OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME VIA EXPERIMENTAL AUTOIMMUNE CYSTITIS RAT MODEL.

Kadekawa K, Nishijima S, Noguchi K, Matsumoto S, Sugaya K. Am J Physiol Regul Integr Comp Physiol. 2024 Aug 1;327(2):R250-R260. doi: 10.1152/ajpregu.00269.2023. Epub 2024 Jun 6. PMID: 38842512.

Although the cause of IC/PBS remains unknown, autoimmune involvement has been strongly suggested to be a contributing factor. To elucidate the pathophysiology of IC/PBS, the authors from Japan characterized the experimental autoimmune cystitis (EAC) in rats. Adult female Sprague-Dawley rats were divided into the EAC and control groups. The EAC rats were generated by administrating a homogenate of donor rat bladder tissue as a bladder antigen. The characteristics of

the two groups were determined by evaluating pain behavior and conducting cystometry, histopathology, and molecular analyses. The EAC rats showed: *1*) a decreased paw withdrawal threshold, *2*) a reduced intercontraction interval on cystometry, *3*) the irregular surfaces of the umbrella cells of epithelium throughout the bladder wall, *4*) accumulation of stress granules in the bladder and vascular endothelium, *5*) the increased expression of genes related to inflammation and ischemia at the mRNA and protein levels, *6*) a significantly increased paw withdrawal threshold with pain treatment, and *7*) the induction of glomerulation of the bladder wall, epithelium denudation, and lymphocyte infiltration in the interstitium by bladder distension. These results suggest that the EAC rats showed pain and frequent urination with the overexpression of inflammatory chemokines, reflecting clinical IC/BPS, and the bladder epithelium and vascular endothelium may be the primary sites of IC/BPS, and bladder injury, such as bladder distension, can cause progression from BPS to IC with Hunner lesions. The experimental autoimmune cystitis model rats showed pain and frequent urination with the overexpression of inflammatory chemokines, reflecting clinical IC/PBS, and the bladder epithelium and vascular endothelium may be the primary sites of IC/BPS, and bladder injury, such as bladder distension, can cause progression from BPS to IC with Hunner lesions.

THE MODEL OF INTERSTITIAL CYSTITIS FOR EVALUATING NEW MOLECULAR STRATEGIES OF INTERSTITIAL REGENERATION IN HUMANS.

Mormone E, Cisternino A, Capone L, Caradonna E, Sbarbati A. Int J Mol Sci. 2024 Feb 15;25(4):2326. doi: 10.3390/ijms25042326. PMID: 38397003; PMCID: PMC10889234.

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Given the recent evidence in the clinical application of regenerative medicine, mostly on integumentary systems, Mormone and colleagues from Italy focused their attention on recent bladder regeneration approaches based on mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), and hyaluronic acid (HA) in the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) in humans. IC/BPS is a heterogeneous chronic disease with not-well-understood etiology, characterized by suprapubic pain related to bladder filling and urothelium dysfunction, in which the impairment of immunological processes seems to play an important role. The histopathological features of IC include ulceration of the mucosa, edema, denuded urothelium, and increased detection of mast cells and other inflammatory cells. A deeper understanding of the molecular mechanism underlying this disease is essential for the selection of the right therapeutic approach. In fact, although various therapeutic strategies exist, no efficient therapy for IC/BPS has been discovered yet. This review gives an overview of the clinical and pathological features of IC/BPS, with a particular focus on the molecular pathways involved and a special interest in the ongoing few investigational therapies in IC/BPS, which use new regenerative medicine approaches, and their synergetic combination. Good knowledge of the molecular aspects related to stem cell-, PRP-, and biomaterial-based treatments, as well as the understanding of the molecular mechanism of this pathology, will allow for the selection of the right and best use of regenerative approaches of structures involving connective tissue and epithelia, as well as in other diseases.

SYMPTOMATIC AUTONOMIC DYSFUNCTION IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Ritts R, Wolff D, Namugosa M, Hsu FC, Ferrara K, Evans R, Walker SJ. Urogynecology (Phila). 2024 Jun 27. doi: 10.1097/SPV.0000000000001536. Epub ahead of print. PMID: 38954605.

IC/BPS is a highly prevalent condition with incompletely understood pathophysiology, especially in relation to the systemic symptoms experienced. The role of autonomic nervous system dysfunction in IC/BPS remains poorly understood. The purpose of this study from the USA was to assess the relationship between autonomic symptom severity and clinical characteristics of patients with IC/BPS. This is a retrospective cohort study of 122 IC/BPS patients who completed the Composite Autonomic Symptoms Score (COMPASS-31) questionnaire. Data were collected on anesthetic bladder capacity (BC), Hunner lesion (HL) status, results for validated IC/BPS symptom questionnaires (O'Leary Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem

Index (ICSI/ICPI) and the Pelvic Pain and Urgency/Frequency (PUF) scale), and comorbid nonurologic associated syndromes. Using the first quartile of COMPASS-31 scores as the cutoff, the authors compared patients within the first quartile (low symptom load; n = 30), to the remainder of the patients (high symptom load; n = 92). Patients scoring ≥20.36 were significantly less likely to be HL positive (10.9% vs 26.7%; P = 0.043) and had a significantly higher BC (823.10 ± 396.07 vs 635.00 ± 335.06; P = 0.027), higher scores on the PUF questionnaire (23.80 ± 4.98 vs; 19.61 ± 5.22 P < 0.001), and a higher number of non-urologic associated syndromes (5.65 ± 2.90 vs 2.60 ± 1.89; P < 0.001). Patients with IC/BPS experience widespread symptoms associated with autonomic nervous system dysfunction. A higher symptom load strongly correlates with a nonbladder-centric phenotype. These findings provide further evidence that total body nervous system dysfunction is present in patients with nonbladder centric IC/BPS.

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

Abreu-Mendes P, Dias D, Magno F, Silva G, Rodrigues-Fonseca J, Dinis P, Cruz F, Pinto RA. Urol Res Pract. 2024 Jan 24;50(1):53-57. doi: 10.5152/tud.2024.23209. PMID: 39115335; PMCID: PMC11059973.

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

THE MICRORNAS (MIRNAS) EXPRESSION IN BENIGN UROLOGICAL DISEASES: A SYSTEMATIC REVIEW.

Atayi M, Mahdavi N, Salehi-Pourmehr H, Pashazadeh F, Kouchakali G, Mirzaei Z, Barati T, Abed S, Fattahi F, Hajebrahimi S. Urol J. 2024 May 11. doi: 10.22037/uj.v21i.7985. Epub ahead of print. PMID: 38733231.

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The exact molecular and cellular processes that cause benign urological diseases in the stromal and epithelial components of the urinary tract are yet unknown. Reviewing and analyzing the data linking microRNAs (miRNAs) expression in the pathophysiology of benign urological conditions, including overactive bladder (OAB), bladder outlet obstruction (BOO), bladder pain syndrome/interstitial cystitis (BPS/IC), and Lower urinary tract dysfunction (LUTD) is the objective of the current systematic review from Iran. Evidence including all case-control, cohort, and cross-sectional studies that measure participants' MicroRNA as a biomarker for benign urological diseases has been gathered On January 2024, through searching MEDLINE via PubMed, Scopus, Web of Science,

Embase, and ProQuest databases. Studies considered eligible that present information on the reference Gene, profile type, and serum levels of microRNA from patients diagnosed with benign urological disease including benign prostate hyperplasia (BPH) or benign prostate enlargement (BPE), overactive bladder (OAB), and bladder outlet obstruction (BOO). These studies appraised by the quality assessment checklist of Joanna Briggs Institute (JBI). A total of 4,587 records related to miRNAs in urological diseases were retrieved. Of these, they identified 28 records for their systematic study. The most frequently associated miRNA was 92a-3p identified which was found upregulated in OAB diagnosis. In BOO, miR-146a-5p was identified to be upregulated. miR-146a-5p was upregulated in BO, and for other benign conditions, different miRNAs were reported. 491-5p miRNAs were found deregulated in OAB-related studies. Other miRNAs were expected to have the same trend in the OAB studies. InSUI miR-93 was the most frequent downregulated miRNA. The other reported miRNAs had similar frequencies. When it comes to the early detection and treatment of benign urological conditions, 92a-3p, miR-21, miR-199a-5p, and miR-146a-5p, and 491-5p have the potential to be employed as both a biomarker and a therapeutic target. The creation of pre-RNA or anti-RNA molecules within carrier vehicles that may be safely administered to patients should be made possible by technological advancements.

THE IMPORTANCE OF PSYCHOLOGICAL ASSESSMENT IN THE MANAGEMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS AND VULVODYNIA: A CASE REPORT.

Okui N, Okui MA. Cureus. 2024 Jul 1;16(7):e63617. doi: 10.7759/cureus.63617. PMID: 39092346; PMCID: PMC11290954.

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This case report from Japan emphasizes the crucial role of psychological assessment in the management of patients with bladder pain syndrome/interstitial cystitis (BPS/IC) and vulvodynia. A 48-year-old woman with a five-year history of refractory BPS/IC and vulvodynia presented with frequent urination, pelvic pain, and severe dyspareunia, which led to sexual aversion and divorce from her partner. Previous treatments, including lifestyle modifications, analgesics, anticholinergics, hydrodistension, intravesical dimethyl sulfoxide, and psychiatric interventions, had been ineffective. Psychological assessments using the Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, and Toronto Alexithymia Scale-20 revealed severe symptoms of depression, anxiety, and alexithymia. Due to the patient's sexual aversion and the absence of a partner, a complete Female Sexual Function Index (FSFI) could not be administered. Instead, a partial FSFI and artificial intelligence-translated reference value of the Female Sexual Distress Scale-Revised were used to assess aspects relevant to the patient's condition. The patient underwent three monthly sessions of Fotona laser therapy, erbium, and neodymium laser at one-month intervals. Treatment outcomes were evaluated using the Numeric Rating Scale-11, Vulvodynia Total, Interstitial Cystitis Symptom Index, and psychological assessment tools. At the six-month follow-up, all physical and psychological symptoms showed significant improvement and complete remission was achieved at 12 months. Despite the overall positive treatment outcomes, the patient's sexual aversion persisted, and accurate measurement was not possible, highlighting the complexity of addressing sexual function in patients with BPS/IC and vulvodynia. This case report underscores the need for a holistic approach to managing these conditions, addressing both the physical and psychological aspects of the disease.

UNDERSTANDING THE SLEEP-PAIN RELATIONSHIP IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Kelly AA, Jones K, Pineau O, Nickel JC, Rose J, Moldwin R, Doiron C, Riedl C, Cervigni M, Wyndaele J, Tripp A. Can Urol Assoc J. 2024 Jun;18(6):194-200. doi: 10.5489/cuaj.8686. PMID: 38381928; PMCID: PMC11230695.

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IC/BPS is a chronic pelvic pain condition with critical symptoms of urinary urgency and frequency, persistent bladder-related pain, and reduced quality of life. Poor-quality sleep can lead to significant

disturbances in daily life and increased pain in IC/BPS patients. Resilience, depressive symptoms, and pain catastrophizing have univariate associations with sleep and pain in IC/BPS, suggesting they may be mechanisms in this sleep and pain relationship. This online study recruited patients self-reporting a diagnosis of IC/BPS through support groups, social media posts (Facebook, Reddit, and Instagram), and urology clinic advertisements. Participants completed questionnaires on demographics, urologic symptoms, pain, pain catastrophizing, depressive symptoms, and resilience. Only those participants who met the RAND Interstitial Cystitis Epidemiology (RICE) criteria for IC/BPS diagnosis were included. A multiple mediation model was first examined, followed by a serial mediation model. Seventy-four participants (M_{age}= 47.0, standard deviation [SD] 16.7, range 18-83 years) met inclusion criteria. A multiple mediation model showed greater sleep disturbance was associated with greater pain severity through depressive symptoms and pain catastrophizing, but not resilience (b=0.79, bootSE =0.26, bootCI [0.33, 1.35]). A serial mediation showed that the sleep-to-pain relationship had a significant indirect effect through pain catastrophizing and depressive symptoms (b=0.78, bootSE =0.26, bootCI [0.35, 1.32]). Findings suggest depressive symptoms and pain catastrophizing may be important psychosocial mechanisms in the sleep-to-pain relationship. These results may help guide future sleep and pain research in IC/BPS and aid in developing and refining treatments.

WNT/B-CATENIN SIGNALING INHIBITS OXIDATIVE STRESS-INDUCED FERROPTOSIS TO IMPROVE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME BY REDUCING NF-KB.

Fang W, Song X, Li H, Meng F, Lv T, Huang J, Ji X, Lv J, Cai Z, Wang Z.Biochim Biophys Acta Mol Cell Res. 2024 Oct;1871(7):119766. doi: 10.1016/j.bbamcr.2024.119766. Epub 2024 May 31. PMID: 38823528.

IC/BPS is a bladder syndrome of unknown etiology. Reactive oxygen species (ROS) plays a major role in ferroptosis and bladder dysfunction of IC/BPS, while the role of ferroptosis in IC/BPS progression is still unclear. This study from China aims to investigate the role and mechanism of ROS-induced ferroptosis in IC/BPS using cell and rat model. The authors collected IC/BPS patient bladder tissue samples and established a LPS-induced IC/BPS rat model (LRM). The level of oxidative stress and ferroptosis in IC/BPS patients and LRM rats was analyzed. Function and regulatory mechanism of ferroptosis in IC/BPS were explored by in vitro and in vivo experiments. The patients with IC/BPS showed mast cells and inflammatory cells infiltration in bladder epithelial tissues. Expression of NRF2 was up-regulated, and GPX4 was decreased in IC/BPS patients compared with normal tissues. IC model cells underwent oxidative stress, which induced ferroptosis. These above results were validated in LRM rat models, and inhibition of ferroptosis ameliorated bladder dysfunction in LRM rats. Wnt/β-catenin signaling was deactivated in IC/BPS patients and animals, and activation of Wnt/β-catenin signaling reduced cellular free radical production, thereby inhibited ferroptosis in IC model cells. Mechanistically, the Wnt/β-catenin signaling pathway inhibited oxidative stress-induced ferroptosis by down-regulating NF-κB, thus contributing to recover IC/BPS both in vitro and in vivo. The authors believe that they have demonstrated for the first time that oxidative stress-induced ferroptosis plays an important role in the pathology of IC/BPS. Mechanistically, the Wnt/β-catenin signaling suppressed oxidative stress-induced ferroptosis by down-regulating NF-κB to improve bladder injury in IC/BPS.

CYTOKINES IN BLADDER PAIN SYNDROME: A REVIEW OF THE LITERATURE.

Lemmon B, Kyrgiou M, Mullins E, Khullar V. Int Urogynecol J. 2024 Jun;35(6):1119-1129. doi: 10.1007/s00192-024-05778-4. Epub 2024 May 21. PMID: 38771505.

Bladder pain syndrome is poorly understood with both the aetiology and pathophysiology being unknown. Symptoms overlap with other disorders, such as overactive bladder (OAB) and chronic pelvic pain disorders such as endometriosis, making a consensus on how to diagnosis and manage patients challenging. The development of biomarkers for BPS may be the key to understanding more about its pathophysiology, as well as aiding diagnosis, subclassification, and discovering new drug

targets for its management. As inflammation is widely understood to hold a central role in BPS, the evaluation of cytokines has gained interest. This article from the United Kingdom summarises the current literature and understanding of urinary, serum, and bladder tissue cytokines found elevated in patients with BPS. A literature search was performed using Pub Med with the keywords "bladder pain syndrome", "painful bladder syndrome", "bladder pain", "Interstitial cystitis" AND "cytokines" or "inflammation". This study was except from institutional approval. Thirty-six cytokines have been identified as being statistically significantly elevated in either the serum, urine, or bladder tissue of patients with bladder pain syndrome in the 22 studies identified in this review of the literature. These cytokines include those from the interleukin group (n = 14), the CXC chemokine group (n = 5), and the C-C chemokine group (n = 7). CXCL-1, CXCL-8, CXCL-9, CXCL-10, CXCL-11 from the CXC chemokine group, and CCL2, CCL4, CCL5, CCL7, and CCL11 from the C-C chemokine group have been found to be significantly elevated in patients with bladder pain in the literature. Many of these analytes also have supporting evidence for their roles in bladder pain from animal models and studies in other chronic inflammatory conditions. It is likely that a single cytokine will not serve as an adequate biomarker of disease in bladder pain syndrome for either diagnosis or disease severity. Instead, panels of inflammatory mediators may reveal more about the different pathways of inflammation leading to similar presentations of bladder pain in patients.

THE POTENTIAL MECHANISM OF TREATING IC/BPS WITH HYPERBARIC OXYGEN BY REDUCING VASCULAR ENDOTHELIAL GROWTH INHIBITOR AND HYPOXIA-INDUCIBLE FACTOR-1A.

Zhang J, Kang J, Wu L. Turk J Med Sci. 2023 Dec 11;54(1):26-32. doi: 10.55730/1300-0144.5762. PMID: 38812622; PMCID: PMC11031152.

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The purpose of this study from China was to investigate the roles of vascular endothelial growth inhibitor (VEGI) and hypoxia-inducible factor-1α (HIF-1α) in the treatment of refractory interstitial cystitis/bladder pain syndrome (IC/BPS) with hyperbaric oxygen (HBO). A total of 38 patients were included. They were assessed before and 6 months after HBO treatment. Three-day voiding diaries were recorded, and O'leary-Sant scores, visual analog scale (VAS) scores, quality of life (QoL) scores, pelvic pain, and urgency/frequency (PUF) scores were evaluated. Bladder capacity was assessed by cystoscopy. Bladder mucosa was collected for Western blot, qRT-PCR, and immunofluorescence staining to compare the expression of VEGI and HIF-1α before and after treatment. Compared with before treatment, patients showed significant improvements in 24-h voiding frequency (15.32 ± 5.38 times), nocturia (3.71 ± 1.80 times), O'Leary-Sant score (20.45 ± 5.62 points), VAS score (41.76 ± 17.88 points), QoL score (3.03 ± 1.44 points), and PUF score (19.95 ± 6.46 points) after treatment ($p < 0.05$). There was no significant difference in bladder capacity before and after treatment ($p \geq 0.05$). The expression levels of VEGI and HIF-1α protein and mRNA were significantly decreased 6 months after treatment compared with before treatment. Immunofluorescence staining results showed that the double positive expression of VEGI and HIF-1α protein in bladder tissue of IC/BPS patients after HBO treatment quantitatively decreased significantly. This study identified a possible mechanism by which VEGI and HIF-1α expression decreased after HBO treatment due to hypoxia reversal, which improved symptoms in IC/BPS patients.

ROLE OF LOCAL ANGIOTENSIN II SIGNALING IN BLADDER FUNCTION.

Anderson HA, Robilotto GL, Mickle AD. Am J Physiol Renal Physiol. 2024 Sep 12. doi: 10.1152/ajprenal.00204.2024. Epub ahead of print. PMID: 39265080.

Local renin-angiotensin signalling is present within various organ systems of the body. Angiotensin II signalling acts as a crucial mechanism of the renin-angiotensin signalling system. In this paper, the authors from the USA review current literature regarding local angiotensin II signalling in the urinary bladder. Their interest in this pathway is due to its potential role in interstitial cystitis/bladder pain syndrome and other bladder diseases, which are chronic in nature and negatively affect patients' quality of life. Current treatments for bladder diseases are generally ineffective due to lack of

understanding of their pathophysiology. They evaluate literature investigating angiotensin II signalling in the bladder across several perspectives, including local expression and production, functional properties, tissue morphology, and clinical implications. Further, they identify gaps in knowledge and suggest areas where we can improve our understanding of angiotensin II signalling in the bladder.

EVALUATION OF CENTRAL SENSITISATION IN BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW.

Knox S, Offiah I, Hashim H. Int Urogynecol J. 2024 Jun;35(6):1109-1118. doi: 10.1007/s00192-024-05793-5. Epub 2024 May 7. PMID: 38713239.

BPS is a debilitating condition characterised by exaggerated bladder sensations and altered bladder function. It is still unknown whether the condition is a peripheral sensory problem or due to abnormal central sensory processing as seen in central sensitisation. This systematic review from the United Kingdom, which followed a published and Prospective Register of Systematic Reviews-registered protocol (CRD42021229962), is aimed at establishing the scope of central sensitisation in patients with BPS to aid optimal management and treatment. Four databases were searched, and appraisal of the identified studies was conducted by two independent reviewers based on eligibility criteria: patients with BPS being investigated for central sensitisation with or without comparison of controls, English-language articles, full text and publication in a peer-reviewed journal. The Methodological Index for non-Randomised Studies was used to determine study quality. They identified 763 papers in total, with 15 studies included in the final analysis. All studies were observational and had a low risk of bias. Measures included in the evaluation of CS were questionnaires, urodynamics, and quantitative sensory testing methods. There was evidence of central sensitisation in patients with BPS in all papers evaluated (15 out of 15). In addition, more significant central sensitisation correlated with severe disease presentation (3 out of 3 papers) and concomitant chronic pain conditions (5 out of 5 papers). Central sensitisation plays an integral role in BPS patient pathology. Many secondary measures are used to evaluate this condition. Stratification of patients based on their pathology (peripheral, central or a combination of the two) will aid in implementing an individualised management strategy.

INTERSTITIAL CYSTITIS-AN IMBALANCE OF RISK AND PROTECTIVE FACTORS?

Westropp JL, Stella JL, Buffington CAT. Front Pain Res (Lausanne). 2024 May 9;5:1405488. doi: 10.3389/fpain.2024.1405488. PMID: 38784787; PMCID: PMC11112028.

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IC presents as a chronic pain condition with variable combinations of symptoms depending on the species and individual patient. It is diagnosed by the presence of lower urinary tract signs and symptoms in combination with a variety of comorbid health problems, a history of life adversities, and the absence of other conditions that could cause the lower urinary tract signs. IC occurs naturally in humans and cats as a dimensional condition, with patients presenting with mild, moderate, and severe symptoms. Most patients appear to recover without specific treatment. A number of rodent models of IC have been used to study its causes and treatments. Unfortunately, current therapies generally fail to ameliorate IC symptoms long-term. The recent classification of IC as a chronic *primary* pain disorder calls for a rethinking of current clinical and research approaches to it. Beginning when a patient encounters a clinician, precipitating, perpetuating, and palliating risk factors can be addressed until a cause or reliably effective therapy is identified, and identifying predisposing and preventive factors can inform epidemiological studies and health promotion interventions. Predisposing, precipitating, and perpetuating risk factors, including environmental, psychological, and biological, increase the activity of the central threat response system (CTRS), which plays a clinically important role in IC symptoms. Studies in cats and rodent models have revealed that environmental enrichment (EE), in the absence of bladder-directed therapies, leads to amelioration of IC symptoms, implying a central role for the CTRS in symptom precipitation and perpetuation. Conceptually moving the source of IC pain to the brain as a motivational state rather

than one resulting from peripheral nociceptive input offers both clinicians and researchers novel opportunities to improve care for patients with IC and for researchers to use more ecologically valid rodent models. It may even be that IC results from an excess of risk to protective factors, making this imbalance a targetable cause rather than a consequence of IC.

A HYPOTHESIS FOR ANATOMICAL PATHWAYS OF CHRONIC PELVIC PAIN OF "UNKNOWN ORIGIN".

Petros P, Papadimitriou J, Bornstein J. Urol Int. 2024 Jun 11:1-5. doi: 10.1159/000539647. Epub ahead of print. PMID: 38861950.

IC/BPS is a disabling bladder condition. ESSIC, the IC/BPS society, defines two types of IC/BPS: with Hunner's lesion (HL) and without. Pathogenesis is stated as unknown, with no cure possible. Scheffler in 2021 reported cystoscopically validated cure of HL IC/BPS by repair of uterosacral ligaments (USLs) and in 2022, Goeschen reported non-HL IC/BPS cure in 198 women following USL repair. Both Scheffler and Goeschen hypothesized IC/BPS may be a phenotype of the Integral Theory's Posterior Fornix Syndrome "PFS" (chronic pelvic pain, OAB, and emptying dysfunctions) and therefore potentially curable. The hypothesis explores whether visceral plexuses (VPs), due to weakened USLs support, serve as a primary source of pelvic pain impulses, leading to development of an inflammatory condition - for example, IC/BPS, a chronic inflammatory condition, which shares similarities with vulvodynia and complex regional pain syndrome (CRPS). According to the hypothesis of the authors from Australia and Israel, such conditions involve axon reflexes. Stimuli such as gravity applied to unsupported nerve branches within the visceral pelvic plexus, trigger centrally propagating impulses, which then progress antidromally to influence innervated tissues through cytokine release and nociceptor stimulation, perpetuating inflammatory processes at the end organs, and pain perception. The hypothesis raises the question, "are IC/BPS, vulvodynia, other pain sites, even nonbacterial "chronic prostatitis" in the male, different phenotypes of the chronic pelvic pain syndrome which includes PFS. If so, the hypothesis opens several new research directions and would predict inflammatory findings in tender end organ pain sites.

ADULT ZYMOSAN RE-EXPOSURE EXACERBATES THE MOLECULAR ALTERATIONS IN THE BRAINSTEM ROSTRAL VENTROMEDIAL MEDULLA OF RATS WITH EARLY LIFE ZYMOSAN-INDUCED CYSTITIS.

Talluri B, Addya S, Terashvili M, Medda BK, Banerjee A, Shaker R, Sengupta JN, Banerjee B. Neurobiol Pain. 2024 Jul 24;16:100160. doi: 10.1016/j.ynpai.2024.100160. PMID: 39252992; PMCID: PMC11381896.

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Recent evidence suggests that the descending modulatory pathways from the brainstem rostral ventromedial medulla (RVM) are important for bladder inflammatory pain. This study from the USA aimed to identify the long-term molecular changes in RVM neurons due to early life cystitis during neuronal development and the effect of re-exposure later in adulthood. RVM tissues from two treatment protocols were used: (1) neonatal zymosan exposures with acute adult rechallenge (RC) and (2) only neonatal zymosan exposures (NRC). RNAseq analysis showed upregulation of several genes associated with synaptic plasticity (Grin1, Grip2, Notch1, Arc, and Scn2b) in the cystitis groups compared to controls in both protocols. The RC protocol exhibited a stronger treatment effect with significantly higher fold differences between the groups compared to the NRC protocol ($p < 0.001$, fold differences RC vs NRC). In microarrays, miR-34a-5p showed cystitis-induced downregulation in both protocols. Bioinformatics analysis identified multiple 3'UTRs complementary binding sites for miR-34a-5p on Grin2b, Notch1, Grip2, Scn2b, and Arc genes. The enhanced response in the RC protocol indicates a possible priming effect of early life cystitis on rechallenge in adulthood. These long-term molecular alterations may play a critical role in the development of chronic bladder pain conditions as seen in patients with interstitial cystitis/bladder pain syndrome.

MATHEMATICAL APPROACH TO SYNERGISTIC MANAGEMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS AND VULVODYNIA: A CASE SERIES UTILIZING PRINCIPAL COMPONENT ANALYSIS, CLUSTER ANALYSIS, AND COMBINATION LASER THERAPY.

Okui N, Okui MA. Cureus. 2024 Jul 31;16(7):e65829. doi: 10.7759/cureus.65829. PMID: 39219964; PMCID: PMC11363212.

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This case series from Japan presents three patients with bladder pain syndrome/interstitial cystitis (BPS/IC) and vulvodynia, demonstrating the efficacy of an individualized treatment approach using cluster analysis and combination laser therapy. Principal component analysis (PCA) was used to visualize the dynamic nature of symptom clusters and guide treatment decisions. Case 1 was a 41-year-old woman initially classified as Cluster 1 (PCA coordinates: 1.65, 0.03) transitioned to Cluster 2 (-16.93, -21.75) after bladder hydrodistension. Subsequent Fotona laser (Ljubljana, Slovenia) treatment resulted in the complete resolution of symptoms. Case 2 was a 55-year-old woman, contraindicated for hormone therapy due to breast cancer history, presented as Cluster 2 (PCA coordinates: -24.16, 8.74). Fotona laser treatment shifted her to Cluster 1 (11.22, -20.22), followed by bladder hydrodistension for complete cure. Case 3 was a 49-year-old woman, initially in Cluster 0 (PCA coordinates: 1.892, 30.11), who underwent fulguration for Hunner's lesions. Post-treatment, she moved to Cluster 2 (-24.31, 1.767) and achieved full recovery after Fotona laser therapy. The dynamic nature of symptom clusters, visualized through PCA, guided treatment decisions. The PCA transformation, represented as $y = W^T z$, where z is the standardized symptom vector and W is the principal component matrix, allows for the objective tracking of symptom changes. Combination Fotona laser therapy, including vaginal erbium YAG and neodymium YAG, has proven effective in managing vulvar pain, particularly when hormone therapy is contraindicated. This approach, addressing both urological and gynecological aspects, resulted in sustained symptom improvement for over 12 months in all cases. This case series highlights the synergistic relationship between BPS/IC and vulvodynia, demonstrating the efficacy of comprehensive, adaptive treatment strategies guided by mathematical analysis for complex pelvic pain syndromes.

DIVERGENT HISTOPATHOLOGICAL AND MOLECULAR PATTERNS IN CHEMICALLY INDUCED INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME RAT MODELS.

Chang YC, Yu CY, Dong C, Chen SL, Sung WW. Sci Rep. 2024 Jul 12;14(1):16134. doi: 10.1038/s41598-024-67162-y. PMID: 38997336; PMCID: PMC11245554.

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complex chronic pain disorder with an elusive etiology and nonspecific symptoms. Although numerous animal models with phenotypes similar to human disease have been established, no available regimen can consistently alleviate clinical symptoms. This dilemma led Chang and colleagues from Taiwan to question whether current animal models adequately represent IC/BPS. They compared four commonly used IC/BPS rat models to determine their diverse histopathological and molecular patterns. Female rats were given single treatments with hydrochloric acid (HCL), acetic acid (AA), protamine sulfate plus lipopolysaccharide (PS + LPS), or cyclophosphamide (CYP) to induce IC/BPS. Bladder sections were stained for histopathologic evaluation, and mRNA expression profiles were examined using next-generation sequencing and gene set analyses. Mast cell counts were significantly higher in the HCL and AA groups than in the PS + LPS, CYP, and control groups, but only the AA group showed significant collagen accumulation. The models differed substantially in terms of their gene ontology and Kyoto encyclopedia of genes and genomes pathways. The authors' observations suggest that none of these rat models fully reflects the complexity of IC/BPS. They recommend that future studies apply and compare multiple models simultaneously to fully replicate the complicated features of IC/BPS.

TRPV1 AND MAST CELL INVOLVEMENT IN REPEATED VARIATE STRESS-INDUCED URINARY BLADDER DYSFUNCTION IN ADULT FEMALE MICE.

Sidwell AB, Girard BM, Campbell SE, Vizzard MA. Am J Physiol Renal Physiol. 2024 Sep 1;327(3):F476-F488. doi: 10.1152/ajprenal.00125.2024. Epub 2024 Jul 11. PMID: 38991005.

The etiology of interstitial cystitis/bladder pain syndrome (IC/BPS) is unknown but likely multifactorial. IC/BPS symptoms can be exacerbated by psychological stress, but underlying mechanisms remain to be defined. Transient receptor potential vanilloid 1 (TRPV1) channels, expressed on nerve fibers, have been implicated in bladder dysfunction and colonic hypersensitivity with stress in rodents. Histamine/H1R activation of $TRPV1^{+}$ nerves increases bladder afferent fiber sensitivity to distension. TRPV1 channels are also expressed on mast cells, previously implicated in contributing to IC/BPS etiology and symptoms. Sidwell and colleagues from the USA examined the contribution of TRPV1 and mast cells to bladder dysfunction after repeated variate stress (RVS). RVS increased ($P \leq 0.05$) serum and fecal corticosterone expression and induced anxiety-like behavior in wild-type (WT) mice. Intravesical instillation of the selective TRPV1 antagonist capsazepine (CPZ) rescued RVS-induced bladder dysfunction in WT mice. *Trpv1* knockout (KO) mice did not increase voiding frequency with RVS and did not exhibit increased serum corticosterone expression despite exhibiting anxiety-like behavior. Mast cell-deficient mice (B6.Cg-*Kit*$^{w\text{-}sh}$) failed to demonstrate RVS-induced increased voiding frequency or serum corticosterone expression, whereas control (no stress) mast cell-deficient mice had similar functional bladder capacity to WT mice. TRPV1 protein expression was significantly increased in the rostral lumbar (L1-L2) spinal cord and dorsal root ganglia (DRG) in WT mice exposed to RVS, but no changes were observed in lumbosacral (L6-S1) spinal segments or DRG. These studies demonstrated TRPV1 and mast cell involvement in RVS-induced increased voiding frequency and suggest that TRPV1 and mast cells may be useful targets to mitigate stress-induced urinary bladder dysfunction.

PROMISING EXPERIMENTAL TREATMENT IN ANIMAL MODELS AND HUMAN STUDIES OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Hu JC, Tzeng HT, Lee WC, Li JR, Chuang YC. Int J Mol Sci. 2024 Jul 23;25(15):8015. doi: 10.3390/ijms25158015. PMID: 39125584; PMCID: PMC11312208.

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The authors from Taiwan note that interstitial cystitis/bladder pain Syndrome (IC/BPS) remains a mysterious and intricate urological disorder, presenting significant challenges to healthcare providers. Traditional guidelines for IC/BPS follow a hierarchical model based on symptom severity, advocating for conservative interventions as the initial step, followed by oral pharmacotherapy, intravesical treatments, and, in refractory cases, invasive surgical procedures. This approach embraces a multi-tiered strategy. However, the evolving understanding that IC/BPS represents a paroxysmal chronic pain syndrome, often involving extravesical manifestations and different subtypes, calls for a departure from this uniform approach. This review provides insights into recent advancements in experimental strategies in animal models and human studies. The identified therapeutic approaches fall into four categories: (i) anti-inflammation and anti-angiogenesis using monoclonal antibodies or immune modulation, (ii) regenerative medicine, including stem cell therapy, platelet-rich plasma, and low-intensity extracorporeal shock wave therapy, (iii) drug delivery systems leveraging nanotechnology, and (iv) drug delivery systems assisted by energy devices. Future investigations will require a broader range of animal models, studies on human bladder tissues, and well-designed clinical trials to establish the efficacy and safety of these therapeutic interventions.

AN INTEGRATED MACHINE LEARNING FRAMEWORK FOR DEVELOPING AND VALIDATING A DIAGNOSTIC MODEL OF MAJOR DEPRESSIVE DISORDER BASED ON INTERSTITIAL CYSTITIS-RELATED GENES.

Chen B, Sun X, Huang H, Feng C, Chen W, Wu D. J Affect Disord. 2024 Aug 15;359:22-32. doi: 10.1016/j.jad.2024.05.061. Epub 2024 May 14. PMID: 38754597.

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Major depressive disorder (MDD) and interstitial cystitis (IC) are two highly debilitating conditions that often coexist with reciprocal effect, significantly exacerbating patients' suffering. However, the molecular underpinnings linking these disorders remain poorly understood. In this study from China, transcriptomic data from GEO datasets including those of MDD and IC patients were systematically analyzed to develop and validate their model. Following removal of batch effect, differentially expressed genes (DEGs) between respective disease and control groups were identified. Shared DEGs of the conditions then underwent functional enrichment analyses. Additionally, immune infiltration analysis was quantified through ssGSEA. A diagnostic model for MDD was constructed by exploring 113 combinations of 12 machine learning algorithms with 10-fold cross-validation on the training sets following by external validation on test sets. Finally, the "Enrichr" platform was utilized to identify potential drugs for MDD. Totally, 21 key genes closely associated with both MDD and IC were identified, predominantly involved in immune processes based on enrichment analyses. Immune infiltration analysis revealed distinct profiles of immune cell infiltration in MDD and IC compared to healthy controls. From these genes, a robust 11-gene (ABCD2, ATP8B4, TNNT1, AKR1C3, SLC26A8, S100A12, PTX3, FAM3B, ITGA2B, OLFM4, BCL7A) diagnostic signature was constructed, which exhibited superior performance over existing MDD diagnostic models both in training and testing cohorts. Additionally, epigallocatechin gallate and 10 other drugs emerged as potential targets for MDD. This work developed a diagnostic model for MDD employing a combination of bioinformatic techniques and machine learning methods, focusing on shared genes between MDD and IC.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: WHEN PART OF THE POSTERIOR FORNIX SYNDROME IS POTENTIALLY CURABLE SURGICALLY.

Goeschen K, Scheffler K, Wyndaele JJ, Bornstein J. Ann Transl Med. 2024 Apr 22;12(2):30. doi: 10.21037/atm-23-1865. Epub 2024 Apr 12. PMID: 38721463; PMCID: PMC11075955.

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In this study from Germany, Belgium and Israel, evidence is offered to show IC/BPS forms part of the posterior fornix syndrome (PFS), which was defined in 1993 as: chronic pelvic pain (CPP), urge, frequency, nocturia, abnormal emptying, post-void residual urine, caused by uterosacral ligament (USL) laxity and cured or improved by USL repair. The IC/BPS definition implies that the urge and pain of IC/BPS is from a single (as yet unknown) pathogenic origin. However, when urge and pain are viewed from the perspective of the PFS, though both have the same lax USL origin, the anatomical pathway from lax USL to symptom manifestation is very different manifestation. For CPP the anatomical pathway is the inability of loose USLs to support pelvic visceral plexuses (VPs); it is hypothesized that inability of weak USLs to mechanically supports VPs, the afferent nerve synapse from end organs may fire off autologous afferent impulses to the brain which interprets them as pain from end organs such as urothelium, vulva, lower abdomen. For urge, the anatomical pathway is very different: lax USLs weaken the directional pelvic muscle forces which stretch the vagina to support the urothelial stretch receptors. The receptors fire off afferent impulses to the cortex at a lower bladder volume, and these are interpreted as "urge to go". Mechanical support of USLs relieves both pain and urge, as does USL repair.

THE EFFICACY AND SAFETY OF MONOCLONAL ANTIBODY THERAPIES FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

Cao ZG, Li FD, Zhang CL, Luo GX, Chang DH. Neurourol Urodyn. 2024 Jul 9. doi: 10.1002/nau.25547. Epub ahead of print. PMID: 38979850.

This study from China aimed to assess the efficacy and safety of monoclonal antibody therapies (MATs) for interstitial cystitis/bladder pain syndrome (IC/BPS). A systematic search was conducted across databases including PubMed, Embase, clinicalTrial.gov, and the Cochrane Library Central Register of Controlled Trials. Randomized controlled trials (RCTs) comparing MATs versus placebo were included. Primary outcomes comprised the Global Response Assessment (GRA) scale and the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI). Additional analyses encompassed mean daily frequency of voids, the O'Leary-Sant Interstitial Cystitis Problem Index, pain scores, and complications. Statistical analyses were performed using Review Manager 5.3. Five high-quality RCTs, comprising 263 patients with IC/BPS, were ultimately selected. MATs were generally effective in treating IC/BPS. Patients receiving MATs exhibited a higher satisfaction rate (odds ratio [OR]: 2.7, confidence interval [CI]: 1.31-5.58, p = 0.007) and lower ICSI scores (mean difference [MD]: -1.44, CI: -2.36 to -0.52, p = 0.002). Moreover, MAT recipients experienced reduced pain (MD: -0.53, CI: -0.79 to -0.26, p < 0.0001) and decreased frequency of urination (MD: -1.91, CI: -2.55 to -1.27, p < 0.00001). Importantly, there were no disparities regarding complication incidence in the MAT and control groups. The current findings indicate that MATs are effective and safe for treating IC/BPS. Nonetheless, future RCTs with larger sample sizes and long-term follow-up are warranted.

USE OF THE SYSTEMIC IMMUNE-INFLAMMATION INDEX TO PREDICT TREATMENT EFFICACY IN PATIENTS WITH BLADDER PAIN SYNDROME.

Sahin MF, Eseoglu E, Akgul M, Malak A, Dogan C, Yazici CM. J Coll Physicians Surg Pak. 2024 May;34(5):556-560. doi: 10.29271/jcpsp.2024.05.556. PMID: 38720216.

The aim of this observational study from Turkije was to determine the relationship between bladder pain syndrome (BPS) and systemic inflammatory index (SII) and to examine the impact of treatment protocols on it. A retrospective analysis was conducted on 30 BPS patients who underwent medical therapy. Upon diagnosis, the patients completed the king's health questionnaire (KHQ), beck depression questionnaire (BDQ), beck anxiety questionnaire (BAQ), and short form (SF-36) quality of life form. Peripheral blood SII was measured. After six months of regular therapy, the SII was recalculated when the patients completed the same forms again. The SII was compared between instances when patients reported more complaints, higher form scores, and instances when they reported fewer and lower scores. The patients had a mean age of 46.1 ± 13.6 years, with four males and 26 females. The mean follow-up duration was 76.3 ± 24.5 months. Five patients of KHQ subcategories showed statistically significant decreases following therapy (52 to 39.17, 66.66 to 54.16, 54.40 to 41.07, 75.55 to 58.14, and 60.55 to 40.47). All patients of SF-36 components increased (p = 779, p = 0.393, p = 0.007, p = 0.004, p = 0.008, p = 0.041, p = 0.010, and p = 0.767, respectively). BDQ and BAQ decreased after therapy (11.55 to 11.41 and 11.86 to 11.24, respectively). Lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII decreased significantly (p = 0.001, 0.019, 0.002 and 0.039, respectively). SII, lymphocyte count, NLR, and PLR decreased after treatment, similar to BDQ and BAQ. SII is a simple and feasible method for evaluating the treatment efficacy of BPS.

HOW INTRAVESICAL PLATELET-RICH PLASMA CAN HELP PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A COMPREHENSIVE SCOPING REVIEW.

Soliman A, Adel M, Elnagar MA, Elsonbaty S, Hefnawy AE. Int Urogynecol J. 2024 Jul 3. doi: 10.1007/s00192-024-05844-x. Epub ahead of print. PMID: 38958727.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a condition characterized by chronic inflammation that affects the bladder. This study from Egypt was aimed at evaluating the effectiveness of intravesical platelet-rich plasma (PRP) injections in patients with IC/BPS. Soliman

and colleagues conducted a comprehensive search strategy to involve studies that investigate the efficacy of intravesical PRP injections or instillations over different time intervals. Various outcome measures were assessed, including pain scores, functional outcomes, urodynamic parameters, and surface expressions on the urothelium. This search strategy revealed 1,125 studies. After screening, ten articles met the inclusion criteria. Intravesical PRP significantly reduced the visual analog scale (VAS) compared with baseline scores. Several clinical trials reported significant improvements in the global response rate (GRA), O'Leary-Sant Symptom (OSS) questionnaire, Interstitial Cystitis Symptom Index (ICSI), and Interstitial Cystitis Problem Index (ICPI). Urodynamic parameters such as maximum flow rate (Qmax) and post-voiding residual (PVR) showed significant improvements in some studies. The study concluded that intravesical PRP injections could be a promising effective treatment option for IC/BPS patients by their significant ability to reduce pain. However, improvement of urodynamic and functional outcomes is still not clear. Further large comparative trials are still warranted to assess the efficacy of PRP instillation.

INTRAVESICAL INSTILLATION OF PLATELET-RICH PLASMA FOR TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PILOT STUDY.

El Hefnawy AS, Hasan MAA, El Sawy E, Abdel-Razik M, El-Tabey N. Curr Urol. 2024 Mar;18(1):49-54. doi: 10.1097/CU9.0000000000000156. Epub 2022 Oct 19. PMID: 38505153; PMCID: PMC10946635.

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The aim of this study from Egypt was to evaluate the feasibility of intravesical instillation of platelet-rich plasma (PRP) to treat IC/BPS. Twenty PRP samples were tested in vitro for stability after exposure to urine samples with different pH. A pilot study involving 21 female patients with IC/BPS was conducted, and 6 weekly doses of autologous PRP (50 mL) were administered. Patients were followed up at the 2nd, 4th, 8th, and 12th weeks after terminating instillation. The primary endpoint was the visual analog scale (VAS) for pain, and the secondary endpoints included the IC symptom index, IC problem index of the O'Leary-Sant questionnaire and global response assessment, urine culture, and uroflowmetry. Success was defined as a reduction in VAS by 30% or more compared with basal level, and adverse events were recorded. The mean ± SD of VAS was significantly reduced compared with basal level (4.4 ± 2.6 vs. 8.8 ± 1.1, respectively, $p = 0.001$). Meanwhile, 80% of cases were considered successful, with a 50.1% reduction in the mean score compared with the basal level. The mean ± SD of IC symptom index and IC problem index significantly improved compared with the basal level. Global response assessment was markedly, moderately, and slightly improved in 2 (10%), 10 (50%), and 5 (25%) patients, respectively, and showed no change in 3 (15%). Three patients had positive urine cultures at follow-up, but 1 withdrew after 2 sessions because of a lack of efficacy. Repeated intravesical instillation of PRP could be considered an effective and safe approach for treating IC/BPS.

INTRAVESICAL INSTILLATION OF HYALURONIC ACID WITH EPIDERMAL GROWTH FACTOR FOR RESTORING UROTHELIAL DENUDATION AND ALLEVIATING OXIDATIVE STRESS IN LIPOPOLYSACCHARIDE-INDUCED INTERSTITIAL CYSTITIS OF RATS.

Lin CC, Yang JM, Hsu TH, Lee HL. Int Neurourol J. 2024 Jun;28(2):106-114. doi: 10.5213/inj.2448028.014. Epub 2024 Jun 30. PMID: 38956770; PMCID: PMC11222823.

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The purpose of this study from Taiwan was to investigate the efficacy of an intravesical instillation of hyaluronic acid (HA) combined with epidermal growth factor (EGF) for the treatment of interstitial cystitis (IC) using a lipopolysaccharide (LPS)-induced IC animal model. A total of 24 female Sprague-Dawley rats were randomized to 4 groups: sham control, IC, HA, and treatment (HA/ EGF) groups. A polyethylene-50 tube was placed inside the bladder of each animal. IC was induced by twice-weekly instillations of LPS for 3 weeks, which resulted in chronic injury of the urothelium. Animals in the sham control group only received saline instillation. Treatment solutions of HA and HA/EGF were given on days 0, 7, and 14 after IC induction (400 µL of HA in a concentration of 0.4 mg/0.5 mL and

400 µL of NewEpi, a commercialized HA/EGF mixture containing 2 µg of EGF and 0.4 mg of sodium hyaluronate). Animals were sacrificed on day 21 for further examinations. The HA/EGF group showed visible improvement in hematuria with a significant reduction of red blood cells in the urine compared to the HA group. Histological examination revealed that HA/EGF treatment reversed the abnormalities developed in IC, including infiltration of inflammatory cells, irregular re-epithelialization, and fibrotic tissue. Moreover, HA/ EGF significantly reduced the levels of proinflammation cytokines (tumor necrosis factor-α, interleukin [IL]-6, and IL-1β) and substantially lowered the elevated oxidative stress biomarker malondialdehyde, yet restored the levels of antioxidant enzymes glutathione peroxidase and superoxide dismutase, with superior results than HA treatment. Cystometry studies indicated that HA/EGF significantly prolonged intercontraction interval and increased micturition volume. HA/EGF has been demonstrated as a more effective treatment for enhancing the urothelium lining and reducing inflammatory changes to alleviate clinical symptoms associated with IC in rats, compared to HA alone.

INTRAVESICAL INSTILLATIONS OF HYALURONIC ACID AS FIRST-LINE TREATMENT IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: USE, EFFICACY AND EFFECTS ON QUALITY OF LIFE.

Plotti F, Cundari GB, Ficarola F, Terranova C, De Cicco Nardone C, Montera R, Luvero D, Guzzo F, Silvagni A, Ferrari A, Caserta D, Angioli R. Healthcare (Basel). 2024 Jun 13;12(12):1190. doi: 10.3390/healthcare12121190. PMID: 38921303; PMCID: PMC11203325.

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The efficacy of hyaluronic acid instillations as therapy for patients with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) has been demonstrated in some clinical studies, with response rates up to 70%. The aim of this study from Italy was to investigate the change in symptoms and quality of life in female patients with IC/BPS after intravesical instillations of hyaluronic acid used as first-line treatment. A retrospective single-center cohort study was conducted. Female patients, whose symptoms were compatible with the diagnosis of IC/BPS as defined by the International Continence Society, were treated with a variable number of intravesical instillations of a hyaluronic acid-based drug. Three validated questionnaires were administered by telephone to all patients, before the beginning of the treatment and 6 months after the last administration of the drug. A total of 50 patients with symptoms compatible with the diagnosis of IC/BPS were included in the study. The median number of instillations performed is 4. For all questionnaires, the median value was significantly reduced following treatment with intravesical instillations (p = 0.000). The present study has shown that intravesical hyaluronic acid treatment results in both statistically and clinically significant symptomatic improvement, thereby improving the quality of life of patients with IC/BPS.

INTRAVESICAL INTERFERON THERAPY VS HYALURONIC ACID FOR PAIN AMONG FEMALE INDIVIDUALS WITH INTERSTITIAL CYSTITIS: A RANDOMIZED CLINICAL TRIAL.

Shen SH, Peng L, Zeng X, Zhang J, Shen H, Luo DY. JAMA Netw Open. 2024 Apr 1;7(4):e244880. doi: 10.1001/jamanetworkopen.2024.4880. Erratum in: JAMA Netw Open. 2024 Apr 1;7(4):e2415703. doi: 10.1001/jamanetworkopen.2024.15703. PMID: 38587846; PMCID: PMC11002698.

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Interstitial cystitis (IC) is a debilitating condition. Although viral infection is a potential etiological cause, few studies have detected the effect of antiviral treatment. The purpose of this study from China was to determine the efficacy and safety of intravesical interferon instillation compared with hyaluronic acid in female patients with IC. This double-masked, randomized phase 2/3 clinical trial with parallel group design was implemented from October 2022 to April 2023 and had a 6-month follow-up period. The study was conducted at a single center. Eligible participants were female patients aged 18 to 70 years with a diagnosis of IC for more than 6 months. The last visit took place in October 2023. Data were analyzed between October and November 2023. Patients were randomized 1:1 to receive either intravesical instillation of interferon or hyaluronic acid. The primary

end point was change in visual analog scale pain score. Secondary end points included changes in voiding frequency, functional bladder capacity, symptom index, and global response assessment. Adverse events were closely monitored. Among the 52 patients, the mean (SD) age was 50.0 (14.1) years and they were randomized to either the interferon group (26 [50%]) or hyaluronic acid (26 [50%]). The visual analog pain score showed the interferon group decreased more significantly than hyaluronic acid (-1.3; 95% CI, -2.3 to -0.3; P = .02) at month 6, with 20 patients (77%) exhibiting a 30% or higher reduction in pain compared with baseline. Secondary end points of voiding frequency, functional bladder capacity, and nocturia episodes showed no significant difference between 2 therapies. However, interferon showed a significantly higher reduction in the Interstitial Cystitis Symptom Index (-3.0; 95% CI, -5.3 to -0.7; P = .01) and the Problem Index (-2.5; 95% CI, -4.5 to -0.4; P = .02) at month 6, with 22 patients (85%) presenting as moderately or markedly improved. The frequencies of adverse events were similar between 2 groups. Only 1 patient discontinued hyaluronic acid because of poor effectiveness. In this randomized clinical trial, female patients with IC could benefit from intravesical interferon therapy, without serious adverse events. These results offered hope for antiviral approaches in IC, but larger-scale, multicenter trials and long-term follow-up should be considered.

ASSESSMENT OF SYMPTOMATIC RESPONSE TO INTRAVESICAL ALKALINIZED LIDOCAINE, BUPIVACAINE, HEPARIN AND STEROIDS IN PATIENTS WITH BLADDER PAIN SYNDROME.

Mahant R, Solanki FS, Tiwari C, Lokhande A, Sharma DB, Sharma D. Trop Doct. 2024 Jul;54(3):255-257. doi: 10.1177/00494755241236993. Epub 2024 Mar 18. PMID: 38497135.

Bladder Pain Syndrome (BPS) is a puzzling and complicated disorder. In this study from India, 12 such patients, with a mean age 48.3 years, were treated with weekly intravesical instillation of admixture of alkalinized lidocaine, bupivacaine, heparin and steroids for six weeks. Evaluating the benefits of this therapy, patients experienced 82.2% & 90.9% relief at 3_{rd} & 6_{th} week of instillation. After completion of six cycles of therapy, patients experienced 68.7% & 65.3% relief at 3_{rd} & 6_{th} month follow up, concluding the early and long term relief of BPS.

AMNIOTIC BLADDER THERAPY: SIX-MONTH FOLLOW UP TREATING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Considine J, O'Hollaren K, Radoiu C, Madan R, Liaw A, Dhar N. Can J Urol. 2024 Jun;31(3):11898-11903. PMID: 38912944.

IC/BPS is characterized by chronic pelvic pain and usually accompanies lower urinary tract symptoms. The authors from the USA have previously reported that amniotic bladder therapy (ABT) provides symptomatic improvement in refractory IC/BPS patients for up to 3 months. Herein, they evaluated the durability of ABT up to 6 months. Consecutive IC/BPS patients received intra-detrusor injections of 100 mg micronized amniotic membrane. Clinical evaluation and patient-reported outcome measurements including Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS) and Overactive Bladder Assessment Tool (OAB) were assessed. Twenty-five consecutive recalcitrant IC/BPS patients were included in the study with an average age of 47.4 ± 14.4 years (29-67 years). After ABT, the IC/BPS symptoms improved gradually up to 3 months in all patients with an average improvement in ICSI, ICPI, BPIC-SS and OAB score of 72.8%, 71.9%, and 66.6%, ($p < 0.001$) respectively, at 3 months. At 4 months after ABT, 7 patients experienced a rebound in symptoms and requested another injection which resulted in a significant improvement in IC/BPS symptoms after 2, 4, and 8 weeks ($p < 0.01$). For the 18 patients who received only one injection, the IC/BPS symptoms were still significantly lower at 5 and 6 months compared to baseline ($p < 0.01$), suggesting a possible durable effect based on the ICSI, ICPI, BPIC-SS, and OAB questionnaire scores. ABT provided an improvement in pain and lower urinary tract symptoms up to 6 months post-treatment in some refractory IC/BPS patients.

PURINE NUCLEOSIDE PHOSPHORYLASE AS A TARGET FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH AND WITHOUT HUNNER LESIONS.

Birder LA, Wolf-Johnston A, Ritov V, Stern JNH, Moldwin R, Kuo HC, Jackson EK. Sci Rep. 2024 Sep 19;14(1):21898. doi: 10.1038/s41598-024-73280-4. PMID: 39300176.

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Chronic visceral pain disorders, such as IC/BPS, are difficult to treat, and therapies are limited in number and efficacy. Emerging evidence suggests that alterations in the enzyme purine nucleoside phosphorylase (PNPase) may participate in oxidative injury and cellular damage. PNPase is important for the metabolism of 'tissue-protective' purine metabolites to 'tissue-damaging' purines that generate free radicals. The aim of this study from the USA and Taiwan was to test whether patients living with IC/BPS without or with Hunner lesions and irrespective of any therapies exhibit purine dysregulation with higher levels of tissue-damaging purine metabolites as measured by liquid chromatography-tandem mass spectrometry. The results demonstrate that levels of urotoxic purine metabolites (hypoxanthine and xanthine) in IC/BPS patients with and without Hunner lesions are elevated compared to healthy controls. These findings suggest there may be pathophysiologic commonalities between patient subtypes. Furthermore, the accumulation of uroprotective purines and depletion of urodamaging purines by PNPase inhibition may be therapeutically effective in both groups of patients.

PRELIMINARY ANALYSIS OF STIMULATION PARAMETERS FOR SACRAL NEUROMODULATION IN DIFFERENT INDICATIONS: A MULTICENTER RETROSPECTIVE COHORT STUDY FROM CHINA.

Meng L, Yan Z, Wang X, Zhang Y, Zhu Z, Zhu W, Ling Q, Sun X, Gu Y, Lv J, Li Y. Int J Surg. 2024 Jun 1;110(6):3536-3542. doi: 10.1097/JS9.0000000000001302. PMID: 38445489; PMCID: PMC11175814.

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Sacral neuromodulation (SNM) is an effective approach for treating lower urinary tract dysfunction (LUTD), and stimulation programming is essential for successful treatment. However, research on SNM programming for various indications is limited. Thus, the authors from China aimed to determine whether there were differences in the stimulation parameters for different SNM indications and the appropriate programming recommendations. Clinical data were retrospectively collected from patients with LUTD who underwent SNM and completed internal pulse generator implantation. The parameters with the highest patient satisfaction or the most symptom improvement during the test period were considered optimal and used to set the programming after internal pulse generator implantation. After screening, 282 patients were enrolled and categorized into four groups based on the following indications: refractory overactive bladder (OAB) (n =61), neurogenic lower urinary tract dysfunction (nLUTD) (n =162), IC/BPS (n =24), and idiopathic nonobstructive urinary retention (NOUR) (n =35). When analyzing the optimal stimulus parameters, disparities in the stimulation amplitude and pulse frequency were noted among the four groups. The stimulation amplitude in the nLUTD group was higher than that in the idiopathic NOUR group (P =0.013). Differences in pulse frequency were observed between the refractory OAB and nLUTD groups (P <0.001) and between the refractory OAB and idiopathic NOUR groups (P =0.001). No differences in the electrode configuration or pulse width settings existed among the four groups. The stimulation parameters for SNM varied among the different indications. For the initial programming of stage I, most patients are recommended to start with stimulation amplitudes below 2 V, although patients with nLUTD may benefit from higher amplitudes. A standard pulse width of 210 μs is recommended for all patients. However, for individuals experiencing nLUTD or idiopathic NOUR, the pulse frequency can begin above the standard 14 Hz but not exceed 50 Hz.

REDUCING PAIN BY IMPROVING BRAIN AND MUSCLE ACTIVITY WITH MOTOR CORTICAL NEUROMODULATION IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Johnson EV, Bachmann M, Yani MS, Eckel SP, Garcia GI, Rodriguez LV, Kutch JJ. Trials. 2024 Sep 12;25(1):609. doi: 10.1186/s13063-024-08450-w. PMID: 39261949.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain condition creating a wide range of urologic and pain symptoms. There is currently limited evidence to understand the mechanisms of IC/BPS. There have been recent studies suggesting that altered function in brain motor areas, particularly the supplementary motor cortex (SMA), relates to altered bladder sensorimotor control and may play an important role in IC/BPS. This study from the USA aims to provide evidence that non-invasive stimulation targeting the motor cortex may help reduce IC/BPS pain, as well as better understand the neural mechanism by which this stimulation targets neuromuscular dysfunction. This study is a two-group quadruple-blinded randomized controlled trial (RCT) of active vs. sham repetitive transmagnetic stimulation (rTMS). In addition, the study will also include functional magnetic resonance imaging (fMRI), pelvic floor electromyography (EMG), pelvic exam, and outcome measures and questionnaires to further study outcomes.

A RANDOMIZED-CONTROLLED PILOT TRIAL OF TELEMEDICINE-DELIVERED COGNITIVE-BEHAVIORAL THERAPY TAILORED FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

McKernan LC, McGonigle T, Vandekar SN, Crofford LJ, Williams DA, Clauw DJ, Bruehl S, Corbett BA, Dmochowski RR, Walsh EG, Kelly AG, Sutherland SL, Connors EL, Ryden A, Reynolds WS. Pain. 2024 Aug 1;165(8):1748-1760. doi: 10.1097/j.pain.0000000000003188. Epub 2024 Feb 27. PMID: 38422486; PMCID: PMC11257824.

IC/BPS is a debilitating urologic pain condition with few treatment advances in the past 25 years. Individuals with IC/BPS often experience significant psychological distress, which worsens symptoms and functioning. To date, there have been no large-scale, randomized controlled trials (RCTs) of comprehensive psychological interventions for IC/BPS. The authors from the USA conducted a 2:1 RCT of an 8-session patient-informed cognitive-behavioral therapy (CBT) intervention designed for IC/BPS for reducing pain-related symptoms and improving quality of life, delivered through telemedicine. Individuals with IC/BPS (N = 78) were randomized to receive either 8 weeks of CBT specifically designed for IC/BPS (n = 52) or an attention control condition (n = 26). Urologic symptoms (Genitourinary Pain Index, GUPI), pain-related symptoms, affective distress, and quality of life were evaluated before, immediately after, and 3 months posttreatment. Both conditions reported significant but similar reductions (P = 0.922) in the a priori primary outcome of genitourinary symptoms at posttreatment (GUPI reduction = 6.6 vs 4.8, for CBT and control, respectively) and long-term follow-up (8.1 vs 6.6, for CBT and control). However, the CBT group had significantly greater improvement in Patient Global Impression of Change (PGIC) scores and was significantly more likely to be treatment responders (PGIC ≥ 6) (37% vs 8%, P = 0.019 for CBT and control), with a large relative effect size (OR = 6.68). A subgroup analysis of CBT recipients showed that responders (PGIC ≥ 6) displayed significant reductions in genitourinary symptoms (P = 0.023), pain intensity (P = 0.027), and pain interference (P = 0.013) posttreatment. Telemedicine-delivered pain CBT for IC/BPS shows promise for improving outcomes, and this trial demonstrates the need for larger RCTs of CBT for IC/BPS.

STEM CELL THERAPY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Shin JH, Park JH, Ryu CM, Shin DM, Choo MS. Low Urin Tract Symptoms. 2024 Jul;16(4):e12527. doi: 10.1111/luts.12527. PMID: 38867432.

IC/BPS is a chronic disease with limited treatment options. Current multidisciplinary approach targeting bladder inflammation and urothelial dysfunction has limited durable effect that major surgery is ultimately required for both Hunner and non-Hunner type IC. The authors from Korea report that various investigational attempts are underway to avoid such operations and preserve the

urinary bladder. Stem cell therapy is a fascinating option for treating chronic illnesses. Stem cells can self-renew, restore damaged tissue, and have paracrine effects. The therapeutic efficacy and safety of stem cell therapy have been demonstrated in numerous preclinical models, primarily chemically induced cystitis rat models. Only one clinical trial (phase 1 study) has investigated the safety of human embryonic stem cell-derived mesenchymal stem cells in three Hunner-type IC patients. Under general anesthesia, participants underwent cystoscopic submucosal stem cell injection (2.0×10^7 stem cells/5 mL). No safety issues were reported up to 12 months of follow-up and long-term follow-up (up to 3 years). Although there were variations in therapeutic response, all patients reported significant improvement in pain at 1 month postoperatively. One patient underwent fulguration of the Hunner lesion after the trial, but others reported an overall improvement in pain. The analysis on phase 1/2a trial which had several modifications in protocol is currently ongoing. Despite several limitations that need to be overcome, stem cell therapy could be a potential therapeutic option for treating IC/BPS. Clinical outcome on phase 1/2a trial is important and might provide more insight into the clinical application of stem cell therapy for IC/BPS.

LACTOFERRIN IN THE TREATMENT OF INTERSTITIAL CYSTITIS: A RETROSPECTIVE PILOT STUDY.

Rosa L, Cutone A, Ianiro G, Valenti P, Paesano R. Biochem Cell Biol. 2024 Aug 1. doi: 10.1139/bcb-2024-0036. Epub ahead of print. PMID: 39088844.

Interstitial cystitis (IC), defined as a painful bladder syndrome (PBS), is a chronic condition that manifests itself as a suprapubic pain associated with an enhancing of frequency/urgency of urination, and for which there is no cure. In this study from Italy, the authors present a retrospective pilot study on women affected from IC/PBS and treated with bovine lactoferrin (bLf). A total of 31 women, affected (20) or unaffected (11) from hereditary thrombophilia (HT), presented the median of 6 episodes of IC/PBS during the 6 months before the study. Treatment consisted of 17 weeks of orally administered Valpalf® capsules, containing bLf plus sodium bicarbonate and citrate. Out of 31 patients, only 3 women had one episode of IC/PBS during the follow-up period, while no episode was observed in 28 women. In the HT group, a significant decrease in both serum IL-6 and D-dimers was found after Valpalf® treatment. Moreover, in Valpalf®-treated women, cystoscopy revealed a global improvement in the appearance of the bladder, especially in term of inflammation/irritation and presence of Hunner ulcers. The authors note that even though their results must be corroborated by randomized double-blinded controlled trials on a larger number of patients, their observations indicate that bLf treatment is efficient in relieving IC/PBS symptoms, without side effects.

THE EFFECT OF MONTELUKAST ON URINARY SYMPTOMS IN CHILDREN WITH BLADDER PAIN SYNDROME: A RANDOMIZED CLINICAL TRIAL.

Arjmand Shabestari A, Akbarzadeh F, Dorreh F, Yousefichaijan P, Almasi-Hashiani A. Clin Pediatr (Phila). 2024 Jun 12:99228241260119. doi: 10.1177/00099228241260119. Epub ahead of print. PMID: 38864166.

Montelukast by inhibiting leukotriene receptors in the bladder can prevent the activation of mast cells. The authors from Iran investigated the effectiveness of Montelukast in reducing the symptoms of children with bladder pain syndrome (BPS). In this randomized clinical trial, children were allocated into groups of intervention (Montelukast and oxybutynin) and the control (oxybutynin). At the beginning and after 14 days, questions from mothers of children about their urinary condition were asked about the frequency of nocturnal enuresis, frequent urination, urinary incontinence, urinary urgency, and their pain severity. There was no significant difference between two groups in terms of frequency of nocturnal enuresis, frequent urination, urinary incontinence, and urinary urgency. Regarding the frequency of pain distribution, the frequency of pain-free people in the Montelukast group was higher than control group (84.4% vs 56.3%, $P = .023$). The results showed that adding Montelukast to oxybutynin has a significant decrease in pain in children with BPS.

BLADDER INSTILLATIONS VS ONABOTULINUMTOXINA INJECTION FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A RANDOMIZED CLINICAL TRIAL.

Welch EK, Dengler KL, DiCarlo-Meacham AM, Wheat JE, Pekny CJ, Aden JK, Vaccaro CM. Am J Obstet Gynecol. 2024 May 18:S0002-9378(24)00609-4. doi: 10.1016/j.ajog.2024.05.027. Epub ahead of print. PMID: 38768800.

IC/BPS is an unpleasant sensation related to the bladder with lower urinary tract symptoms lasting more than 6 weeks, unrelated to an otherwise identifiable cause. The etiology is likely multifactorial including urothelial abnormalities, neurogenic pain upregulation, and potentially bladder and vaginal microbiome alterations. Despite treatment effectiveness of both bladder instillations and intradetrusor onabotulinumtoxinA injection for this condition, a head-to-head comparison has not been performed. The purpose of this study from the USA was to compare the efficacy of bladder instillations and intradetrusor onabotulinumtoxinA injection for treatment of IC/BPS. Patients with O'Leary-Sant (OLS) questionnaire scores of ≥6, meeting clinical criteria for IC/BPS, and desiring procedural management were randomized to bladder instillations or intradetrusor onabotulinumtoxinA injection. The primary outcome was the difference in OLS scores at 2 months posttreatment between groups. Secondary outcomes included evaluation of sexual function, physical/mental health status, pain, patient satisfaction, treatment perception, retreatment, and adverse event rates. Forty-seven patients were analyzed with 22 randomized to bladder instillations and 25 to onabotulinumtoxinA injection. There were no differences in demographic and clinical characteristics between groups. From baseline to 2 months posttreatment, there was a decrease in OLS subscales in all patients (Interstitial Cystitis Symptom Index [ICSI] -6.3 (confidence interval [CI] -8.54, -3.95), P<.0001; Interstitial Cystitis Problem Index [ICPI] -5.9 (CI -8.18, -3.57), P<.0001). At 2 months posttreatment, patients in the onabotulinumtoxinA group had significantly lower OLS scores compared to those in the bladder instillation group (ICSI 6.3±4.5 [onabotulinumtoxinA] vs 9.6±4.2 [instillation], P=.008; ICPI 5.9±5.1 [onabotulinumtoxinA] vs 8.3±4.0 [instillation], P=.048). The difference in OLS scores between groups did not persist at 6 to 9 months posttreatment. There were no statistically significant differences between baseline and posttreatment time points for the remaining questionnaires. Eight percent of patients who received onabotulinumtoxinA injection experienced urinary retention requiring self-catheterization. Patients who underwent onabotulinumtoxinA injection were significantly less likely to receive retreatment within 6 to 9 months compared to patients who received bladder instillations (relative risk 13.6; 95% CI, 1.92-96.6; P=.0002). There were no differences between groups regarding patient satisfaction, perception of treatment convenience, or willingness to undergo retreatment. Both onabotulinumtoxinA injection and bladder instillations are safe, effective treatments for patients with IC/BPS, with significant clinical improvement demonstrated at 2 months posttreatment. The authors believe that their findings suggest that intradetrusor onabotulinumtoxinA injection is a more effective procedural treatment for this condition than bladder instillation therapy and associated with decreased rates of retreatment.

MODIFIED BOTULINUM TOXIN TYPE A INJECTIONS IMPROVE SYMPTOMS ASSOCIATED WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN WOMEN: A RETROSPECTIVE COHORT STUDY.

Wang Y, Zheng J, Li Z, Jiang Y, Yu J, Li S, Chen X. Urology. 2024 Jul;189:27-33. doi: 10.1016/j.urology.2024.04.039. Epub 2024 May 4. PMID: 38710455.

The purpose of this study from China was to investigate the efficacy and safety of modified botulinum toxin type A (BoNT-A) injections (with additional periurethral injection [PUI] of BoNT-A) for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). This single-center, retrospective cohort study included 52 adult female patients with IC/BPS, with 24 patients receiving conventional BoNT-A injections and 28 receiving modified BoNT-A injections. The primary outcome measure was patient-reported global response assessment. Secondary outcomes included daytime frequency, nocturia, number of urinary urgency episodes in the voiding diary, pain visual analog score, O'Leary-Sant interstitial cystitis symptom index and interstitial cystitis problem index, pelvic

pain and urgency/frequency scores, risk factors for recurrence, and postoperative recurrence-free time. The median duration of follow-up was 16.0 months (interquartile range 11.75-21 months). Patients who underwent modified BoNT-A injections showed significant improvement in postoperative global response assessment, symptom questionnaires, and pain assessment compared with those who underwent conventional surgery. A statistically significant difference was observed between the 2 groups in terms of recurrence-free time (12.5 vs 18.0 months, P = .02). Subgroup analysis suggested that additional PUI of BoNT-A was more effective in patients with combined severe periurethral pain. No serious complications occurred in both groups, and all minor postoperative complications were temporary. The authors concluded that modified BoNT-A injection is an effective treatment for IC/BPS that significantly reduces pain and improves voiding symptoms. It is particularly effective in patients with combined periurethral pain. In such patients, PUI of BoNT-A should be added to the routine intravesical injection of BoNT-A.

EFFECTS OF ONABOTULINUM TOXIN-A INJECTION ON SEXUAL FUNCTION IN WOMEN WITH REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PROSPECTIVE STUDY.

Karaburun MC, Kubilay E, Öztuna D, Gökçe Mİ, Süer E, Gülpınar Ö. Low Urin Tract Symptoms. 2024 Mar;16(2):e12511. doi: 10.1111/luts.12511. Erratum in: Low Urin Tract Symptoms. 2024 May;16(3):e12514. doi: 10.1111/luts.12514. PMID: 38527461.

The purpose of this study from Turkije and Cyprus was to determine the effect of intravesical onabotulinum toxin-A (BoNT-A) treatment on sexual functions in female patients with refractory IC/BPS. Female patients with IC/BPS refractory to previous treatments were included in the study between January 2020 and April 2022. Patients were treated with the trigone-sparing injection (Group 1) or trigone-included injection (Group 2) techniques. 100 Units of BoNT-A was applied submucosally on 20 different points. The patients were evaluated with visual analog scale (VAS), O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Female Sexual Function Index (FSFI) questionnaires, 3-day voiding diary, uroflowmetry, and post-voiding residual volume analysis in the preoperative period, as well as on the 30th and 90th days postoperatively. For the repeated measurements, analysis of variance was used to assess the time-dependent variation across groups. The baseline FSFI score of the patients was 15.96 ± 3.82. Following the treatment, the FSFI scores were 22.43 ± 4.93 and 24.41 ± 5.94 on the 30th and 90th days, respectively ($p < .001$). The authors observed statistically significant improvement in all FSFI subdomains ($p < .05$). Statistically significant improvements with treatment on ICSI, ICPI, and VAS scores were achieved ($p < .05$). Preoperative FSFI scores were similar in Group 1 and Group 2 ($p = .147$). While the preoperative FSFI scores were 17.00 ± 3.73 and 14.84 ± 3.72 for Group 1 and Group 2, respectively, the scores after the treatment were 22.85 ± 5.01 and 21.98 ± 5.01 on the 30th day, and 24.62 ± 6.06 and 24.19 ± 6.05 on the 90th day postoperatively. Significant improvement was observed in FSFI scores with treatment, and no difference was observed between the two groups in terms of treatment response ($p = .706$). According to the authors, intravesical BoNT-A injection in the treatment of women with refractory IC/BPS improves sexual functions. It also significantly improves pain and symptom scores. Both trigone-sparing and trigone-including injections are similarly safe and effective.

POST-MARKETING SAFETY CONCERNS WITH ELAGOLIX: A DISPROPORTIONALITY ANALYSIS OF THE FDA ADVERSE EVENT REPORTING SYSTEM.

Chang E, Shi YF, Liu JF, Wei W. Expert Opin Drug Saf. 2024 May 7:1-8. doi: 10.1080/14740338.2024.2351451. Epub ahead of print. PMID: 38700323.

Elagolix is approved for the treatment of moderate-to-severe pain associated with endometriosis. However, the long-term safety of elagolix in a large sample of real-world patients is unknown, according to Chang and colleagues from China. The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) reports were collected and analyzed from January 2019 to June 2023. Disproportionality analyses, including the reporting odds ratio (ROR), the proportional

reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) algorithms, were employed in data mining to quantify the signals of elagolix-related adverse events (AEs). After removing the non-drug-related AE signals, they detected several AE signals such as hot flushes, bone pain, suicidal ideation, depression, and increased liver enzymes, which were known during the clinical trial phase. In addition to this, several unexpected important AEs were detected that were not mentioned in the drug insert, including cystitis interstitial, parosmia, and epiploic appendagitis. The median onset time of elagolix-associated AEs was 28.5 days. The authors report that their study provides a comprehensive picture of the safety of elagolix in the post-marketing setting, while also identifying potential new AE signals. These findings emphasize the importance of continued monitoring of the potential risks of elagolix.

THE EFFICACY OF CO_2 VAGINAL LASER IN THE TREATMENT OF RECURRENT, POST-COITAL AND INTERSTITIAL CYSTITIS: A MULTICENTRIC PROSPECTIVE STUDY.

Luvero D, Silvagni A, Angioli AM, Filippini M, Plotti F, Montera R, De Cicco Nardone C, Notaro E, Branda F, Angioli R. J Clin Med. 2024 Jun 17;13(12):3550. doi: 10.3390/jcm13123550. PMID: 38930079; PMCID: PMC11204505.

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This multicentric prospective study was carried out at Fondazione Policlinico Universitario Campus Bio Medico and Ospedale di Stato of St. Marino Republic. Between 1 January 2019, and 31 December 2022, all pre- and post-menopausal women diagnosed with recurrent, post-coital, and interstitial cystitis at both centers were included in the study. The main aim of the Italian study was to assess the effectiveness of vaginal CO_2 laser treatment, alone or combined with intravesical hyaluronic acid instillations, in managing cystitis symptoms, such as dysuria, pollakiuria, and urgency, across the entire patient cohort. The secondary objective was to investigate the reduction in number of annual cystitis episodes post-treatment. Each woman underwent three to four sessions of micro-ablative CO_2 vaginal laser treatment. A follow-up examination was conducted 12 months after the final laser session (up to December 2023), during which a post-treatment VAS assessment evaluated dysuria, daily pollakiuria, and urgency. The enrolled patients recorded the number of cystitis episodes experienced during the 12-month pre- and post-treatment period. Results indicated the laser's efficacy in reducing the total number of cystitis episodes per year and an improvement in symptoms up to one year post-treatment. Greater efficacy of the CO_2 laser treatment, particularly when combined with intravesical hyaluronic acid instillation, was observed in both pre- and post-menopausal women. Fractional CO_2 laser therapy represents a safe and efficacious, non-hormonal approach for pre- and post-menopausal women diagnosed with recurrent, post-coital, and interstitial cystitis.

CURRENT UPDATES RELATING TO TREATMENT FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS.

Park JJ, Kim KT, Lee EJ, Chun J, Lee S, Shim SR, Kim JH. BMC Urol. 2024 Apr 24;24(1):95. doi: 10.1186/s12894-024-01485-w. PMID: 38658949; PMCID: PMC11040764.

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Despite the publication of several meta-analyses regarding the efficacy of certain therapies in helping individuals with IC/BPS, these have not provided a comprehensive review of therapeutic strategies. This study from Korea aimed to determine the efficacy of various therapies for IC/BPS and identify potential moderating factors using randomized controlled trials (RCTs). PubMed, Cochrane, and Embase databases were searched to identify prospective RCTs using inclusion criteria: 1) patients diagnosed with IC, 2) interventions included relevant treatments, 3) comparisons were a specified control or placebo, 4) outcomes were mean differences for individual symptoms and structured questionnaires. The pairwise meta-analysis and network meta-analysis (NMA) were performed to compare the treatments used in IC/BPS. Hedges' g standardized mean differences (SMDs) were used for improvement in all outcomes using random-effects models. Efficacy outcomes

included individual symptoms such as pain, frequency, urgency, and nocturia, as well as structured questionnaires measuring IC/BPS symptoms. A comprehensive literature search was conducted which identified 70 RCTs with 3,651 patients. The analysis revealed that certain treatments, such as instillation and intravesical injection, showed statistically significant improvements in pain and urgency compared to control or placebo groups in traditional pairwise meta-analysis. However, no specific treatment demonstrated significant improvement in all outcomes measured in the NMA. The results of moderator analyses to explore influential variables indicated that increasing age was associated with increased nocturia, while longer follow-up periods were associated with decreased frequency. This systematic review and meta-analysis provide insights into the efficacy of various treatments for IC. Current research suggests that a combination of therapies may have a positive clinical outcome for patients with IC, despite the fact that treatment for this condition is not straightforward.

COMBINATION OF URINARY BIOMARKERS AND MACHINE-LEARNING MODELS PROVIDED A HIGHER PREDICTIVE ACCURACY TO PREDICT LONG-TERM TREATMENT OUTCOMES OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Jhang JF, Yu WR, Huang WT, Kuo HC. World J Urol. 2024 Mar 20;42(1):173. doi: 10.1007/s00345-024-04843-3. PMID: 38507059.

The purpose of this study from Taiwan was to identify predictive factors for satisfactory treatment outcome of the patients with IC/BPS using urine biomarkers and machine-learning models. The IC/BPS patients were prospectively enrolled and provide urine samples. The targeted analytes included inflammatory cytokines, neurotrophins, and oxidative stress biomarkers. The patients with overall subjective symptom improvement of ≥ 50% were considered to have satisfactory results. Binary logistic regression, receiver-operating characteristic (ROC) curve, machine-learning decision tree, and random forest models were used to analyze urinary biomarkers to predict satisfactory results. Altogether, 57.4% of the 291 IC/BPS patients obtained satisfactory results. The patients with satisfactory results had lower levels of baseline urinary inflammatory cytokines and oxidative biomarkers than patients without satisfying results, including interleukin-6, monocyte chemoattractant protein-1 (MCP-1), C-X-C motif chemokine 10 (CXCL10), oxidative stress biomarkers 8-hydroxy-2'-deoxyguanosine (8-OHDG), 8-isoprostane, and total antioxidant capacity (TAC). Logistic regression and multivariable analysis revealed that lower levels of urinary CXCL10, MCP-1, 8-OHDG, and 8-isoprostane were independent factors. The ROC curve revealed that MCP-1 level had best area under curve (AUC: 0.797). In machine-learning decision tree model, combination of urinary C-C motif chemokine 5, 8-isoprostane, TAC, MCP-1, and 8-OHDG could predict satisfactory results (accuracy: 0.81). The random forest model revealed that urinary 8-isoprostance, MCP-1, and 8-OHDG levels had the most important influence on accuracy. Machine learning decision tree model provided a higher accuracy for predicting treatment outcome of patients with IC/BPS than logistic regression, and levels of 8-isoprostance, MCP-1, and 8-OHDG had the most important influence on accuracy.

EFFICACY AND PREDICTIVE FACTORS OF CLINICAL RESPONSE TO HYALURONIC ACID + CHONDROITIN SULFATE BLADDER INSTILLATIONS FOR THE TREATMENT OF BPS/IC

G. Polisini, E. Ammirati, P. Geretto, A. Manassero, A. Giammò. Continence, Volume 10, June 2024, 101224. https://doi.org/10.1016/j.cont.2024.101224

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The purpose of this study from Italy was to assess the efficacy of intravesical hyaluronic acid and chondroitin sulfate (HACS) instillations in treating patients with BPS/IC, as well as to identify predictive factors for clinical response. Patients diagnosed with BPS/IC and treated with Ialuril® (HACS) bladder instillations between January 2018 and August 2020 were included. Data collected included Visual Analog Scale (VAS) scores, number of pain episodes, 3-day frequency volume chart measurements (at baseline and last follow-up), Patient Global Impression of Improvement (PGI-I) questionnaire responses, age, history of urinary tract infections (UTIs), and

endoscopic findings from cystoscopy with hydrodistension. Statistical analyses included Mann–Whitney's non-parametric U-test and chi-square test with a 95% confidence interval ($p \leq 0.05$) to identify predictive factors of treatment success. A total of 104 patients were treated with a median follow-up of 29 months (IQR 14–40), predominantly female with a mean age of 60 ± 16 years. At the last follow-up, there was a median reduction of 1 point in the VAS score (IQR 1–1), whilst only 20% experienced a reduction of ≥2 points. A statistically significant correlation was observed in the reduction of days with pain per month before and after treatment (ΔDPV) (median reduction: 6 days, IQR 2–7, $p < 0.001$). No adverse events were reported during treatment. Regarding prognostic factors, three statistically significant correlations were found: between PGI-I success and age ($p=0.050$), between ΔVAS score and recurrent UTIs ($p=0.044$), and between ΔDPV and recurrent UTIs ($p=0.04$). The study did not demonstrate any significant reduction of VAS score or diurnal and nocturnal voiding frequency after treatment, on the contrary it did show a reduction in the number of days with pain. Consequently, 88.3% of patients reported positive subjective improvement on the PGI-I questionnaire, and none discontinued treatment. Endoscopic findings did not appear to correlate with treatment response. Age and the presence of recurrent UTIs may influence the response to intravesical HACS therapy in terms of PGI-I, VAS score, and reduction in days with pain.

HUNNER LESION DISEASE

CYSTOSCOPIC CHARACTERISTIC FINDINGS OF INTERSTITIAL CYSTITIS AND CLINICAL IMPLICATIONS.

Yu WR, Jiang YH, Jhang JF, Kuo HC. Tzu Chi Med J. 2023 Aug 22;36(1):30-37. doi: 10.4103/tcmj.tcmj_172_23. PMID: 38406570; PMCID: PMC10887339.

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IC/BPS is a chronic inflammatory bladder disease of unknown etiology, characterized by bladder pain and frequency urgency symptoms. Based on the cystoscopic findings after hydrodistention under anesthesia, the phenotype of IC/BPS includes no glomerulation, characteristic glomerulation, and with Hunner's lesion. IC is specifically defined if characteristic Hunner's lesions are seen in cystoscopy or after hydrodistention. If there are glomerulations without Hunner's lesion, BPS should be considered. The definition of Hunner's lesion and glomerulations differs based on different definition and observations. Currently, there has been no clear description and grading of the glomerulations and Hunner's lesion. Because the classification of IC/BPS has an impact on the treatment strategy and associated with therapeutic outcome, it is essential to have a clear definition and consensus on the characteristic cystoscopic findings of IC/BPS. This article reviews the literature and presents the figures of Hunner's lesions and description of different mucosal lesions after cystoscopic hydrodistention.

[OUTPATIENT TREATMENT AND QUALITY OF LIFE OF PATIENTS WITH INTERSTITIAL CYSTITIS AND HUNNERS LESION: COHORT CROSS-SECTIONAL STUDY].

Karasev A E, Bresso T I, Markova O D, Kasyan G R, Pushkar D Y. Urologiia. 2024 Mar;(1):5-9. Russian. PMID: 38650399.

The purpose of this study from Russia was to assess the quality of life of patients with interstitial cystitis (IC) and to study effective options used to control symptoms on outpatient basis. The results of a descriptive prospective cross-sectional cohort study are presented. The medical charts of patients who were treated in the City Clinical Hospital named after Spasokukotsky from 2021 to 2023 were analyzed. Eighty inpatient medical charts of various patients with a final diagnosis of IC with Hunner's lesion were identified. Only 53 patients were interviewed due to the inclusion/exclusion criteria. Respondents were asked to complete a survey consisting of 15 questions. The survey was carried out online for patients who did not require surgical treatment at the time of the study, and offline for patients admitted for repeated surgical treatment. The average age of respondents was 59.011.1 years. 58% (31) of patients noted the presence of constant pain in the pelvic area during the day, while 85% (45) of patients reported pain outside the bladder area, in

the urethra and perineum. The intensity of pain in the pelvic area was 4.9 (2.3-5.6) points. Higher pain scores 6.24 (5.8-9.0) were observed in 47% (25) of patients admitted for repeat surgical treatment. 62% (33) of patients had a titer of bacteria in a urine test above 104, while 51% (27) of patients experienced relief of symptoms after taking antibacterial drugs. For the treatment and symptomatic relief, the following are most often used: pentosan sodium polysulfate (26%, n=14), antibacterial drugs of the nitrofuran group (25%, n=13), amitriptyline (15%, n=8), non-steroidal anti-inflammatory drugs (11%, n=6) patients. 23% (12) of respondents received intravesical therapy. The time from the onset of symptoms to the final diagnosis was 48 (24-96) months. Although infection is a criterion for excluding the diagnosis of IC, more than 62% of patients have positive urine culture. The results obtained indicate the need to improve existing approaches to the diagnosis of IC, as well as to develop treatment algorithms for painful bladder syndrome to control symptoms.

UPK3A$^+$ UMBRELLA CELL DAMAGE MEDIATED BY TLR3-NR2F6 TRIGGERS PROGRAMMED DESTRUCTION OF UROTHELIUM IN HUNNER-TYPE INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Peng L, Chen JW, Chen YZ, Zhang C, Shen SH, Liu MZ, Fan Y, Yang SQ, Zhang XZ, Wang W, Gao XS, Di XP, Ma YC, Zeng X, Shen H, Jin X, Luo DY. J Pathol. 2024 Jun;263(2):203-216. doi: 10.1002/path.6275. Epub 2024 Mar 29. PMID: 38551071.

Urothelial damage and barrier dysfunction emerge as the foremost mechanisms in Hunner-type interstitial cystitis/bladder pain syndrome (HIC). Although treatments aimed at urothelial regeneration and repair have been employed, their therapeutic effectiveness remains limited due to the inadequate understanding of specific cell types involved in damage and the lack of specific molecular targets within these mechanisms. The authors from China harnessed single-cell RNA sequencing to elucidate the heterogeneity and developmental trajectory of urothelial cells within HIC bladders. Through reclustering, they identified eight distinct clusters of urothelial cells. There was a significant reduction in UPK3A$^+$ umbrella cells and a simultaneous increase in progenitor-like pluripotent cells (PPCs) within the HIC bladder. Pseudotime analysis of the urothelial cells in the HIC bladder revealed that cells faced challenges in differentiating into UPK3A$^+$ umbrella cells, while PPCs exhibited substantial proliferation to compensate for the loss of UPK3A$^+$ umbrella cells. The urothelium in HIC remains unrepaired, despite the substantial proliferation of PPCs. They propose that inhibiting the pivotal signaling pathways responsible for the injury to UPK3A$^+$ umbrella cells is paramount for restoring the urothelial barrier and alleviating lower urinary tract symptoms in HIC patients. Subsequently, they identified key molecular pathways (TLR3 and NR2F6) associated with the injury of UPK3A$^+$ umbrella cells in HIC urothelium. Finally, they conducted in vitro and in vivo experiments to confirm the potential of the TLR3-NR2F6 axis as a promising therapeutic target for HIC. These findings hold the potential to inhibit urothelial injury, providing promising clues for early diagnosis and functional bladder self-repair strategies for HIC patients.

OTHER INFLAMMATORY BLADDER DISORDERS

CYSTITIS CYSTICA AND CYSTITIS GLANDULARIS.

Abdel Magied MH, Badreldin AM, Leslie SW. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–2024 Apr 19. PMID: 35881730.

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Cystitis cystica is a common benign condition of the urinary bladder with a reactive inflammatory change of the bladder mucosa associated with subepithelial vesicles or cysts formation and glandular metaplasia (cystitis glandularis). Invaginations of hyperplastic urothelial extensions into the superficial lamina propria are called von Brunn nests. These inflammatory projections are considered reactive but benign and non-malignant. Cystitis cystica develops when the urothelial cells in the lumens of von Brunn nests degenerate, causing cystic changes. Additional metaplasia results in cystitis glandularis, characterized by mucin-producing goblet cells that may uncommonly progress to

vesical adenocarcinoma. Cystitis glandularis is a further proliferative progression of cystitis cystica characterized by glandular metaplasia of the urothelium and goblet cells. Cystitis cystica and cystitis glandularis occur mainly in response to chronic irritation or inflammation and may occur together. They are usually asymptomatic but may present with non-specific signs and symptoms that require thoughtful attention to exclude other morphologically similar malignant lesions such as bladder adenocarcinoma. A nephrogenic adenoma is a rare, benign bladder tumor that is similar in cystoscopic appearance to cystitis glandularis and represents a type of superficial bladder proliferative disorder. The adenoma is often associated with genitourinary (bladder) stones, trauma, exstrophy, malakoplakia, Mullerian lesions, chronic or recurrent bladder infections, interstitial cystitis, renal transplantation, radiation therapy, pelvic lipohypertrophy, intravesical therapy, foreign bodies, or surgery such as bladder augmentation. The adenoma may grow to cause obstructive urinary symptoms and may be multifocal.

CHLOROGENIC ACID INTRAVESICAL THERAPY CHANGES ACUTE VOIDING BEHAVIOR OF SYSTEMIC LIPOPOLYSACCHARIDE INFLAMMATION-INDUCED CYSTITIS BLADDER IN MICE.

Yeh CH, Praveen Rajneesh C, Liao CH, You WC, Chen KC, Wu YN, Chiang HS. Toxics. 2024 Mar 25;12(4):239. doi: 10.3390/toxics12040239. PMID: 38668463; PMCID: PMC11053829.

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This study from Taiwan explores the potential efficacy of chlorogenic acid (CGA) in mitigating lipopolysaccharide (LPS)-induced cystitis in a mice model. C57BL/6J mice were divided into four groups: normal control (NC), LPS, LPS + low CGA, and LPS + high CGA. Evaluation methods included cystometrogram (CMG), histopathological, western blot, and immunohistological analysis. In the LPS group, CMG revealed abnormal voiding behavior with increased micturition pressure, voided volume (VV), and decreased voided frequency. Low CGA treatment in LPS mice demonstrated improved micturition pressure and inter-contraction intervals (ICI). However, high CGA treatment exhibited prolonged ICI and increased VV, suggesting potential adverse effects. Histological analysis of LPS-treated mice displayed bladder inflammation and interstitial edema. Low CGA treatment reduced interstitial edema and bladder inflammation, confirmed by Masson's trichrome staining. Western blotting revealed increased cytokeratin 20 (K20) expression in the low CGA group, indicating structural abnormalities in the bladder umbrella layer after LPS administration. In conclusion, low CGA treatment positively impacted voiding behavior and decreased bladder edema and inflammation in the LPS-induced cystitis mice model, suggesting its potential as a supplement for inflammation cystitis prevention. However, high CGA treatment exhibited adverse effects, emphasizing the importance of dosage considerations in therapeutic applications.

TREATMENT OF CHRONIC POST-RADIATION CYSTITIS WITH TRANS-URETHRAL AMNIOTIC BLADDER THERAPY APPEARS DURABLE AT 9 MONTHS: A CLINICAL STUDY.

Lutchka J, Vercnocke J, Fisher E, Radoiu C, Jeberaeel J, Lucas S, Dhar N. Urologia. 2024 Aug;91(3):623-627. doi: 10.1177/03915603241248014. Epub 2024 Apr 22. PMID: 38646941.

Chronic radiation cystitis (CRC) develops after radiation therapy and can present with symptoms like urinary frequency, urgency, pelvic pain, and nocturia. The authors from the USA have previously reported that amniotic bladder therapy (ABT) provides symptomatic improvement in refractory CRC patients for up to 3 months. Herein, they evaluated the durability of ABT up to 6 months. CRC patients recalcitrant to previous treatments received ABT comprised of intra-detrusor injections of 100 mg micronized AM diluted in 10 mL 0.9% preservative-free sodium chloride. Clinical evaluation and questionnaires (Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), Overactive Bladder (OAB) Assessment Tool, SF-12 Health Survey) were repeated at pre-op and 2, 4, 8, 12, 16, 20, 24, and 36 weeks post-injection. Five consecutive patients with a mean age of 64.4 ± 20.1 years with a median CRC duration of 10 years were included and followed for 6 months. After ABT, the lower urinary tract symptoms improved as early as 2 weeks and were maintained up to 20 weeks. BPIC

significantly improved from 36.6 ± 1.1 at baseline to 12.6 ± 1.5 at 16 weeks and 13.8 ± 2.9 at 20 weeks. At 24 and 36 weeks, the improvement was maintained in four (80%) of the five patients (BPIC = 13.8 ± 1.0). Uroflow assessment showed voiding volume improved two-fold in four of the five patients at 24 weeks compared to baseline. The data suggest that a significant number of CRC patients may have durable benefit after ABT. Despite this, some of them can show symptoms rebound at 24 weeks.

GUIDELINES AND CLASSIFICATIONS

DEFINITION CHANGE AND UPDATE OF CLINICAL GUIDELINES FOR INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME.

Homma Y, Akiyama Y, Kim JH, Chuang YC, Jeong SJ, Meng E, Kitta T, Jhang JF, Furuta A, Lee KS, Maeda D. Low Urin Tract Symptoms. 2024 Sep;16(5):e12532. doi: 10.1111/luts.12532. PMID: 39267358.

The East Asian clinical guidelines for interstitial cystitis (IC) and bladder pain syndrome (BPS) have been revised by updating the previous guidelines. The symptoms of IC and BPS, collectively called as hypersensitive bladder (HSB) symptoms, are virtually indistinguishable between IC and BPS; however, IC and BPS should be considered as a separate entity of disorders. This East Asian study group defines IC as a bladder disease with Hunner lesions, usually associated with HSB symptoms and bladder inflammation, and BPS as a condition with HSB symptoms in the absence of Hunner lesions and any confusable diseases. Pathophysiology totally differs between IC and BPS. IC involves immunological inflammation probably resulting from autoimmunity, while BPS is associated with the interaction of multiple factors such as neurogenic inflammation, exogenous substances, urothelial defects, psychological stress, and neural hyperactivity. Histopathology also differs between IC and BPS. IC is associated with severe inflammation of the whole bladder accompanied by plasma cell infiltration and urothelial denudation, while BPS shows little pathological changes. Management should begin with a differential diagnosis of IC or BPS, which would require cystoscopy to determine the presence or absence of Hunner lesions. The patients should be treated differently based on the diagnosis following the algorithm, although pain management would be common to IC and BPS. Clinical studies are also to be designed and analyzed separately for IC and BPS.

KEEP IT SIMPLE: A PROPOSAL FOR A NEW DEFINITION OF UNCOMPLICATED AND COMPLICATED URINARY TRACT INFECTIONS FROM THE EAU UROLOGICAL INFECTIONS GUIDELINES PANEL.

Bonkat G, Wagenlehner F, Kranz J. Eur Urol. 2024 May 13:S0302-2838(24)02353-4. doi: 10.1016/j.eururo.2024.05.007. Epub ahead of print. PMID: 38744631.

The European Association of Urology Urological Infections Guidelines Panel is proposing a new classification scheme for categorizing urinary tract infections (UTIs) into uncomplicated and complicated types. This classification would provide clarity and facilitate effective clinical management of UTIs and acknowledges the importance of addressing clinical and sex-specific nuances in the care of individual patients.

CLASSIFICATION SYSTEMS FOR CHRONIC PELVIC PAIN IN MALES: A SYSTEMATIC REVIEW.

Cyr MP, Nahon I, Worman R, Cowley D, Hodges PW. BJU Int. 2024 Jul 29. doi: 10.1111/bju.16485. Epub ahead of print. PMID: 39075791.

The purpose of this study from Australia was to systematically review the classification systems for male chronic pelvic pain (CPP). The Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), and Web of Science were searched. Any publication, with no restriction to publication date, was eligible. Publications had to propose a classification system for CPP in males or provide additional information of a system that had been identified. Systems were assessed with an adapted Critical Appraisal of Classification Systems tool. A total of 33 relevant publications were identified, with 22 proposing an original classification system. Systems aimed to: (i) diagnose CPP and/or differentially diagnose CPP from other conditions, (ii)

differentially diagnose subtypes within CPP, or (iii) identify features that could inform underlying mechanisms and/or treatment selection. Conditions referred to as chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/bladder pain syndrome were most represented. Clinical signs/symptoms, pathoanatomical investigations, and presumed pain mechanisms were used for classification. Quality of systems was low to moderate, implying limitations to consider for their interpretation. Many classification systems for CPP in males exist. Careful consideration of their intended purpose is required. Future work should examine whether outcomes for patients are improved when decisions are guided by their use.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IS IMPRECISE: TIME TO CLEAVE INTO INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME AS SEPARATE CONDITIONS.

Donohoo N, Orlando A, Chai TC. J Urol. 2024 Jul;212(1):223-224. doi: 10.1097/JU.0000000000003953. Epub 2024 Apr 5. PMID: 38578287.

LOWER URINARY TRACT

SHOULD HORMONE REPLACEMENT THERAPY (ANY ROUTE OF ADMINISTRATION) BE CONSIDERED IN ALL POSTMENOPAUSAL WOMEN WITH LOWER URINARY TRACT SYMPTOMS? REPORT FROM THE ICI-RS 2023.

*Taithongchai A, Mohamed-Ahmed R, Sinha S, Gibson W, Giarenis I, Robinson D, Abrams P. Neurourol Urodyn. 2024 Aug;43(6):1321-1327. doi: 10.1002/nau.25384. Epub 2024 Jan 30. PMID: 3828*This International Consultation on Incontinence-Research Society report aims to summarize the evidence and uncertainties regarding the use of hormone replacement therapy by any route in the management of lower urinary tract symptoms (LUTS) including recurrent urinary tract infections (rUTI), with a review of special considerations for the elderly. Research question proposals to further this field have been highlighted. An overview of the existing evidence, guidelines, and consensus regarding the use of topical or systemic estrogens in the management of LUTS. There are currently evidence and recommendations to offer topical estrogens to postmenopausal women with overactive bladder symptoms as well as postmenopausal women with rUTIs. Systemic estrogens however have been shown in a meta-analysis to have a negative effect on LUTS and therefore are not currently recommended. Although available evidence and recommendations exist for the use of topical estrogens, few women are commenced on these in primary care. There remain large gaps still within our knowledge of the use of estrogens within the management of LUTS, particularly on when it should be commenced, the length of time treatment should be continued for, and barriers to prescribing.

A BRIEF PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE BLADDER.

Quaghebeur J, Bush M, Shkarupa D, Wyndaele JJ, De Wachter S. Ann Transl Med. 2024 Apr 22;12(2):24. doi: 10.21037/atm-23-1770. Epub 2024 Apr 18. PMID: 38721465; PMCID: PMC11075957.

The remit of this review is confined to experimental works and publications relevant to the integral theory of female urinary incontinence (IT). Since its first publication in 1990, the IT has challenged the general view that the pathogenesis of overactive bladder (OAB) (urge, frequency, nocturia) is unknown and there is no cure. According to the IT, normal function bladder control is binary, either closed or open. Control is cortical via a peripheral feedback component: oppositely acting reflex striated pelvic muscles contract against suspensory ligaments to close the urethra for continence, open it prior to evacuation, and stretch the vagina like a trampoline to prevent excess impulses from the urothelial stretch receptors which may cause unwanted urgency at low bladder volumes (OAB). The pathogenesis of female urinary incontinence is from outside the bladder, mainly weak ligaments or vagina, due to collagen deficiency. Damage in childbirth (collagen depolymerization) and age (collagen loss) make ligaments vulnerable to damage. With weak ligaments, muscles contracting

against them weaken: the muscles cannot close the urethra (manifested as stress incontinence), open it (manifested as emptying problems or retention) or stretch the vagina to prevent the urothelial stretch receptors firing off prematurely (manifested as urge incontinence). Weak pubourethral ligaments can cause stress urinary incontinence (SUI), or SUI plus urge (mixed incontinence). Weak uterosacral ligaments (USLs) can cause urge, frequency, nocturia and emptying difficulties. Treatment consisting of surgical/non-surgical strengthening of ligaments can cure or improve SUI, OAB, and emptying dysfunctions. In summary, bladder control is from outside the bladder, binary, with cortical and peripheral components. A small change in definition, from "overactive" to "overactivated" is consistent with this concept, retains the acronym "OAB", and opens the door to probability of cure and a massive increase in research endeavours.

URINE BIOMARKER COULD BE A USEFUL TOOL FOR DIFFERENTIAL DIAGNOSIS OF A LOWER URINARY TRACT DYSFUNCTION.

Yu WR, Jiang YH, Jhang JF, Kuo HC. Tzu Chi Med J. 2023 Dec 13;36(2):110-119. doi: 10.4103/tcmj.tcmj_221_23. PMID: 38645782; PMCID: PMC11025593.

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A precision diagnosis of lower urinary tract dysfunctions (LUTD) such as bladder outlet obstruction, detrusor overactivity (DO), interstitial cystitis/bladder pain syndrome (IC/BPS), dysfunctional voiding (DV), or detrusor underactivity (DU) needs invasive videourodynamic study. Exploring non-invasive tools to help screening LUTD is necessary for clinicians in their daily practice. This article from Taiwan reviews recently clinical studies of using urinary inflammatory proteins and oxidative stress biomarkers in the identification of specific LUTD among men and women with lower urinary tract symptoms (LUTS). Some important findings have been reported: (1) Using urine chemokines CXCL-1 and interleukin-8 (IL-8), it is possible to discriminate overactive bladder (OAB) symptoms in women between DO and urinary tract infection. (2) Urinary levels of oxidative stress biomarkers such as 8-hydroxydeoxyguanosine (8-OHdG) and 8-isoprostane have a potential being used as a tool to identify women with mixed DO and stress urinary incontinence. (3) Urine levels of total antioxidant capacity (TAC), and prostaglandin E2 (PGE2) are positively correlated with voiding detrusor pressure in patients with DU. (4) Urine levels of brain-derived neurotrophic factor (BDNF) and PGE2 were significantly higher in the DU patients with detrusor function recovery. (5) Women with DV had higher urinary levels of tumor necrosis factor-alpha (TNF-α) and 8-OHdG, and urinary IL-2 level was significantly lower. (6) Urine level of 8-isoprostane was higher in the patients with idiopathic DO and neurogenic DO. (7) Higher urine cytokine levels of monocyte chemoattractant protein-1 (MCP-1), regulated on activation, normal T-cell expressed and secreted (RANTES), CXCL-10, IL-7, and eotaxin-1 in patients with IC/BPS than controls. (8) The urine levels of IL-8, CXCL-10, BDNF, IL-6, and RANTES were significantly higher in patients with Hunner's IC than non-Hunner's IC. (9) Male patients with IC/BPS had a significantly higher level of eotaxin, MCP-1, TNF-α, 8-OHdG, and TAC. Combining a higher eotaxin and a higher TNF-α can provide a satisfactory diagnostic value in discriminating IC/BPS from other LUTD in men. These studies provide evidence that measurement of cluster of urine biomarkers could be used as a diagnostic tool to differentiate different LUTD in patients with similar LUTS.

DOES COVID-19 CAUSE OR WORSEN LUT DYSFUNCTION, WHAT ARE THE MECHANISMS AND POSSIBLE TREATMENTS? ICI-RS 2023.

Khullar V, Lemmon B, Acar O, Abrams P, Vahabi B. Neurourol Urodyn. 2024 Aug;43(6):1458-1463. doi: 10.1002/nau.25441. Epub 2024 Mar 20. PMID: 38506116.

UK USA ICI

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and produced a worldwide pandemic in 2020. There have been 770,875,433 confirmed cases and 6,959,316 attributed deaths worldwide until September 19, 2023. The virus can also affect the lower urinary tract (LUT) leading to bladder inflammation and producing lower urinary tract

symptoms (LUTS) in both the acute and chronic phases of disease. At the 2023 meeting of the International Consultation on Incontinence-Research Society (ICI-RS), the literature relating to COVID-19 and bladder dysfunction was reviewed. The LUTS reported, as well as the pathophysiology of these bladder symptoms, were the subject of considerable discussion. A number of different topics were discussed including lower LUTS reported in COVID-19, how SARS-CoV-2 may infect and affect the urinary tract, and proposed mechanisms for how viral infection result in new, worsened, and in some persisting LUTS. The workshop discussed the interaction between the virus and the immune system, covering current evidence supporting theories underlying the causes of acute and chronic LUTS related to COVID-19 infection. Research questions for further investigation were suggested and identified.

EFFECTIVENESS AND PATIENT PERSPECTIVE ON THE USE OF INTRAVESICAL GENTAMICIN INSTILLATIONS TO TREAT RECURRENT URINARY TRACT INFECTIONS IN NEUROGENIC LOWER URINARY TRACT DYSFUNCTION.

Cameron AP, Castrodad PM, Troost J, Forchheimer M, Tate DG. Neurourol Urodyn. 2024 Jun 11. doi: 10.1002/nau.25513. Epub ahead of print. PMID: 38860440.

Patients with neurogenic lower urinary tract dysfunction (NGLUTD) who require catheterization either with clean intermittent catheters (CIC) or indwelling catheters suffer with frequent urinary tract infections (UTIs). This study from the USA assessed the efficacy, patient persistence, satisfaction, and the impact on quality of life (QoL) of gentamicin nightly bladder instillations with 15 mg. This is a prospective survey of 36 patients with NGLUTD and recurrent UTIs prescribed long-term gentamicin to prevent UTIs. Eligible patients completed a questionnaire about their use and satisfaction with gentamicin therapy, as well as survey questionnaires to address QoL. A retrospective chart review was also performed to obtain medical history, confirm drug persistence, and obtain accurate UTI data for the 12 months preceding and after starting instillations. The rate of laboratory proven symptomatic UTI requiring antibiotic treatment decreased from 3.9 to 1.1 infections per year with no increase in antibiotic resistance and no significant side effects reported by patients. Eight patients stopped therapy before a full year for various reasons, but the remaining 72% of patients have continued to use the therapy now with a mean of 4.2 years later. Satisfaction among those continuing the medication was very high. Gentamicin bladder instillations with 15 mg nightly in patients with indwelling catheters or CIC with NGLUTD are very effective and safe with high patient satisfaction. This therapy can be maintained long-term with continued efficacy.

DRUG-INDUCED BLADDER DISORDERS

BRITISH ASSOCIATION OF UROLOGICAL SURGEONS CONSENSUS STATEMENTS ON THE MANAGEMENT OF KETAMINE UROPATHY.

Belal M, Downey A, Doherty R, Ali A, Hashim H, Kozan A, Kujawa M, Pakzad M, Rashid T, Osman N, Sahai A, Biers S; BAUS Section of Female, Neurological and Urodynamic Urology. BJU Int. 2024 May 22. doi: 10.1111/bju.16404. Epub ahead of print. PMID: 38778743.

The purpose of this study from the United Kingdom was to provide guidance in the form of consensus statement in the management of ketamine uropathy. A literature review of ketamine uropathy was performed. The consensus method was of a modified nominal group technique and has been use in the previous British Association of Urological Surgeons (BAUS) consensus documents and was led by the Female, Neurological and Urodynamic Urology Section of the BAUS. A number of consensus statements detailing the assessment and management of urological complications relate to the recreational use of ketamine (ketamine uropathy) in both elective and emergency urology settings. Comprehensive management pathway for ketamine-related urinary tract dysfunction and uropathy has been detailed.

A REAL-WORLD PHARMACOVIGILANCE STUDY OF ESKETAMINE NASAL SPRAY.

Chen Y, Gu H, Li W, Chen Y. Medicine (Baltimore). 2024 Sep 6;103(36):e39484. doi: 10.1097/MD.0000000000039484. PMID: 39252329.

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Mining and updating the post-marketing safety signals of esketamine nasal spray for better identification of adverse drug event (ADE) signals and medication monitoring during clinical use to ensure patient medication safety. In this study from China, downloading data from the US Food and Drug Administration Adverse Event Reporting System from Q1 2019 to Q2 2023, the reporting odds ratio, proportional reporting ratio, Multi-item Gamma Poisson Shrinker, and Bayesian Confidence Propagation Neural Network methods of the disproportionality method were used to mine and analyze ADEs, and finally to screen for signals of ADEs with esketamine nasal spray as the primary suspected drug. The Preferred Terminology of the Medical Dictionary of Regulatory Activities (version 26.0) was used to standardize the description of ADEs and to attribute ADEs to the System Organ Classification. A total of 5132 ADEs reports of esketamine nasal spray as the primary suspected drug were obtained from the Food and Drug Administration Adverse Event Reporting System. The most frequently observed ADEs are dissociation, sedation, and hypertension, while some new rare signals have been detected, such as interstitial cystitis, substance abuse, and drug diversion. The present study identified significant new ADEs signals for esketamine nasal spray, which may provide a source for healthcare professionals to assess patients' symptoms and risk identification.

METHIMAZOLE RELATED INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A CASE REPORT.

Guo X, Li Y, Chen Y, He Z. Asian J Surg. 2024 Jul 27:S1015-9584(24)01600-2. doi: 10.1016/j.asjsur.2024.07.227. Epub ahead of print. PMID: 39069408.

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Letter to the Editor

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disease characterized by lower urinary symptoms and bladder pain, affecting millions globally. IC/BPS patients often experience mental stress, sleep disorder, and sexual dysfunction, with a considerable low quality of life. Given the lack of direct causal evidence in the pathogenesis of IC/BPS, the etiology of IC/BPS is still unknown. In this letter to the editor from China, the authors describe a case of IC/BPS induced by methimazole, an antithyroid medication used as first line agent in treating hyperthyroidism. A 55-year-old menopausal woman had a 3-year history of urinary urgency, frequency, and pain. Her medical history included hypertension and hyperthyroidism, managed with methimazole (Thyrozol®). She reported urinating 30 times a day and 5 times at night, with pain centered in the lower abdomen, relieved after urination. The visual analog scale (VAS) of pain was 8 and the Interstitial Cystitis Symptom Index (ICSI) was 17. And the UPOINT system showed 4 positive domains: "U", "O", "I", and "N". Laboratory results indicated abnormal urinalysis with red blood cells (RBC) of 30–40/HP and white blood cells (WBC) of 2–4/HP, though blood tests and urine culture were negative. Urine cytology showed acute and chronic inflammatory cells without tumor cells, and urinary ultrasound revealed a bladder capacity of 79 ml. After comprehensive evaluation, the diagnosis of suspected IC/BPS was made. Cystoscopy and hydrodistension revealed pale mucosa in the posterior bladder wall and triangular region, with scattered hemorrhagic spots after dilatation. The maximum bladder capacity was 200 ml after dilation for 5 min at 80 cm water column pressure. A random biopsy showed mucosal tissue with vasodilatation, congestion of the lamina propria, and infiltration of inflammatory cells, including lymphocytes, eosinophils, neutrophils, plasma cells, and a few mast cells. The patient was discharged two days later. Follow-up was scheduled 3 months later. She urinated about 20 times per day at 150 ml, and 2 times at night. The VAS score of pain was 1 and the ICSI was 8. And there were 2 symptom remission of U and T domains in the UPOINT system. According to the Global Response Assessment (GRA), hydrodistension was effective at postoperative 3 months. However, symptoms reappeared after one year, but no treatments were given. About 6

years later, the patient underwent a subtotal thyroidectomy for worsening hyperthyroidism and stopped taking methimazole. Within one week of discontinuation, her urinary symptoms improved significantly. The bladder pain promptly faded, and the urinary urgency, frequency symptoms subsided almost all. However, two years later, because of the reappearance of hyperthyroidism, she resumed methimazole and experienced similar urinary symptoms again. After undergoing radiation therapy and stopping methimazole, her urinary symptoms disappeared entirely. To date, she has not experienced urinary urgency, frequency and pain.
The authors report that to their knowledge, this is the first case on methimazole's effect upon IC/BPS as so far. Though the pathogenetic mechanism still needs further exploration, awareness of this side effect is of great importance. And attention must be paid to IC/BPS patients who are meanwhile taking methimazole to treat hyperthyroidism.

MICROBIOTA

THE MICROBIOTA IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW.

Fu C, Zhang Y, Liang L, Lin H, Shan K, Liu F, Feng N. BJU Int. 2024 Jun 18. doi: 10.1111/bju.16439. Epub ahead of print. PMID: 38890150.

Fu and colleagues from China comprehensively reviewed and critically assessed the literature on microbiota differences between patients with interstitial cystitis (IC)/bladder pain syndrome (BPS) and normal controls to provide clinical practice guidelines. They evaluated previous research on microbiota disparities between IC/BPS and normal controls, as well as distinctions among IC/BPS subgroups. A comprehensive literature search was conducted across PubMed/MEDLINE, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials. Relevant studies were shortlisted based on predetermined inclusion and exclusion criteria, followed by quality assessment. The primary focus was identifying specific taxonomic variations among these cohorts. A total of 12 studies met the selection criteria. Discrepancies were adjudicated by a third reviewer. The Newcastle-Ottawa Scale was used to assess study quality. Predominantly, the studies focused on disparities in urine microbiota between IC/BPS patients and normal controls, with one study examining gut microbiota differences between the groups, and two studies exploring vaginal microbiota distinctions. Unfortunately, analyses of discrepancies in other microbiota were limited. Findings revealed evidence of distinct bacterial abundance variations, particularly involving Lactobacillus, alongside variations in specific metabolites among IC/BPS patients compared to controls. Currently, there is evidence suggesting significant variations in the diversity and species composition of the urinary microbiota between individuals diagnosed with IC/BPS and control groups. In the foreseeable future, urologists should consider urine microbiota dysbiosis as a potential aetiology for IC, with potential clinical implications for diagnosis and treatment.

A SYSTEMATIC AND COMPREHENSIVE REVIEW OF THE ROLE OF MICROBIOTA IN URINARY CHRONIC PELVIC PAIN SYNDROME.

Hashemi N, Tondro Anamag F, Javan Balegh Marand A, Rahnama'i MS, Herizchi Ghadim H, Salehi-Pourmehr H, Hajebrahimi S. Neurourol Urodyn. 2024 Jul 12. doi: 10.1002/nau.25550. Epub ahead of print. PMID: 38994675.

Many genitourinary tract disorders could be attributed partly to the microbiota. This study from Iran and the Netherlands sought to conduct a systematic review of the role of the microbiota in urinary chronic pelvic pain syndrome (UCPPS). The authors searched Embase, Scopus, Web of Science, and PubMed with no time, language, or study type restrictions until December 1, 2023. The JBI Appraisal Tool was used to assess the quality of the studies. Study selection followed the PRISMA statement. Studies addressing microbiome variations among patients suffering from interstitial cystitis/bladder pain syndrome (IC/BPS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and a control group were considered eligible. A total of 21 studies (1 UCPPS, 12 IC/BPS, and 8 CP/CPPS) comprising

1125 patients were enrolled in the final data synthesis. It has been shown that the reduced diversity and discrepant composition of the gut microbiota may partly be attributed to the UCPPS pathogenesis. In terms of urine microbiota, some operational taxonomic units were shown to be elevated, while others became less abundant. Furthermore, various bacteria and fungi are linked to specific clinical features. Few investigations denied UCPPS as a dysbiotic condition. Urinary and intestinal microbiota appear to be linked with UCPPS, comprising IC/BPS and CP/CPPS. However, given the substantial disparity of published studies, a battery of prospective trials is required to corroborate these findings.

MENDELIAN RANDOMIZATION STUDY REVEALS CAUSAL EFFECTS OF SPECIFIC GUT MICROBIOTA ON THE RISK OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS).

Jiang P, Li C, Su Z, Chen D, Li H, Chen J, Mi H. Sci Rep. 2024 Aug 8;14(1):18405. doi: 10.1038/s41598-024-69543-9. PMID: 39117770; PMCID: PMC11310512.

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Evidence from previous studies have demonstrated that gut microbiota are closely associated with occurrence of interstitial cystitis/bladder pain syndrome (IC/BPS), yet the causal link between the two is not well known. In this study, the authors from China performed a two-sample Mendelian randomization (MR) analysis to determine the possible causal association between gut microbiota with IC/BPS. Gut microbiota summary level data were derived from the genome-wide association study (GWAS) conducted by MiBioGen and the IC/BPS GWAS summary level data were obtained from the GWAS Catalog. Next, they performed an MR study to investigate the causal link between gut microbiota and IC/BPS. The primary method for causal analysis was the inverse variance weighted (IVW), and the MR results were validated through multiple sensitivity analyses. A positive association was found between IC/BPS and eight gut microbial taxa, including genus Bacteroides, genus Haemophilus, genus Veillonella, genus Coprococcus1, genus Butyricimonas, family Bacteroidaceae, family Christensenellaceae, and order Lactobacillales. Sensitivity analysis revealed lack of significant pleiotropy or heterogeneity in the obtained results. This MR analysis reveals that a causal association exists between some gut microbiota with IC/BPS. This finding may be expected to guide future research and development of IC/BPS preventions and treatments based on the bladder-gut axis. However, given the clinical complexity and diagnostic challenges of IC/BPS, along with the limitations of using large-scale GWAS summary data for analysis, the authors note that their MR results require further validation through additional research.

CAUSAL EFFECTS OF GUT MICROBIOTA ON RISK OF INTERSTITIAL CYSTITIS: A TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY.

Gao J, Shao S, Shen Y. Front Microbiol. 2024 Jul 12;15:1434117. doi: 10.3389/fmicb.2024.1434117. PMID: 39070264; PMCID: PMC11272578.

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In this study from China, the authors note that the correlation between gut microbiota and interstitial cystitis has garnered significant attention in previous studies. Nevertheless, the causal relationship between them remains to be clarified. Genetic variation serves as a tool in Mendelian randomization analyses, facilitating the inference of causal relationships between exposure factors and disease outcomes. Summary statistics derived from a comprehensive genome-wide association study conducted by the MiBioGen consortium were utilized as exposure factors, while interstitial cystitis data sourced from the GWAS Catalog served as the disease outcome. Then, a two-sample Mendelian randomization analysis was performed by applying inverse variance-weighted, MR-Egger, Weighted Median, Simple Mode, and Weighted Mode. In addition, heterogeneity and horizontal pleiotropy were excluded by sensitivity analysis. IVW results confirmed that genus *Haemophilus* (OR = 2.20, 95% CI: 1.16-4.15, p = 0.015), genus *Butyricimonas* (OR = 2.26, 95% CI: 1.15-4.45, p = 0.018), genus *Bacteroides* (OR = 4.27, 95% CI: 1.36-13.4, p = 0.013) and *Coprococcus1* (OR = 3.39, 95% CI: 1.28-8.99, p = 0.014) had a risk effect on interstitial cystitis. Sensitivity analysis did not find outlier

SNPs. The authors suggest that their analysis has identified a causal relationship between specific genera and interstitial cystitis. However, further validation through randomized controlled trials is essential to substantiate these findings.

CHRONIC PELVIC PAIN, PELVIC FLOOR, GENITAL PAIN

SYMPTOM FLARES IN WOMEN WITH CHRONIC PELVIC PAIN: QUESTIONNAIRE STUDY WITHIN A COHORT STUDY (TRANSLATIONAL RESEARCH IN PELVIC PAIN (TRIPP)).

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

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

CHRONIC PELVIC PAIN OF "UNKNOWN ORIGIN" IN THE FEMALE.

Petros P, Bornstein J, Scheffler K, Wagenlehner F, Abendstein B, Zaytseva A. Ann Transl Med. 2024 Apr 22;12(2):26. doi: 10.21037/atm-23-1758. Epub 2024 Apr 15. PMID: 38721452; PMCID: PMC11075965.

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The purpose of this review from Israel, Germany, Austria, Russia and Australia is confined to the experimental scientific works and surgeries based on the Integral Theory Paradigm (ITP). Chronic pelvic pain (CPP) is a major societal problem which is said to occur in up to 20% of women. The pathogenesis of CPP of "unknown origin" is said to be unknown and CPP is said to be incurable. According to the ITP, however, CPP is said to be mainly caused by the inability of loose or weak uterosacral ligaments (USLs) to mechanically support visceral nerve plexuses (VPs), T11-L2 and S2-4. These fire off *de novo* impulses, interpreted by the cortex as pain coming from the end organs. CPP, when it occurs simultaneously in multiple pelvic sites, is associated with uterine/apical prolapse (often minimal) and bladder symptoms such as overactive bladder (OAB), nocturia, retention. This combination of symptoms was described in 1993 as the "posterior fornix syndrome" (PFS). As such, CPP when associated with the PFS, is potentially curable by surgical repair of USLs. However, patients with CPP generally complain only of one symptom, CPP. This is known as the "Pescatori iceberg" effect. Other PFS symptoms are "under the surface" and must be sought out by direct

questioning. The diagnostic algorithm is helpful in locating other associated symptoms. Definitive diagnosis of CPP, caused by USL laxity, is immediate alleviation of pain by mechanical support of USLs by using the speculum test or by tampons in the posterior fornix. Treatment of CPP can be non-surgical, by strengthening USLs by squatting exercises, supporting USLs mechanically with tampons or USL surgery. Coexisting bladder symptoms are (variously) improved or cured.

GENITAL PAIN AND THE SPECTRUM OF BLADDER-RELATED SYMPTOMS: FINDINGS FROM THE PREVENTION OF LOWER URINARY TRACT SYMPTOMS RESEARCH CONSORTIUM RISE FOR HEALTH STUDY, USA.

Harlow BL, McGwin G Jr, Sutcliffe S, Fitzgerald CM, Lowder JL, Newman DK, Meister M, Camenga DR, Stapleton A, Chary V, Lukacz ES. Int Urogynecol J. 2024 Jul 13. doi: 10.1007/s00192-024-05868-3. Epub ahead of print. PMID: 39002046.

Women with vulvovaginal or genital pain more commonly experience interstitial cystitis/bladder pain syndrome (IC/BPS) and urinary tract infections. However, the relationship between genital pain and bladder health is lacking. Women in the Prevention of Lower Urinary Tract Symptoms Consortium's RISE FOR HEALTH population-based study in the USA answered questions about bladder health globally, and across nine bladder health domains of holding, efficacy, social-occupation, physical activity, intimacy, travel, emotion, perception, and freedom. Bladder function was assessed across six indices including urinary frequency, sensation, continence, comfort, emptying, and dysbiosis (e.g., urinary tract infections). Participants were grouped by no pain beyond transitory events (i.e., minor headaches, toothaches, or sprains), nongenital-related pain only, and any genital pain using a validated pain diagram. Mean adjusted scores and indices were compared using general linear modelling. Of 1,973 eligible women, 250 (12.7%) reported genital pain, 609 (30.9%) reported nongenital pain only, and 1,114 (56.5%) reported no pain. Women with any genital pain had lower (worse) adjusted mean scores across all bladder health scales (BHS; BHS global adjusted mean 47.5; 95% CI 40.8-54.1), compared with those with nongenital pain only (53.7; 95% CI 47.6-59.8), and no pain (59.3; 95% CI 53.3-65.4). Similarly, adjusted mean total Bladder Functional Index scores were lower for those with genital pain (63.1; 95% CI 58.4-67.9) compared with nongenital pain (72.1; 95% CI 67.7-76.5) and no pain (77.4; 95% CI 73.0-81.8). Heightened awareness of the relationship between genital pain and bladder health should prompt clinicians caring for women with genital pain to assess bladder health and function.

A PAIN DESENSITIZATION ALGORITHM FOR PHENOTYPING AND TREATING CHRONIC PELVIC PAIN.

Rogério LSR, Chung MK, Butrick CW, Antolak SJ Jr, Bevilaqua DR, Kureishy S, Conforto MEC. JSLS. 2024 Apr-Jun;28(2):e2024.00009. doi: 10.4293/JSLS.2024.00009. PMID: 39290721; PMCID: PMC11406477.

Chronic pelvic pain remains challenging for physicians to manage due to central and peripheral sensitization and multiple pain generators including the bladder, pelvic floor, and pudendal nerve. Pain management providers have used nerve blocks for years for diagnosis and treatment. The authors from the USA and Brazil developed a desensitization algorithm that provides a stepwise approach to improve patients pain scores. This study is a prospective observational cohort study of 182 women aged 15-90 years old with chronic pelvic pain using an algorithm from 2016 to 2018. Treatment started with an Anesthetic Challenge Test of the bladder to guide us through a protocol of intravesical therapy and/or pudendal nerve blocks as a second step. ACT POSITIVE patients, who received intravesical therapy: 84% had a Visual Analog Score pain improvement of at least 50%, 64% improved at least 80% (41% pain-free). Those desiring additional relief that received further Pudendal Blocks: 83% had final improvement of at least 50% (67% pain-free). ACT NEGATIVE patients received Pudendal Blocks with 80% of subjects achieving at least 50% relief, 65% improved at least 80% (35% pain-free). All final groups showed a statistically significance of $P < .05\%$ when compared to their initial pain scores. Management of women with chronic pelvic pain would ideally start with treating a specific diagnosis which, in most cases, is difficult to establish since the majority

have more than one pain generator. This algorithm simplified the approach and reduced the severity of pain scores prior to any further necessary surgical interventions.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

PENTOSAN POLYSULFATE MACULOPATHY-ASSOCIATED CYSTOID MACULAR EDEMA RESPONSIVE TO INTRAVITREAL STEROIDS.

Pant P, Grewal DS. Retin Cases Brief Rep. 2024 Sep 1;18(5):549-552. doi: 10.1097/ICB.0000000000001440. PMID: 39178366.

The purpose of this study from the USA was to report a case of angiographically silent cystoid macular edema (CME) secondary to pentosan polysulfate sodium (PPS) maculopathy responsive to intravitreal steroids. A 52-year-old female patient with a history of 4 years of PPS use for interstitial cystitis presented with PPS maculopathy that developed CME 2.5 years after drug cessation and had associated progression of pigmentary and atrophic changes. Her CME was nonresponsive to topical ketorolac and dorzolamide but was responsive to intravitreal triamcinolone acetonide and subsequently intravitreal dexamethasone implant (Ozurdex) with reduction in central subfield thickness and improvement in visual acuity. It was concluded that cystoid macular edema secondary to PPS maculopathy may be angiographically silent yet responsive to intravitreal steroids alone without the use of vascular endothelial growth factor agents. There is potential for both anatomic and functional improvements in such cases demonstrating the value of such treatment. Cystoid macular edema may be a delayed finding that can develop despite drug cessation. Steroid monotherapy should be further evaluated as possible first-line management for PPS maculopathy-associated CME.

PENTOSAN POLYSULFATE MACULOPATHY WITH 13 YEARS OF FOLLOW-UP IMAGING.

Pinto AM, Jain N, Gupta RR. J Vitreoretin Dis. 2024 Jan 31;8(3):325-333. doi: 10.1177/24741264241228375. PMID: 38770071; PMCID: PMC11102730.

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The purpose of this study from the USA was to describe a case of pentosan polysulfate maculopathy progression with 13 years of follow-up imaging. A case was analyzed and a literature review performed. A 65-year-old woman was referred to the retina service for a second opinion of a bilateral progressive pigmentary maculopathy. Her medical history was significant for interstitial cystitis that was actively treated with daily pentosan polysulfate since 2003. Multimodal imaging and fundus examination were consistent with pentosan polysulfate maculopathy. A review of records showed previous fundus imaging dating back 13 years that permitted longitudinal assessment of the disease course. Imaging findings were more prominent than the fundus examination findings. There was a 5-year period from the onset of parafoveal atrophy to foveal involvement. A pseudopodial pattern of disease expansion was seen on fundus autofluorescence. The authors note that, to their knowledge, this case represents the longest documented follow-up imaging of the progression of pentosan polysulfate maculopathy in the literature.

PENTOSAN POLYSULFATE MACULOPATHY.

Margines JB, Tripathy K, Hobbs SD. 2024 Mar 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 36944010.

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Pentosan polysulfate (PPS) is a semisynthetic pentasaccharide heparinoid with anticoagulant properties. It 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. PPS is the only medication approved by the United States Food and Drug Administration to treat interstitial cystitis (IC). IC 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, affecting over 1 million Americans, the vast majority of whom are 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, 3 times a day. Twenty-two years after its approval as a second-line agent for interstitial cystitis, a 6-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.

ASSOCIATED DISORDERS - SJÖGREN'S DISEASE (FORMERLY SJÖGREN'S SYNDROME)

SERONEGATIVE SJÖGREN SYNDROME: A FORGOTTEN ENTITY?

Lee AYS, Rischmueller M, Reed JH. The Journal of Rheumatology 2024;51:7–9 doi:10.3899/jrheum.2023-0247 First Release October 15, 2023

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As a highly varied disease, Sjögren syndrome (SS; also termed Sjögren disease) is estimated to affect 0.01% to 0.72% of the population, with an overwhelming bias toward the female gender. SS causes a significant burden to the quality of life of patients and inhibits their function. Patients present with a spectrum of clinical manifestations from sicca (dryness) symptoms to potentially severe extraglandular and/or systemic features, such as inflammatory arthritis, interstitial lung disease, neurological dysfunction, cryoglobulinemia, and malignant lymphoma. The hallmark of SS is B cell hyperreactivity and consequently, autoantibodies such as antinuclear antibodies (ANAs; including anti-Ro60/ Ro52/La) and rheumatoid factors. These autoantibodies are present in 45% to 75% of patients. When patients lack serum anti-Ro52/Ro60 (SSA/Ro), the diagnosis of SS relies upon meeting internationally defined classification criteria, which include reduction of measured tear and/or salivary flow, and the finding of focal lymphocytic sialadenitis on minor salivary gland biopsy (MSGB). Patients fulfilling SS criteria who do not express classic serum antibodies are called patients with seronegative SS. However, there is no universally accepted definition of which autoantibodies should define seropositive from seronegative SS. Hence, the proportion of patients with seronegative SS varies in the literature, ranging from 8% to 37% of SS cohorts.

SERONEGATIVE PRIMARY SJÖGREN'S SYNDROME, A DISTINCT SUBTYPE OF PRIMARY SJÖGREN'S SYNDROME IN CHINESE PATIENTS.

Lan J, Deng C, Huang H, Rao P, Chen Y, Shi Y, Chen J, Shi G, Liu Y, Chen S. BMC Rheumatol. 2024 Apr 16;8(1):15. doi: 10.1186/s41927-024-00384-9. PMID: 38627838; PMCID: PMC11020423.

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The purpose of this study from China was to investigate the clinical and immune characteristics of patients with primary Sjögren's syndrome (pSS) who were negative for anti-Sjögren's-syndrome-related antigen A antibodies (anti-SSA) and anti-Sjögren's-syndrome-related antigen B antibodies (anti-SSB) in Chinese population. A retrospective study was performed and 232 patients with pSS were analyzed. Patients positive for anti-SSA or/and anti-SSB were termed as seropositive pSS, and these negative for both anti-SSA and anti-SSB (non-antinuclear antibodies) as seronegative pSS. Clinical manifestations and laboratory findings were compared between the two groups. Among the 232 patients with pSS, 192 (82.8%) were seropositive pSS and 40 (17.2%) were seronegative pSS. Compared to seropositive pSS, seronegative pSS were older and with higher percentage of low disease activity (ESSDAI < 5), xerostomia and xerophthalmia, with higher platelet count and level of creatine kinase. This subgroup was with lower levels of gamma globulin, immunoglobulin G, immunoglobulin A and autoantibodies including rheumatoid factor and antinuclear antibody in serum, and less immunoglobulin G deposition in labial gland. Seronegative pSS was a distinct subtype of pSS different from seropositive pSS. Clinical manifestations in seronegative pSS subgroup were restricted to exocrine gland and less B lymphocyte activation, while seropositive pSS were

prone to present with systemic involvement and high disease activity. Specific underlying pathogenesis mechanisms and therapeutic strategies in this subgroup needed to be further studied.

IDENTIFICATION OF DISTINCT SUBGROUPS OF SJÖGREN'S DISEASE BY CLUSTER ANALYSIS BASED ON CLINICAL AND BIOLOGICAL MANIFESTATIONS: DATA FROM THE CROSS-SECTIONAL PARIS-SACLAY AND THE PROSPECTIVE ASSESS COHORTS.

Yann Nguyen, Gaëtane Nocturne, Julien Henry, Wan-Fai Ng, Rakiba Belkhir, Frédéric Desmoulins, Elisabeth Bergé, Jacques Morel, Aleth Perdriger, Emmanuelle Dernis, Valérie Devauchelle-Pensec, Damien Sène, Philippe Dieudé, Marion Couderc, Anne-Laure Fauchais, Claire Larroche, Olivier Vittecoq, Carine Salliot, Eric Hachulla, Véronique Le Guern, Jacques-Eric Gottenberg, Xavier Mariette, Raphaèle Seror

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Sjögren's Disease (formerly known as Sjögren's Syndrome) is a heterogenous autoimmune disease with a wide range of symptoms-including dryness, fatigue, and pain-in addition to systemic manifestations and an increased risk of lymphoma. In this study from France, the authors aimed to identify distinct subgroups of the disease, using cluster analysis based on subjective symptoms and clinical and biological manifestations, and to compare the prognoses of patients in these subgroups. This unsupervised clustering classification based on symptoms and clinical and biological manifestations did not correlate with a previous classification based on symptoms only. On the basis of symptoms and clinical and biological manifestations, the authors identified three distinct subgroups of patients with Sjögren's disease with different prognoses. Their results suggest that these subgroups represent different heterogeneous pathophysiological disease mechanisms, stages of disease, or both. These findings could be of interest when stratifying patients in future therapeutic trials.

ASSOCIATED DISORDERS - IMMUNE DISORDERS

UNIPARENTAL DISOMY OF CHROMOSOME 4: A CASE OF WHOLE CHROMOSOME UPD PRESENTING WITH LRBA DEFICIENCY.

Ak B, Parıltay E, Gümüşburun R, Dalgıç CT, Aykut A, Durmaz A, Akın H, Ardeniz Ö, Lo B. J Clin Immunol. 2024 Sep 18;45(1):10. doi: 10.1007/s10875-024-01803-9. PMID: 39289195.

Lipopolysaccharide-responsive beige-like anchor protein (LRBA) encodes a widely expressed cytosolic protein that participates in polarized vesicle trafficking. Homozygous loss-of-function LRBA mutations can lead to immune deficiency due to the lack of immune regulation, classified as a part of Tregopathies. The authors from Turkije present a case of a 49-year-old female, with polyarthralgia in metacarpophalangeal and proximal interphalangeal joints bilaterally, and morning stiffness, leading to the diagnosis of rheumatoid arthritis treated with pulse steroid therapy. She had experienced sepsis and in-depth scrutiny revealed panhypogammaglobulinemia. After being referred to the immunology clinic, she was followed under the diagnosis of common variable immunodeficiency (CVID)-like inborn errors of immunity (IEI). Physical examination and diagnostic follow-up revealed massive splenomegaly accompanied by portal hypertension, and ulcerations in the colon. She also presented with periodic hematuria and dysuria. Cystoscopic biopsy revealed mast cell-derived interstitial cystitis which has not been previously reported in LRBA deficiency in the literature to their knowledge. A multi-gene next-generation sequencing panel performed for immune deficiencies (264 genes and 524 amplicons), resulted in the identification of an apparently homozygous LRBA mutation (p.Arg722His) in the Beige and Chediak-Higashi (BEACH) domain. The SNP array showed copy neutral absence of heterozygosity of the entire chromosome 4, which is consistent with uniparental isodisomy of chromosome 4. In conclusion, this case study underscores the critical role of LRBA in immune regulation and highlights the clinical heterogeneity associated with LRBA deficiency. The patient's presentation with severe immune dysregulation, including massive splenomegaly, portal hypertension, and the novel finding of mast cell-derived interstitial

cystitis, expands the clinical spectrum of LRBA mutations. The identification of an apparently homozygous LRBA mutation via next-generation sequencing further emphasizes the importance of genetic analysis in diagnosing monogenic defects manifested as CVID-like phenotype. This is the first reported case of LRBA deficiency due to whole chromosome UPD to their knowledge. Future research should focus on elucidating the full range of clinical manifestations and developing targeted therapies for patients with LRBA deficiency.

ASSOCIATED DISORDERS – VULVODYNIA, UROGENITAL

THE ASSOCIATION BETWEEN VULVODYNIA AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW.

Bosio S, Perossini S, Torella M, Braga A, Salvatore S, Serati M, Frigerio M, Manodoro S. Int J Gynaecol Obstet. 2024 Apr 24. doi: 10.1002/ijgo.15538. Epub ahead of print. PMID: 38655714.

Vulvodynia (VVD) is a debilitating chronic vulvar pain significantly affecting patients' quality of life. IC/BPS is a chronic and complex illness characterized by an unpleasant sensation related to the filling of the bladder and it strongly impacts patients' lives. The exact mechanisms of the two syndromes remain unknown, but there is an overlap between suspected pathophysiologies. The purpose of this study from Italy was to present an overview of the current research on the association between VVD and IC/BPS. A systematic search of three electronic databases was conducted. Studies examining the correlation between VVD and IC/BPS with male and female patients aged over 18 years were included. Studies assessing the coexistence of VVD and IC/BPS were included. Reviews, letters to the editor, conference abstracts, book chapters, guidelines, Cochrane reviews, and expert opinions were excluded. Two reviewers screened the studies for eligibility. Eligible studies were screened for quality. A total of 13 studies were included in the final review. Among them, 11 presented a positive association between the two syndromes. The studies highlighted that VVD and IC/BPS share common comorbidities and possibly etiopathogenic pathways. It was concluded that VVD and IC/BPS are both complex and multifactorial syndromes. This review highlights an association between them, but additional studies on the topic should be conducted for a more precise conclusion.

PSYCHOSEXOLOGICAL CORRELATES OF 372 WOMEN WITH VULVODYNIA, OVERACTIVE PELVIC FLOOR, POSTCOITAL CYSTITIS, AND INTERSTITIAL CYSTITIS.

Ricucci N, Colonnello E, Limoncin E, Mollaioli D, Sansone A, Jannini EA, Ciocca G. J Sex Med. 2024 Apr 30;21(5):471-478. doi: 10.1093/jsxmed/qdae029. PMID: 38515245.

Among the plethora of urogynecological conditions possibly affecting women, some of them, less explored, have significant impacts on sexological and psychological health, with a mutual influence. The aim of this study from Rome, Italy was to investigate the sexological and psychological correlates of four urogynecological pathologies in a sample of women of childbearing age: overactive pelvic floor, vulvodynia, postcoital cystitis, and interstitial cystitis. Women cured of these conditions were also included, to assess the same aspects after the remission of physical symptoms. The authors recruited 372 women with an average age of 33.5 years through an online platform shared by a popular forum for women with urogynecological pathologies between March and May 2021. The participants filled out a socio-anamnestic questionnaire and a set of psychometric tests. Participant data were collected by use of the Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, Toronto Alexithymia Scale-20, Female Sexual Function Index, and Orgasmometer-F, and the SPSS (Statistical Package for Social Sciences) v.26 was used for data analysis. Overactive pelvic floor was reported by 66.4% of the women, vulvodynia by 55%, postcoital cystitis by 58.8%, and interstitial cystitis by 8.3%, and these conditions were often comorbid with each other, with 9.4% and 7% of women reporting having suffered psychological and sexual abuse, respectively. The presence of past abuse was correlated with overactive pelvic floor ($P < .05$), vulvodynia ($P < .01$), and major depression ($P < .01$). Significantly more depression occurred in women with vulvodynia than in the other subgroups ($P < .05$), except for women with only an overactive pelvic floor. There was no difference between the subgroups in the occurrence of alexithymia, sexual function, and orgasm ($P <$

.05). Interestingly, the prevalence of sexual dysfunction increased in cured women. The lack of significant differences, except for depression, between the pathological subgroups suggests a similar clinical and psychological relevance of the four pathologies studied. The persistence of sexual dysfunctions in cured women may be related to a residual dysfunctional relational modality with the partner. The evaluation of both psychological and sexological variables in a group of less-explored urogynecological conditions represents a strength of this study, while a lack of a face-to-face assessment could represent a limitation. The results of the present study should promote psychosexological interventions in women with these diseases, both during the pathological state and after remission.

UNSUPERVISED MACHINE LEARNING REVEALS A VULVODYNIA-PREDOMINANT SUBTYPE IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Okui N. Cureus. 2024 Jun 18;16(6):e62585. doi: 10.7759/cureus.62585. PMID: 39027744; PMCID: PMC11257649.

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Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic condition characterized by pelvic pain and urinary symptoms. Despite its significant impact on patients' quality of life, the heterogeneity of BPS/IC symptoms and the presence of comorbidities such as vulvodynia may not be adequately captured by validated questionnaires. Identifying vulvodynia in BPS/IC patients is crucial for providing appropriate treatment options. This study from Japan aimed to identify subtypes of BPS/IC patients using unsupervised machine learning and to investigate the prevalence of vulvodynia in each subtype. The study identified distinct subtypes of BPS/IC patients using unsupervised machine learning, with Cluster 2 representing a vulvodynia-predominant subtype. This finding, along with the potential of targeted therapies such as non-ablative erbium YAG laser for vulvodynia, underscores the importance of assessing extravesical symptoms, particularly vulvodynia, for the diagnosis and treatment of BPS/IC. A tailored approach, including laser therapy for vulvodynia-predominant patients, may be necessary for optimal management of BPS/IC. The vulvodynia swab test plays a crucial role in assessing vulvodynia symptoms, underlining the limitations of validated questionnaires in capturing the full spectrum of BPS/IC symptoms. A comprehensive evaluation of patients, including the vulvodynia swab test, is essential for accurate subtyping and management of BPS/IC. Further research with larger sample sizes and investigation of the relationship between identified subtypes and other clinical data is warranted to advance understanding and management of BPS/IC.

THE PUDENDAL SYNDROME: A PHOTO ESSAY OF NERVE COMPRESSION DAMAGE VISUALIZED AT NEUROLYSIS IN PATIENTS WITH CHRONIC NEUROPATHIC PELVIC PAIN.

Antolak SJ Jr. Neurourol Urodyn. 2024 Jul 20. doi: 10.1002/nau.25555. Epub ahead of print. PMID: 39032061.

The aim of this study from the USA was (1) to use intraoperative photographs to visualize and explain pudendal nerve compressions and anatomical variations of compression sites in patients with chronic pelvic pain; (2) to emphasize the diagnostic importance of sensory examination with a safety pin at the six pudendal nerve branches in all patients with chronic pelvic pain; the dorsal nerves (penis or clitoris; the perineal nerves; and the inferior rectal nerves). Between 2003 and 2014, "definite" pudendal neuropathy was diagnosed by examination and with two neurophysiologic tests. Neurolysis, via a transgluteal approach, was recommended only after 14 weeks of conservative care failed to adequately improve symptoms and validated symptom scores. Photographs of surgical findings were culled for their educational impact. An illustration of each photo clarifies the surgical anatomy. The transgluteal incision permits access to pudendal anatomy and compression sites from the subpiriformis area through the interligamentary space and the pudendal canal (Alcock canal). Compressions were acquired or congenital and severity varied significantly. Pinprick sensory testing diagnoses pudendal neuropathy in 92% of both genders. Mid-nerve compression occurred

commonly between the sacrotuberous and sacrospinous ligaments less frequently in the Alcock canal, but also at aberrant pathways, for example, between layers of the sacrotuberous ligament; a separate inferior rectal nerve passing through the sacrospinous ligament; at an anomalous lateral pathway posterior to the ischial spine. The results of international surgeons are discussed. Decompression surgery was recommended in approximately 35% of patients in this practice, when pudendal neuropathy (pudendal syndrome), did not respond to two conservative levels of treatment: (1) nerve protection and medications and, (2) a series of three pudendal nerve perineural injections given at 4-week intervals. Significant nerve compression is consistently observed. Pathophysiology includes axonopathy from ischemia and demyelination. Neuropathy is readily diagnosed using a pinprick sensory examination of six pudendal nerve branches. Monitoring with the National Institutes of Health Chronic Prostatitis Symptom Index records cures >13 years.

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