

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization for interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
www.painful-bladder.org

IPBF e-Newsletter and Research Update Issue 60, October 2021

An IPBF update, including Research Highlights, for patient support groups, healthcare professionals and friends around the world in the field of interstitial cystitis, bladder pain syndrome/painful bladder syndrome, hypersensitive bladder, Hunner lesion, ketamine cystitis, chronic pelvic pain and associated disorders.

This issue of the IPBF e-Newsletter includes the following topics:

- AUA 2021 IC/BPS Educational Course
- ICS Podcast Platform
- Pelvic Health Support Canada
- Overview of upcoming events
- New books/publications
- COVID-19: Information About COVID-19 And Useful Online Resources
- RESEARCH UPDATE
- Donations & Sponsoring

AMERICAN UROLOGICAL ASSOCIATION (AUA) 2021 VIRTUAL ANNUAL MEETING: IC/BPS EDUCATIONAL COURSE

With COVID-19 continuing to impact everyone and everything around the world, the AUA21 annual meeting was once again a virtual meeting 10-13 September, see <https://www.aua2021.org/>. However, live webinar educational courses were held in advance from June – August as part of the AUA Summer School and thereafter available on demand. These included the excellent and comprehensive educational course on IC/BPS presented by Dr Philip Hanno and Dr Quentin Clemens:

Interstitial Cystitis/Bladder Pain Syndrome: Current Diagnosis and Management -- Future Trends.

This first part of the course looked at etiology, confusable disorders, associated disorders, and treatment algorithm. A look at historic developments and old versus new guidelines clarified how many misunderstandings have occurred on the way.

Professor Hanno emphasized that today a flexible office cystoscopy performed at an early stage is **essential** to rule out (or confirm) Hunner lesion and also to identify bladder cancer, stones and urethral diverticulum. If lesions are found, the unique Hunner lesion treatment algorithm should be followed for these patients.

It is not only important to diagnose patients with IC/BPS, but just as important to avoid mistakenly diagnosing those with confusable disorders as having IC/BPS, he noted.

Differentiating between IC/BPS and overactive bladder (OAB) turns out to be not so easy as originally thought and is complicated by the fact that a subset of OAB patients appear to have pain in and/or outside the pelvis.

A key history question here is: how would you feel if there were no toilet available? IC/BPS patients would feel intolerable pain or discomfort (sensory urgency) while OAB patients would be afraid of leaking (urge incontinence).

An aspect which should not be forgotten is that of associated disorders and chronic overlapping pain conditions, some of which can be both a confusable and associated disorder such as endometriosis and pelvic floor disorders.

Professor Hanno also spoke about the different approaches to treatment in Europe (and other parts of the world) where GAG-replenishment instillations are more commonly used than in the USA.

Phenotyping is considered to be the key to the future and improving treatment outcomes per individual patient. More research is needed in this field since at present Hunner lesion is the only proven subtype. The question now is: is Hunner lesion a subtype or a distinct, separate disease as is increasingly believed around the world. It was stressed that patients with and without Hunner lesion should not be combined in clinical studies.

Professor J. Quentin Clemens, MAPP Research Network Chair, then gave the second part of the course on how the MAPP Network is helping us to understand urologic chronic pelvic pain syndrome, presenting the latest research findings from the MAPP which caps a 35 year research effort by the National Institutes of Health (NIH). For those who get a little confused by the different terminology, it might be useful to note the following definitions used by the MAPP:

- **Interstitial Cystitis/Bladder Pain Syndrome:**
 - chronic bladder pain/pressure/discomfort
 - in men or women
- **Chronic Prostatitis/Chronic Pelvic Pain Syndrome**
 - chronic pelvic pain in men (perineum, ejaculation)
- **Urologic Chronic Pelvic Pain Syndrome**
 - either/both of the above.

Research suggests two phenotypes: pain-predominant and urinary-predominant. Professor Clemens noted that we should consider abandoning composite symptom scores for clinical and research use.

The clinical “pearls” he tentatively suggested on the basis of the MAPP were:

Early cystoscopy to identify lesions, standard symptoms assessment (pain symptoms, urinary symptoms), body map (screen for other pain conditions, systemic therapies), standardized pelvic examination to qualify pelvic floor muscle tenderness (treat with physiotherapy).

He ended on a positive note by expressing the hope that we will soon be able to stratify patients into clinically meaningful subgroups that will yield:

- Better designed clinical trials
- More consistent management strategies
- Improved patient outcomes.

For further information, go to www.mappnetwork.org

INTERNATIONAL CONTINENCE SOCIETY (ICS) PODCAST PLATFORM

The International Continence Society (www.ics.org) has launched a new educational platform: the ICS Podcast. These podcasts, free to all, are made available to enhance the listeners understanding of various topics related to continence and pelvic floor disorders. The hosts bring you the most up to date evidence-based content on a variety of subjects. The ICS aims to release more podcasts every two weeks. They are available at www.ics.org/podcast or via your favourite podcast app.

PELVIC HEALTH SUPPORT (PHS) CANADA

PHS Canada is a newly launched digital resource support group that aims to raise awareness, educate and support those living with pelvic health conditions including interstitial cystitis/bladder pain syndrome. Founder & President of PHS Canada is Marnie Glavin who writes “It is my greatest hope that your experience with PHS Canada will provide you with the tools you need to become more informed, supported and able to find the help you need”.

We wish them every success!

<https://www.pelvichealthsupport.ca/>

OVERVIEW OF UPCOMING EVENTS:

INTERNATIONAL CONTINENCE SOCIETY (ICS)

14-17 October 2021. Virtual annual meeting.

<https://www.ics.org/2021>

5th WORLD CONGRESS ON ABDOMINAL & PELVIC PAIN AND 7th ANNUAL CONGRESS OF CONVERGENCES PP

10-13 November 2021, Lyons, France. This is a face-to-face meeting. Includes a Round table with ESSIC on Bladder Pain Syndrome (Session 10) with speakers M. Cervigni, S. Arlandis, C. Saussine, JJ. Wyndaele on 13 November, 11.00-12.00.

<http://www.convergencespp.com/medias/files/convergences-pp2021.pdf>

INTERNATIONAL ALLIANCE OF PATIENTS’ ORGANIZATIONS (IAPO)

3RD ASIA PACIFIC PATIENTS CONGRESS (APPC 2021)

16-17 November 2021. This is a virtual event, so no travelling required!

See programme: <https://apacpatientcongress.org/APPC/programme/>

SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE AND UROGENITAL RECONSTRUCTION (SUFU)

SUFU22 WINTER MEETING

22-26 February 2022, Marriott Marquis San Diego Marina,
San Diego, CA, USA
<https://sufuorg.com/meetings/upcoming-sufu/meeting-information.aspx>

37TH ANNUAL EAU CONGRESS (EAU22)

18-21 March 2022, Amsterdam, The Netherlands
<https://eaucongress.uroweb.org/>

12TH CONGRESS OF THE EUROPEAN PAIN FEDERATION (EFIC)

27-30 April 2022, Dublin, Ireland.
<https://efic-congress.org/>

AMERICAN UROLOGICAL ASSOCIATION (AUA22)

13-16 May 2022
New Orleans Ernest N. Morial Convention Center
900 Convention Center Boulevard, New Orleans, LA 70130, USA
<https://www.auanet.org/annualmeeting>

EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY – EULAR22

1-4 June 2022, Copenhagen, Denmark. A hybrid conference.
<https://congress.eular.org/>

INTERNATIONAL CONTINENCE SOCIETY (ICS) ANNUAL MEETING 2022

7-10 September 2022, Vienna, Austria.
<https://www.ics.org/2022>

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (IASP)

WORLD CONGRESS ON PAIN
19-23 September 2022, Metro Toronto Convention Centre, Toronto, Canada.
<https://iaspworldcongress2022.org/>

NEW BOOKS/PUBLICATIONS

FIBROMYALGIA SYNDROME

Editors: Jacob N. Ablin, Yehuda Shoenfeld
Publisher: Springer, Cham, 2021
Hardcover ISBN978-3-030-78637-3, Softcover ISBN978-3-030-78640-3, eBook ISBN978-3-030-78638-0
<https://link.springer.com/book/10.1007%2F978-3-030-78638-0>

Covers the assessment of disabilities associated with fibromyalgia. Integrates concepts relevant to pathogenesis, epidemiology and treatment of the disorder. Addresses common misconceptions surrounding the mechanisms of fibromyalgia. Provides detailed guidance on the application of the latest pharmacological treatment options

StatPearls [Internet]: Review: AMITRIPTYLINE

Amit Thour, Raman Marwaha. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2021 Jul 29. PMID: 30725910 Bookshelf ID: NBK537225. Free Books & Documents
<https://www.ncbi.nlm.nih.gov/books/NBK537225/>

StatPearls provides a useful and very extensive review of all aspect of amitriptyline online. See extract below.
Extract: Amitriptyline is FDA approved medication to treat depression in adults. The Non-FDA approved indications are anxiety, post-traumatic stress disorder, insomnia, chronic pain (diabetic neuropathy, fibromyalgia), irritable bowel syndrome, interstitial cystitis (bladder pain syndrome), migraine prophylaxis, postherpetic neuralgia, and sialorrhea. This activity reviews the indications, contraindications, activity, adverse events, and other key elements of amitriptyline in the clinical setting related to the essential points needed by members of an interprofessional team managing the care of patients that can benefit from amitriptyline therapy.

ALONG THE HEALING PATH – Recovering from interstitial cystitis

20th Anniversary Edition

Author: Catherine M. Simone
Publisher: IC Hope, Ltd, Cleveland, Ohio
<https://www.ic-hope.com/>

A holistic patient perspective to help patients determine their individual situation, offering ideas to help them along the healing path.

COVID-19: INFORMATION ABOUT COVID-19 AND USEFUL ONLINE RESOURCES

- The International Alliance of Patients' Organizations (IAPO) has put together a very extensive COVID-19 resources hub at <https://www.iapo.org.uk/covid-19-resources-hub> which patients and their support groups around the world may find useful.
- Harvard Medical School: <https://www.health.harvard.edu/diseases-and-conditions/covid-19-basics>
- National Institutes of Health (NIH):
 - <https://www.coronavirus.gov/>
 - <https://covid19.nih.gov/>
 - <https://combatcovid.hhs.gov/>
- United Kingdom National Health Service (NHS):
<https://www.nhs.uk/conditions/coronavirus-covid-19/>
- WHO Coronavirus disease (COVID-19) <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
- CDC (Centers for Disease Control and Prevention): Things to Know about the COVID-19 Pandemic.
<https://www.cdc.gov/coronavirus/2019-ncov/your-health/need-to-know.html>
- CDC (Centers for Disease Control and Prevention), USA: symptoms of coronavirus
<https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>
- CDC (Centers for Disease Control and Prevention), USA: risk of reinfection
<https://www.cdc.gov/coronavirus/2019-ncov/your-health/reinfection.html>
- European Medicines Agency (EMA) <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19#what's-new-section>
<https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19>
- For speakers of Dutch, Dr Joop P. van de Merwe in the Netherlands is continually updating a very interesting and highly informative, well-documented overview of all aspects of COVID-19 (in Dutch). The introductory page with a link to the overview can be found at:
<https://www.jpvandemerwe.nl/corona>
- The US Sjogren's Foundation had an interesting news article in August on issues surrounding a 3rd vaccination dose: <https://www.sjogrens.org/news/2021/sjogrens-foundation-covid-19-vaccination-committee-issues-recommendation-on-3rd-dose-for>

RESEARCH UPDATE

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

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

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

NIH MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) RESEARCH NETWORK

(For more information about the MAPP Research Network, [click here](#))

IMI-PAINCARE RESEARCH CONSORTIUM

(For more information about IMI-PainCare, [click here](#))

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: BASIC SCIENCE, DIAGNOSIS AND TREATMENT**CURRENT UNDERSTANDING AND FUTURE PERSPECTIVES OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME**

Tomohiro Ueda, Philip M Hanno, Ryoichi Saito, Jane M Meijlink, Naoki Yoshimura. *Int Neurourol J.* 2021 Jun;25(2):99-110. doi: 10.5213/inj.2142084.042. Epub 2021 Jun 30. PMID: 34218637 PMCID: PMC8255826 DOI: 10.5213/inj.2142084.042

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disease characterized by suprapubic pain and lower urinary tract symptoms. Perhaps because of the heterogeneous nature of this disease and its multifactorial etiology, clinical trials in allinclusive populations of IC/BPS patients without phenotyping in the last decade have mainly failed to discover new therapeutic modalities of IC/BPS. Thus, phenotyping IC/BPS, aimed at identifying bladder-centric and/or bladder-beyond pathologies, including cystoscopic observation of Hunner or non-Hunner lesions of the bladder mucosa, is particularly important for the future of IC/BPS management. Based on recent discussions at international conferences, including the International Consultation on IC, Japan, it has been proposed that Hunner-lesion IC should be separated from other non-Hunner IC/BPS because of its distinct inflammatory profiles and epithelial denudation compared with non-Hunner IC/BPS. However, there are still no standard criteria for the diagnosis of Hunner lesions other than typical lesions, while conventional cystoscopic observations may miss atypical or small Hunner lesions. Furthermore, diagnosis of the bladder-centric phenotype of IC/BPS requires confirmation that identified mucosal lesions are truly a cause of bladder pain in IC/BPS patients. This review article discusses the current status of IC/BPS pathophysiology and diagnosis, as well as future directions of the proper diagnosis of bladder-centric IC/BPS, in which pathophysiological mechanisms other than those in inflammatory pathways, such as angiogenic and immunogenic abnormalities, could also be involved in both Hunner-lesion IC and non-Hunner IC/BPS. It is hoped that this new paradigm in the pathophysiological evaluation and diagnosis of IC/BPS could lead to pathology-based phenotyping and new treatments for this heterogeneous disease.

IDENTIFICATION OF KEY GENES IN HUMAN UROTHELIAL CELLS CORRESPONDING TO INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN A LIPOPOLYSACCHARIDE-INDUCED CYSTITIS MODEL

Liao Peng, Bo-Ya Li, Wei Wang, Xiao-Shuai Gao, Xiao Zeng, De-Yi Luo. *Neurourol Urodyn.* 2021 Jul 10. doi: 10.1002/nau.24743. Online ahead of print. PMID: 34245600 DOI: 10.1002/nau.24743

The cellular functions of bladder urothelial cells in interstitial cystitis/bladder pain syndrome (IC/BPS) have not been well revealed and understood. This study from Sichuan, China aims to identify key genes and significant pathways in urothelium corresponding to IC/BPS in a lipopolysaccharide (LPS)-induced cystitis model and provide novel clues related to diagnosis and treatment of IC/BPS. Human urothelial cells (HUCs) were incubated with LPS (50 µg/ml for 24 h). Microarray was applied to analyze the differentially expressed genes (DEGs) between HUCs under LPS treatment and the control group. DEGs in the two groups were identified and then used for enrichment analysis. Subsequently, protein-protein interaction (PPI) network based on DEGs was constructed. Lastly, the top five key genes were identified through the Cytoscape (version 3.7.2) using the "Clustering Coefficient" algorithm. One hundred and seventy-one DEGs (96 upregulated genes and 75 downregulated genes) were identified between the LPS treatment and control group. The established PPI network was composed of 169 nodes and 678 edges. Moreover, C19orf33, TRIM31, MUC21, ELF3, and IFI27 were identified as hub genes in the PPI network. Subsequently, a statistically increased expression level of TRIM31 and ELF3 was validated by real-time quantitative-polymerase chain reaction and immunohistochemistry in bladder tissues from 20 patients with IC/BPS. TRIM31 and ELF3 may be the two hub genes in urothelium corresponding to IC/BPS. More studies are warranted to further validate the findings. The identified marker genes may be useful targets for further studies to develop diagnostic tools and more effective therapies for a broader group of women with IC/BPS.

P2X7 RECEPTOR BLOCKADE PROTECTS AGAINST ACROLEIN-INDUCED BLADDER DAMAGE: A POTENTIAL NEW THERAPEUTIC APPROACH FOR THE TREATMENT OF BLADDER INFLAMMATORY DISEASES

Zhinoos Taidi, Tommy Zhou, Kate H Moore, Kylie J Mansfield, Lu Liu. *Front Pharmacol.* 2021 Aug 12;12:682520. doi: 10.3389/fphar.2021.682520. eCollection 2021. PMID: 34456718 PMCID: PMC8397461 DOI: 10.3389/fphar.2021.682520

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Inflammatory conditions of the urinary bladder have been shown to be associated with urothelial damage and loss of function. The purinergic P2X7 receptor has been implicated in several inflammatory conditions. The aim of this study from Australia was to investigate the role of the P2X7 receptor in acrolein-induced inflammatory damage using the porcine urinary bladder. For this purpose, an ex-vivo model of porcine urothelial damage induced by direct instillation of acrolein into the whole bladder lumen was used. To determine the role of the P2X7 receptor, the bladders were pre-incubated with a selective P2X7 receptor antagonist, A804598 (10 µM), for 1 h. The effects of the acrolein-induced urothelial damage on the bladder's function were assessed by examining the bladder wall contractile response, structure changes, apoptosis, and oxidative stress in the bladder tissues. The acrolein treatment led to significant damage to the urothelium histology, tight junction expression, and contractile responses. Acrolein also induced apoptosis in the mucosa layer. All these acrolein-induced responses were attenuated by pre-treatment with the P2X7 receptor antagonist A804598. Acrolein also significantly induced DNA oxidation in the submucosal layer; however, the P2X7 receptor antagonism did not show any protective effect towards the acrolein-induced oxidative stress. These findings suggested that the P2X7 receptor is involved in the acrolein-induced damage to the urothelium; therefore, the P2X7 receptor antagonists may be a new therapeutic option for the treatment of bladder inflammation.

[DIFFERENCE IN ELECTRON MICROSCOPIC FINDINGS AMONG INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH DISTINCT CLINICAL AND CYSTOSCOPIC CHARACTERISTICS](#)

Yu Khun Lee, Jia-Fong Jhang, Yuan-Hong Jiang, Yung-Hsiang Hsu, Han-Chen Ho, Hann-Chorng Kuo. Sci Rep. 2021 Aug 26;11(1):17258. doi: 10.1038/s41598-021-96810-w. PMID: 34446784 PMCID: PMC8390653 DOI: 10.1038/s41598-021-96810-w

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Urothelial dysfunction may be a key pathomechanism underlying interstitial cystitis/bladder pain syndrome (IC/BPS). In this study from Taiwan, the authors therefore examined if clinical severity is associated with the extent of urothelial damage as revealed by electron microscopic (EM) analysis of biopsy tissue. One hundred IC/BPS patients were enrolled and 24 patients with stress urinary incontinence served as controls. Clinical symptoms were evaluated by visual analog scale pain score and O'Leary-Sant Symptom score. Bladder biopsies were obtained following cystoscopic hydrodistention. The presence of Hunner's lesions and glomerulation grade after hydrodistention were recorded and patients classified as Hunner-type IC (HIC) or non-Hunner-type IC (NHIC). HIC patients exhibited more severe defects in urothelium cell layers, including greater loss of umbrella cells, umbrella cell surface uroplakin plaque, and tight junctions between adjacent umbrella cells, compared to control and NHIC groups. Both NHIC and HIC groups demonstrated more severe lamina propria inflammatory cell infiltration than controls. O'Leary-Sant Symptom scores were significantly higher among patients with more severe urothelial defects. Thus, urothelium cell layer defects on EM are associated with greater clinical symptom severity.

[A SYSTEMATIC REVIEW OF THERAPEUTIC APPROACHES USED IN EXPERIMENTAL MODELS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Tadeja Kuret, Dominika Peskar, Andreja Erman, Peter Veranič. Biomedicines. 2021 Jul 22;9(8):865. doi: 10.3390/biomedicines9080865. PMID: 34440069 PMCID: PMC8389661 DOI: 10.3390/biomedicines9080865

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a multifactorial, chronic bladder disorder with limited therapeutic options currently available. The present review from Slovenia provides an extensive overview of therapeutic approaches used in in vitro, ex vivo, and in vivo experimental models of IC/BPS. Publications were identified by electronic search of three online databases. Data were extracted for study design, type of treatment, main findings, and outcome, as well as for methodological quality and the reporting of measures to avoid bias. A total of 100 full-text articles were included. The majority of identified articles evaluated therapeutic agents currently recommended to treat IC/BPS by the American Urological Association guidelines (21%) and therapeutic agents currently approved to treat other diseases (11%). More recently published articles assessed therapeutic approaches using stem cells (11%) and plant-derived agents (10%), while novel potential drug targets identified were proteinase-activated (6%) and purinergic (4%) receptors, transient receptor potential channels (3%), microRNAs (2%), and activation of the cannabinoid system (7%). Their results show that the reported methodological quality of animal studies could be substantially improved, and measures to avoid bias should be more consistently reported in order to increase the value of preclinical research in IC/BPS for potential translation to a clinical setting.

[CYSTOSCOPIC FINDINGS IN WOMEN WITH MINIMAL AND MAXIMAL LOWER URINARY TRACT SYMPTOMS](#)

Ioana Marcu, Jeffrey A Gavard, Golnar Vazirabadi, Joe Y Shi, Andrew C Steele, Fah Che Leong, Mary T McLennan, Jennifer A Bickhaus, Mary B Holloran-Schwartz, Patrick Yeung Jr, Eugen C Campian. *Transl Androl Urol.* 2021 Jul;10(7):2910-2920. doi: 10.21037/tau-21-195. PMID: 34430393 PMCID: PMC8350252 DOI: 10.21037/tau-21-195

Free full article

Glomerulations are not specific for interstitial cystitis/bladder pain syndrome (IC/BPS). Controversy exists about whether cystoscopic findings differ between patients with and without lower urinary tract symptoms. Marcu and colleagues from the USA sought to compare the prevalence of cystoscopic findings in women with "no or minimal" urinary symptoms to those with a "high" symptom burden. This is a secondary analysis of a prospective cohort study performed at a University Educational Facility. Participants in this study were part of a larger prospective study, in which female patients scheduled to undergo routine gynecologic procedures were all consented for cystoscopy with hydrodistension (CWHHD). The authors defined the "minimally symptomatic group" as those with ≤ 1 on each of the O'Leary/Sant Interstitial Cystitis Symptom Index (ICSI) subscores and without history of IC/BPS. The "highly symptomatic" cohort of women had composite ICSI score ≥ 12 and a Burning/Pain subscore of 4 or 5. All were non-smokers. A total of 84 women underwent CWHHD, with 33 having minimal symptoms and 51 being highly symptomatic. The two groups were not statistically different when assessing for 'any glomerulations' compared to 'no glomerulations.' However, minimally symptomatic women had an eight-fold lower prevalence of significant glomerulations than highly symptomatic women. Extensive glomerulations (≥ 10 in 3 or 4 quadrants) are rare in women with minimal urinary symptoms. These findings contrast with prior limited prospective data which quoted similar incidence of glomerulations in IC/BPS patients and asymptomatic patients. This study highlights the importance of evaluating objective evidence on CWHHD and merits further investigation as part of the ongoing conversation regarding the definition of bladder health and pathology.

[PILOT RANDOMIZED CONTROLLED TRIAL OF A HYPNOSIS INTERVENTION FOR WOMEN WITH BLADDER PAIN SYNDROME](#)

Alex J Soriano, Julie B Schnur, Heidi S Harvie, Diane K Newman, Guy H Montgomery, Lily A Arya. *Neurourol Urodyn.* 2021 Aug 22. doi: 10.1002/nau.24771. Online ahead of print. PMID: 34420228 DOI: 10.1002/nau.24771

The purpose of this study was to evaluate the feasibility and acceptability of a randomized controlled trial of a hypnosis intervention for the treatment of bladder pain syndrome/interstitial cystitis (BPS/IC) in women. The authors conducted a parallel arm, non-blinded, pilot randomized controlled trial of standardized hypnosis sessions including a hypnosis web tool versus usual care in adult women with BPS/IC. Pilot study outcomes included feasibility domains: process, resources and management, safety, and acceptability. Clinical outcomes of lower urinary tract symptoms and quality of life were measured using validated questionnaires at baseline and at the end of the 4-week intervention. They randomized 29 out of 30 (96.7%) eligible women. In the hypnosis group, 12 of 15 (80.0%) subjects completed the 4-week intervention and follow up, and 13 of 14 (92.9%) in the usual care group. In the hypnosis group, adherence to the standardized sessions was 80% and participants used the web-based tool for an average of 5.6 ± 2.7 times per week. Scores for emotional distress, relaxation, pain severity and expected bladder symptoms significantly improved during the first two of three planned hypnosis sessions. Improvement in quality of life scores was greater in the hypnosis group than the usual care group. There were no significant between-group differences in urinary symptoms or bladder pain. No adverse events were reported. A hypnosis intervention for the treatment of bladder pain syndrome/interstitial cystitis is feasible, acceptable, safe, and may improve quality of life.

[PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS AND HIGH TONE PELVIC FLOOR DYSFUNCTION](#)

Catherine Chandler Moody, Tola B Fashokun. *Obstet Gynecol Clin North Am.* 2021 Sep;48(3):585-597. doi: 10.1016/j.ogc.2021.05.010. PMID: 34416939 DOI: 10.1016/j.ogc.2021.05.010

This article provides an overview of 2 conditions that defy straightforward characterization and treatment: interstitial cystitis/painful bladder syndrome often coexists with high tone pelvic floor dysfunction. These conditions are common in gynecologic patients who present with chronic pelvic pain and are often misdiagnosed due to their syndromic nature and amorphous definitions. Clinicians should maintain a high level of suspicion for these processes in patients with chronic pelvic pain or recurrent urinary tract infection symptoms. Optimal treatment uses a multimodal approach to alleviate symptoms.

[DIFFERENTIAL EXPRESSION OF MICRORNAS CORRELATES WITH THE SEVERITY OF EXPERIMENTAL AUTOIMMUNE CYSTITIS](#)

Vijay Kumar, Sonia Kiran, Haidar A Shamran, Udai P Singh. *Front Immunol.* 2021 Jul 14;12:716564. doi: 10.3389/fimmu.2021.716564. eCollection 2021. PMID: 34335632 PMCID: PMC8317613 DOI: 10.3389/fimmu.2021.716564

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Interstitial cystitis (IC)/bladder pain syndrome (BPS) primarily affects women. It varies in its severity and currently has no effective treatment. The symptoms of IC include pelvic pain, urgency and frequency of urination, and discomfort or pain in the bladder and lower abdomen. The bladders of IC patients exhibit infiltration by immune cells, which lends credence to the hypothesis that immune mechanisms also play a role in the etiology and pathophysiology of IC. The Differentially expressed microRNAs (miRs) in immune cells may serve as crucial immunoregulators in the IC. Therefore, the authors sought to determine whether miRs might play a regulatory role in the progression and pathogenesis of IC, using experimental autoimmune cystitis (EAC) model. The authors hypothesize that the mechanism of EAC induction might involve the modulation of specific miRs that increase local and systemic levels of chemokines and cytokines. This study identifies novel miRs expressed in UB and ILNs that will make it possible to highlight mechanisms of EAC pathogenesis and may provide potential biomarkers and/or serve as the basis of new therapies for the treatment of IC.

[SAFETY, TOLERABILITY, AND EFFICACY OF LIRIS 400 MG IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH OR WITHOUT HUNNER LESIONS](#)

Robert Evans, Alfred Kohan, Robert Moldwin, Daniel Radecki, Till Geib, Kenneth M Peters. *Neurourol Urodyn.* 2021 Sep;40(7):1730-1739. doi: 10.1002/nau.24702. Epub 2021 Jul 20. PMID: 34288094 DOI: 10.1002/nau.24702

Two phase 2 studies were conducted to assess the efficacy and safety of lidocaine-releasing intravesical system (LiRIS) in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) with or without. Both were multicenter, randomized, double-blind, placebo-controlled, and enrolled women aged ≥ 18 years. In Study 001, patients were randomized 2:1:1 to LiRIS 400 mg/LiRIS 400 mg, placebo/LiRIS 400 mg, or placebo/placebo for a continuous 28 (2×14)-day period. In Study 002, patients were randomized 1:1 to LiRIS 400 mg or placebo for a continuous (single treatment) 14-day period. In total, 59 and 131 patients received treatment in Studies 001 and 002, respectively. There was no statistically significant difference in the primary endpoint, the change from baseline to Week 4 of follow-up post-removal in mean daily average bladder numeric rating scale (NRS) pain score in either study. There was no statistically significant difference between groups in daily worst NRS pain score, number of micturitions/day or urgency episodes/day. There was no clear trend for reduction in number of HL for LiRIS vs placebo. The frequency of treatment-emergent adverse events was similar between treatment groups in both studies; most were mild or moderate intensity. These studies did not demonstrate a treatment effect of LiRIS 400 mg compared with placebo, either in patients with IC/BPS with HL, or in those without HL.

[INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME TREATMENT: A SYSTEMATIC REVIEW OF SEXUAL HEALTH OUTCOMES](#)

Andrew Chen, Robert H Shahiyan, Jennifer T Anger. *Review Sex Med Rev.* 2021 Jul 1;S2050-0521(21)00008-1. doi: 10.1016/j.sxmr.2020.12.005. Online ahead of print. PMID: 34219009 DOI: 10.1016/j.sxmr.2020.12.005

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition with highly prevalent negative consequences on sexual health and quality of life. However, there is a lack of consensus regarding treatment options that improve sexual function in this population. This study from the USA aims to review the current literature on sexual health outcomes in patients treated for IC/BPS. The authors conducted a systematic review of the literature on sexual health outcomes after treatment of IC/BPS. PubMed, MEDLINE, EMBASE, CINHALL, and Google Scholar were queried, and results were screened using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Inclusion criteria for this review were: IC/BPS was clearly defined in the cohort, sexual health outcomes were measured as the primary or a secondary outcome, manuscript was written in English from January 2000 to April 2020. Studies on cystectomy were excluded as radical surgery is a confounding factor for sexual dysfunction. They identified 1611 items with their search algorithm and determined that 10 studies ultimately met inclusion criteria. 4 of 10 studies reported improved sexual function after treatment. 4 of 10 studies were randomized control trials and reported no improvement in sexual function in each of the therapies that were investigated. Data were conflicting regarding the effect of intravesical hyaluronic acid. According to the authors, this systematic review demonstrates the lack of focus on sexual health outcomes in studies of the IC/BPS. There was no strong evidence that any modality used to treat IC/BPS also improves sexual function despite the higher prevalence in this population.

[ANESTHETIC BLADDER CAPACITY IS A CLINICAL BIOMARKER FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SUBTYPES](#)

Andre Plair, Robert J Evans, Carl D Langefeld, Catherine A Matthews, Gopal Badlani, Stephen J Walker. Urology. 2021 Jul 22;S0090-4295(21)00682-8. doi: 10.1016/j.urology.2021.07.009. Online ahead of print. PMID: 34303757 DOI: 10.1016/j.urology.2021.07.009

The purpose of this study from the USA was to further examine anesthetic bladder capacity as a biomarker for interstitial cystitis/bladder pain syndrome (IC/BPS) patient subtypes, evaluating demographic and clinical characteristics in a large and heterogeneous female patient cohort. This is a retrospective review of data from 257 women diagnosed with IC/BPS who were undergoing therapeutic bladder hydrodistention (HOD). Assessments included medical history and physical examination, validated questionnaire scores, and anesthetic BC. Linear regression analyses were computed to model the relationship between anesthetic BC and patient demographic data, symptoms, and diagnoses. Variables exhibiting suggestive correlations were candidates for a multiple linear regression analysis and were retained if significant. Multiple regression analysis identified a positive correlation between BC and endometriosis as well as negative correlations between BC and both ICSI score and the presence of Hunner's lesions. There were higher average numbers of pelvic pain syndrome (PPS) diagnoses and neurologic, autoimmune, or systemic pain (NASP) diagnoses in IC/BPS patients with a non-low BC, but no statistical difference in the duration of diagnosis between patients with low and non-low BC. These data, generated from a large IC/BPS patient cohort, provide additional evidence that higher BC correlates with higher numbers of non-bladder-centric syndromes while lower BC correlates more closely with bladder-specific pathology. Taken together, the results support the concept of clinical subgroups in IC/BPS.

[LOW ENERGY SHOCK WAVE THERAPY ATTENUATES MITOCHONDRIAL DYSFUNCTION AND IMPROVES BLADDER FUNCTION IN HCL INDUCED CYSTITIS IN RATS](#)

Hung-Jen Wang, Pradeep Tyagi, Tsu-Kung Lin, Chao-Cheng Huang, Wei-Chia Lee, Michael B Chancellor, Yao-Chi Chuang. Biomed J. 2021 Jul 2;S2319-4170(21)00072-X. doi: 10.1016/j.bj.2021.06.006. Online ahead of print. PMID: 34224911 DOI: 10.1016/j.bj.2021.06.006

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The authors examined the effects of low energy shock wave (LESW) on bladder and mitochondrial function in a rat model of HCl induced cystitis, and the influence of dynamic bladder filling volume on LESW responses. Dysregulation of mitochondria function may impact the urothelial barrier and contribute to bladder dysfunction in patients with Interstitial cystitis/bladder pain syndrome (IC/BPS). Female Sprague-Dawley rats underwent urethral catheterization and intravesical instillation of 0.2 ml of 0.4N HCl or 0.2 ml saline kept for 90 s. After HCl instillation, the bladder received LESW treatment while filled with 0 ml, 0.2 ml or 0.4 ml saline or no LESW treatment. Continuous cystometry (CMG) was performed on day 8. The bladder was harvested after CMG for histology and Western blotting. HCl provoked bladder overactivity, bladder wall inflammation marked by infiltration of mast cells, increased bax/bcl2 ratio consistent with increased TUNEL staining and increased release of mitochondrial-integrity markers (cleaved caspase 3 and Cytochrome c). LESW treatment suppressed HCl provoked bladder overactivity in association with lower inflammatory reaction, mast cells infiltration, and a lower bax/bcl2 ratio also reflected by reduced TUNEL staining and mitochondrial-integrity markers irrespective of the volume of saline in bladder at the time of LESW. These findings support that the anti-inflammatory effect of LESW in chemical cystitis is associated with the reversal of the molecular-cellular perturbations in mitochondrial dependent intrinsic apoptotic pathway.

[THE RELATIONSHIP BETWEEN ILLNESS PERCEPTION AND WORSENING OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME SYMPTOMS: A CROSS-SECTIONAL STUDY](#)

Kamaluddeen Garba, Miriam Avery, Muhammadbukhoree Yusuh, Omar Abdelwahab, Scott Harris, Brian R Birch, Bashir A Lwaleed. Neurourol Urodyn. 2021 Sep 9. doi: 10.1002/nau.24787. Online ahead of print. PMID: 34498775 DOI: 10.1002/nau.24787

This study from Southampton UK evaluated disease perception in a cohort of patients with interstitial cystitis/painful bladder syndrome (IC/PBS) using the Brief Illness Perception-Questionnaire (BIP-Q) and to evaluate how this might relate to disease severity. The study is a cross-sectional survey amongst members of Bladder Health UK who had previously received a clinical diagnosis of IC/PBS. A hyperlink containing the questionnaire was sent to the patient group's website and interested members accessed and completed the survey. Participants' inclusion was based on a prior clinical diagnosis of IC/PBS, current O'Leary Sant scores supportive of the diagnosis, and age between 18 and 80. A sample size of 171 was used in the study. The Brief Illness Perception Questionnaire (BIP-Q) and the O'Leary/Sant symptoms and problem indices questionnaire were used to collect data. A multivariable logistic regression analysis was used to test the relationship between

items of BIP-Q and severity of IC/PBS. Content analysis was used for the causal domain and subsequently analysed as percentages. 601 members accessed the questionnaire of whom 159 returned completed questionnaires. 122 of 159 ($\geq 75\%$) respondents believe that their illness will continue indefinitely. The majority of the respondents indicated that IC/PBS had a negative impact on their daily lives, caused them worry and made them emotionally unstable. Of the 8 BIP-Q items, those most predictive of disease severity were (adjusted odd ratio and confidence intervals): consequence 0.094 (0.023-0.386); treatment control 2.702 (1.256-5.812); identity 0.141 (0.033-0.600); concern 9.363 (1.521-57.632). The authors believe that their findings show that IC/PBS negatively impacts the participants' quality of life and emotional well-being. Higher expectation for treatment benefit and increasing levels of patient concern are predictive for severity of IC/PBS.

SYNERGY OF HYDEAL-D® AND HYALURONIC ACID FOR PROTECTING AND RESTORING UROTHELIUM: IN VITRO CHARACTERIZATION

Marco Ruggeri, Mauro Pavan, Matteo Soato, Susi Panfilo, Carlo Barbera, Devis Galesso, Dalila Miele, Silvia Rossi, Alba Di Lucia, Franca Ferrari, Giuseppina Sandri. Pharmaceutics. 2021 Sep 11;13(9):1450. doi: 10.3390/pharmaceutics13091450. PMID: 34575526 DOI: 10.3390/pharmaceutics13091450

Interstitial cystitis (IC) or painful bladder syndrome is a chronic dysfunction due to an inflammatory condition, characterized by bladder pain and urinary frequency. Currently, no gold standard therapy is available since IC does not respond to conventional ones. Given these premises, the aim of this work was the in vitro characterization of biological properties (mucoadhesion and anti-inflammatory activity) of a commercial product (HydealCyst-HydC) based on hyaluronic acid (HA) and the benzyl ester of HA (Hydeal-D®) intended for bladder instillation to restore and/or protect the urothelial layer of glycosamino glycans (GAGs). The in vitro characterization demonstrated that an interaction product is formed between HA and Hydeal-D® that has a role in the rheological behavior and mucoadhesive properties. HA was identified as a key component to form the mucoadhesive joint, while the interaction of HA with Hydeal-D® improved polysaccharide stability and prolonged the activity ex vivo. Moreover, HydC is cytocompatible with urothelial cells (HTB-4) and possesses an anti-inflammatory effect towards these cells by decreasing the secretion of IL-6 and IL-8, which were both increased in patients with IC, and by increasing the secretion of sulfated GAGs. These two findings, along with the resilience properties of the formulation due to mucoadhesion, suggest the active role of HydC in protecting and restoring urothelium homeostasis.

THE DIAGNOSTIC AND THERAPEUTIC EFFICACY OF CYSTOSCOPY WITH HYDRODISTENSION AND RANDOM BIOPSIES IN CLINICALLY SUSPECTED INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yuke Chen, Ziqi Ying, Yunxiang Xiao, Yi Liu, Shiliang Wu. Eur J Obstet Gynecol Reprod Biol. 2021 Aug 27;265:156-161. doi: 10.1016/j.ejogrb.2021.08.025. Online ahead of print. PMID: 34492610 DOI: 10.1016/j.ejogrb.2021.08.025

This study from China explored the diagnostic and therapeutic efficacy of cystoscopy with hydrodistension and random biopsies for clinically suspected interstitial cystitis/bladder pain syndrome (IC/BPS). The authors reviewed the data of 55 clinically suspected IC/BPS patients underwent cystoscopy with hydrodistension and random biopsies. Global Response Assessment was used to evaluate the efficacy. Disease severity was assessed by thorough history, physical examination, 3-day frequency volume chart, visual analog scale of pain, Interstitial Cystitis Symptom Index (ICSI) and clinical phenotype system (UPOINT). According to the pathologic outcomes from random biopsies, three out of the 55 clinically suspected IC/BPS were diagnosed as bladder carcinoma. Among the 52 IC/BPS patients, thirty-six patients (69.2%) had initial chief complaints of urinary frequency and urgency. Under cystoscopy, twenty-nine patients and 23 patients were classified as Hunner ulcer type and diffuse global mucosal bleeding (grade III glomerulation). The median functional bladder capacity of the 52 IC/BPS patients was 100 ml. Hydrodistension was effective in 28 patients (53.8%) at postoperative 3 months, which decreased to 25% at post-hydrodistension 6 months and to 13.5% at 12 months. For the 28 hydrodistension-effective patients, the remission degrees of daytime frequency, nocturia, VAS bladder pain and ICSI score were 50.3%, 49.4%, 68.1% and 48%, which were significantly higher than the 16.9% (daytime frequency, $P < 0.001$), 20.5% (nocturia, $P = 0.021$), 7.4% (VAS pain score, $P < 0.001$) and 6.1% (ICSI, $P < 0.001$) in the hydrodistension-negative group. According to the UPOINT system, the hydrodistension-effective cases had significantly higher rates of symptom remission in U ($P = 0.002$), P ($P = 0.026$), O ($P < 0.001$), and T ($P < 0.001$) domains than the corresponding negative cases. In effective group, the O domain had the most remission rate (26 out of 28, 92.9%, $P < 0.001$), followed by the U domain (12 out of 28, 42.9%, $P < 0.001$) and T domain (12 out of 28, 42.9%, $P < 0.001$). Histopathological analysis from random biopsies could distinguish bladder carcinoma

from clinically suspected IC/BPS. Hydrodistension is more likely to be effective when chronic pelvic pain is obviously alleviated. The efficacy of hydrodistension could act in a certain period of time.

DEMOGRAPHIC DIFFERENCES AND DISPARITIES IN THE MISDIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN A NATIONAL COHORT OF VA PATIENTS

Kai B Dallas, Catherine Bresee, Amanda De Hoedt, Justin F Senechal, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. Urology. 2021 Aug 2;S0090-4295(21)00709-3. doi: 10.1016/j.urology.2021.07.019. Online ahead of print. PMID: 34348123 DOI: 10.1016/j.urology.2021.07.019

This study explored the association between misdiagnosis of IC/BPS and demographics. Interstitial cystitis/bladder pain syndrome (IC/BPS) is associated with significant diagnostic uncertainty, resulting in frequent misdiagnosis as there is little known about the potential impact of key demographic factors. All patients in the VA system between 1999-2016 were identified by ICD-9/10 codes for IC/BPS (595.1/N30.10) (n = 9,503). ICD code accuracy for true IC/BPS (by strict criteria) was assessed by in-depth chart abstraction (n = 2,400). Associations were explored between rates of misdiagnosis and demographics. IC/BPS criteria were met in only 651 (48.8%) of the 1,334 charts with an ICD code for IC/BPS reviewed in depth. There were no differences in the misdiagnosis rate by race or by ethnicity, after adjusting for differences in age and gender. In IC/BPS-confirmed cases, female patients were diagnosed at a younger age than males. Black and Hispanic patients were diagnosed at a younger age compared to White and non-Hispanic patients, respectively. There was a high rate of misdiagnosis of IC/BPS overall, with only 48.8% of patients with an ICD code for IC/BPS meeting diagnostic criteria. There were no significant associations between diagnostic accuracy and race/ethnicity. Black and Hispanic patients were more likely to receive a diagnosis of IC/BPS at a younger age, suggesting there may be differing natural histories or presentation patterns of IC/BPS between racial/ethnic groups.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENT IS ASSOCIATED WITH SUBSEQUENT INCREASED RISKS OF OUTPATIENT VISITS AND HOSPITALIZATIONS: A POPULATION-BASED STUDY

Kun-Lin Hsieh, Hung-Yen Chin, Tsia-Shu Lo, Cheng-Yu Long, Chung-Han Ho, Steven Kuan-Hua Huang, Yao-Chi Chuang, Ming-Ping Wu. PLoS One. 2021 Sep 7;16(9):e0256800. doi: 10.1371/journal.pone.0256800. eCollection 2021. PMID: 34492065 PMCID: PMC8423233 DOI: 10.1371/journal.pone.0256800

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is not only a chronic urinary bladder pain syndrome but is also associated with multifactorial etiology. This study from Taiwan tested the hypothesis that IC/BPS is associated with subsequent increased risks of outpatient visits and hospitalizations. Using a nationwide database, the diagnoses were based on the International Classification Codes (ICD-9-CM) (595.1) of at least three outpatient services during 2002-2008, and a cystoscopic finding of Hunner type and/or glomerulations with pre-audit criteria. All recruited cases monitored for subsequent outpatient visits and hospitalizations for 2 years, including all-cause and specialty-specific departments, were classified according to medical specialty and age group. IC/BPS patients have more overall outpatient department (OPD) visits and an overall adjusted incidence rate ratio (IRR) of 1.64. As for specialty, IRRs were higher in psychiatry (2.75), Chinese medicine (2.01), and emergency medicine (2.00), as well as urology and gynecology. The IRRs decreased as age advanced (2.01, 1.71, and 1.44, respectively), except for gynecology (2.42, 2.52, and 2.81). A similar phenomenon happens in hospitalization with IRR of 1.69. Due to claim data characteristics, whether ulcer type IC/BPS findings can be deductive to non-ulcer type remains inclusive. Current results indicate the impacts of healthcare burden in broad spectrum about IC/PBS patients. IC/BPS has been suggested to be associated with lower threshold of healthcare visits and some coexisting disease and is comprised of systemic dysregulation and is beyond the scope of local bladder-urethra disease. Adequate recognition of associated or comorbid factors and possible recommendation or referral for IC/BPS patients can help provide better healthcare quality.

[BLADDER PAIN SYNDROME - DOES DETRUSOR MASTOCYTOSIS PREDICT SYMPTOMATIC IMPROVEMENT FOLLOWING BLADDER HYDRODISTENTION UNDER ANESTHESIA?] [Article in Hebrew]

Chen Shenhar, Alon Kass, Maxim Yakimov, Roni Tomashev Dinkovich, Shay Golan, Jack Baniel, Gabriel Gilon, Shachar Aharony. Harefuah. 2021 Sep;160(9):586-593. PMID: 34482671

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, debilitating syndrome involving bladder pain and lower urinary tract symptoms (LUTS), with a substantial effect on patients' quality of life. IC/BPS poses a diagnostic challenge, and its available treatment options remain only moderately effective. Bladder-wall biopsies from IC/BPS patients commonly uncover mastocytosis. While mast-cells are suspected as pivotal in disease pathogenesis, the clinical significance of their presence remains unclear. Clinical guidelines differ on whether or not bladder biopsies should be a part of routine IC/BPS workup. The aim of this study from Israel was to

determine whether detrusor mastocytosis can serve as a prognostic marker for treatment response and improvement duration. The authors retrospectively collected patient data for IC/BPS patients who underwent bladder hydrodistension under anesthesia. They used statistical modelling to determine the effect of mastocytosis and other possible predictive factors - age, comorbidity, Hunner lesions - on the presence and duration of symptom improvement. A total of 35 patients underwent hydrodistension, of whom 28 had bladder biopsies; 11 of them had mastocytosis. Within a median follow-up of 8.8 [1.7-24.2] months, 11 of the patients with mastocytosis and 9 of the patients without it, experienced symptomatic improvement. Improvement duration was 8 months longer in those with mastocytosis. Univariate logistic regression models were used to estimate odds ratios (OR). Mastocytosis and Charlson Comorbidity score were the only variables with a statistically significant OR. Univariate survival models were fitted, and improvement duration was estimated to be longer in patients with mastocytosis. A multivariate Cox regression model found no variable to be statistically significant, though mastocytosis was borderline significant. It was concluded that mastocytosis defines a discernible phenotype of IC/BPS, which exhibits higher rates and longer duration of hydrodistention treatment response. Notwithstanding limitations of sample size and retrospective study design, the authors were able to demonstrate that mastocytosis can serve as a prognostic factor for symptom improvement after hydrodistension in IC/BPS patients. Prospective studies are required to validate this finding and to investigate the mechanisms involved.

[IMMUNOMODULATION-A MOLECULAR SOLUTION TO TREATING PATIENTS WITH SEVERE BLADDER PAIN SYNDROME?](#)

Björn Wullt, Daniel S C Butler, Ines Ambite, Julia Kinsolving, Christian Krintel, Catharina Svanborg. Eur Urol Open Sci. 2021 Aug 6;31:49-58. doi: 10.1016/j.euros.2021.07.003. eCollection 2021 Sep. PMID: 34467240 PMCID: PMC8385293 DOI: 10.1016/j.euros.2021.07.003

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Patients with bladder pain syndrome experience debilitating pain and extreme frequency of urination. Numerous therapeutic approaches have been tested, but as the molecular basis of disease has remained unclear, specific therapies are not available. Recently, a systematic gene deletion strategy identified interleukin-1 (IL-1) hyperactivation as a cause of severe cystitis in a murine model. Treatment with an IL-1 receptor antagonist (IL-1RA) restored health in genetically susceptible mice, linking IL-1-dependent inflammation to pain and pathology in the bladder mucosa. The objective of this study from Sweden was to investigate whether IL-1RA treatment might be beneficial in patients with bladder pain syndrome. Patients diagnosed with bladder pain syndrome were invited to participate and subjected to daily IL-1RA injections for 1 wk, followed by a treatment break. Patients with other urological disorders accompanied by pain were included as controls. When symptoms returned, treatment was resumed and responding patients were maintained on treatment long term, with individualized dosing regimens. Symptom scores were recorded and molecular effects were quantified by neuropeptide and gene expression analysis. DNA samples were subjected to exome genotyping. IL-1RA treatment reduced bladder pain and the frequency of urination in 13/17 patients. Substance P levels in urine were lowered, and responders returned to a more normal lifestyle. Neuroinflammatory-dependent and IL-1-dependent gene networks were inhibited, as well as regulators of innate immunity. Genotyping revealed disease-associated IL1R1, NLRP3, and IL1RN DNA sequence variants in the responders. Controls did not benefit from IL-1RA treatment, except for one patient with cystitis cystica. In this clinical study, IL-1RA treatment is proposed to reduce chronic bladder pain, immediately and in the long term. Despite the limited number of study patients, the potent acute effect and lasting symptom relief indicate that this therapeutic approach may be worth exploring in controlled clinical trials.

Patient summary: Treatment with an interleukin-1 (IL-1) receptor antagonist is proposed for treating bladder pain syndrome, as it can result in symptom relief and increase quality of life. Reduced neuroinflammation and IL-1 signalling provided molecular evidence of the treatment effects.

[THE STUDY ON THE FUNCTION AND CELL SOURCE OF INTERLEUKIN-6 IN INTERSTITIAL CYSTITIS/BLADDER PAINFUL SYNDROME RAT MODEL](#)

Zhenming Zheng, Jiapeng Zhang, Caixia Zhang, Wenshuang Li, Kaiqun Ma, Hao Huang, Kuiqing Li, Yousheng Yao. Immun Inflamm Dis. 2021 Aug 18. doi: 10.1002/iid3.505. Online ahead of print. PMID: 34407316 DOI: 10.1002/iid3.505

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The elevated expression of interleukin-6 (IL-6) in patients with interstitial cystitis/bladder painful syndrome (IC/BPS) has been demonstrated, but the role of IL-6 in IC/BPS and its source remain to be explored. In this study from Guangdong, China, an IC/BPS rat model was created in female rats by using long-term intermittent

intravesical hyaluronidase (0.5 ml, 4 mg/ml). After modelling, IL-6 stimulation group, and anti-IL-6R group were treated with recombinant rat IL-6 and tocilizumab, respectively. Symptomatic changes were detected by Vonfrey pain score and urodynamics, and hematoxylin-eosin (HE) staining, mast cell staining and Masson staining were used to evaluate the changes of inflammation in the bladder tissue of rats. Cell sources of IL-6 was explored through enzyme linked immunosorbent assay (ELISA) test, reverse transcription polymerase chain reaction (RT-PCR), and western-blot test on the supernatant of coculturing rat bladder epithelial cells and rat macrophages. The Vonfrey pain scores of the model group and IL-6 stimulation group were significantly higher than those of the control group, while the anti-IL-6R group were significantly lower. Compared with the blank control group, urodynamic results showed that the urination interval of the model group and IL-6 stimulation group was significantly shortened, and the maximum bladder capacity was significantly reduced, and anti-IL-6R treatment significantly alleviated the inflammatory response of bladder tissue. The results of HE, Mast cell staining, and Masson staining showed that the inflammatory response of bladder tissue after anti-IL-6R treatment was significantly reduced. Through cells coculture, the relative expression of IL-6 from model group was found significantly higher than blank control group by RT-PCR, ELISA, and western blot test. It was concluded that IL-6 played an essential role in the development of IC/BPS rat model as a proinflammation cytokine. Further evidence from coculture proved that macrophages are the cell resource of IL-6 in IC/BPS.

[HUMAN UMBILICAL CORD MESENCHYMAL STEM CELL THERAPY MITIGATES INTERSTITIAL CYSTITIS BY INHIBITING MAST CELLS](#)

Yuancheng Xu, Fei Yang, Juncong Xie, Wenbiao Li, Bolong Liu, Jialiang Chen, Honglu Ding, Jiarong Cai. *Med Sci Monit.* 2021 Aug 6;27:e930001. doi: 10.12659/MSM.930001. PMID: 34354037 PMCID: PMC8353995 DOI: 10.12659/MSM.930001

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Interstitial cystitis (IC) is a recurrent and chronic inflammatory disease that compromises patients' quality of life. Effective treatments for IC are limited. This study from Guangdong, China aimed to evaluate the therapeutic potency of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) in an IC-induced rat model and investigate the potential molecular mechanism in a mast cell model (rat basophilic leukemia cells, RBL-2H3) in treating IC in a coculture system. The rat model of IC was induced by cyclophosphamide (CYP). Rats were randomly divided into 3 groups: sham, IC+PBS, and IC+MSC. In the coculture system, RBL-2H3 cells were sensitized overnight to Compound 48/80 (C48/80), cocultured with UC-MSCs for 3 days, and collected for subsequent experiments. RBL-2H3 cells were randomly divided into 3 groups: sham, C48, and UC-MSCs (C48+MSC). The UC-MSCs marked by thymidine analog 5-ethynyl-2-deoxyuridine (EdU) were transplanted in the treatment group and were densely distributed in the bladder. Accordingly, the conscious cystometry was measured and the bladder tissues were harvested. Compared with the sham group, the treated IC rats exhibited shorter bladder voiding intervals, more integral epithelia, and less collagen fiber aggregation, infiltration and degranulation of mast cells, and inflammatory cytokines in the bladder tissue. In the coculture system, compared with the C48 group, the UC-MSC-treated RBL-2H3 cells had suppressed degranulation. UC-MSCs treatment showed a promising therapeutic effect on treating IC in vivo and in vitro. UC-MSCs inhibit mast cell degranulation in IC and could be a potential therapeutic target to ameliorate inflammation in IC.

[\[QUALITY OF LIFE AND RELATED FACTORS IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME\]](#) [Article in Chinese]

J W Wang, J C Liu, L F Meng, W Zhang, X D Liu, Y G Zhang. *Beijing Da Xue Xue Bao Yi Xue Ban.* 2021 Aug 18;53(4):653-658. doi: 10.19723/j.issn.1671-167X.2021.04.005. PMID: 34393223 PMCID: PMC8365056 DOI: 10.19723/j.issn.1671-167X.2021.04.005

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The purpose of this study from Beijing, China was to evaluate the quality of life of patients with interstitial cystitis/bladder pain syndrome (IC/BPS), to compare the difference between IC/BPS and overactive bladder (OAB) pain syndrome, and to explore the related factors affecting the quality of life of IC/BPS patients. The demographic data of female outpatients with IC/BPS in Beijing Hospital and other medical centers in China were collected. The quality of life of the patients was investigated by multi-angle questionnaires and compared with the data of OAB patients. According to the influence degree of quality of life, the patients with IC/BPS were divided into mild-moderate group and severe group. In this study, 109 patients with IC/BPS were included. The average age was (46.4±14.3) years and the average course of disease was (39.4±51.6) months. Compared with the OAB patients, the patients in IC/BPS group had a longer average course of disease, a lower proportion of the patients of first visit for the disease, a higher score of the American Urological Association symptom index (AUA-

SI), a lower body mass index (BMI) ratio ($P=0.016$), and a lower incidence of constipation. IC/BPS had the greatest impact on family life, followed by social activity. The score of IC/BPS related symptoms on family life was significantly higher than that of the OAB group. The top three symptoms of the IC/BPS patients were pain (45%), frequency (28%) and urgency (17%). The score of quality of life in the IC/BPS patients was significantly higher than that in the OAB patients. Caffeine intake and constipation might be the factors influencing the quality of life of the patients with IC/BPS. IC/BPS has a great influence on the quality of life of patients. Caffeine intake and constipation may be related factors affecting the quality of life of patients with IC/BPS. Urologists should recommend changes in diet and lifestyle to reduce symptoms and improve the patients' quality of life.

[CIRCTHBS1 FACILITATES THE PROGRESSION OF INTERSTITIAL CYSTITIS DEPENDING ON THE REGULATION OF MIR-139-5P/MFN2 AXIS](#)

Chen Jiang, Ming Xu, Jin Zhu, Dongrong Yang, Boxin Xue. Drug Dev Res. 2021 Aug 9. doi: 10.1002/ddr.21864. Online ahead of print. PMID: 34368980 DOI: 10.1002/ddr.21864

Circular RNA (circRNA) have been found to play an important role in the progression of many diseases, including interstitial cystitis (IC). However, the role of circTHBS1 in IC progression is still unclear. In this study from Suzhou, China, exploring the role and potential molecular mechanism of circTHBS1 in the development of IC, the enzyme-linked immunosorbent assay was used to assess the levels of inflammatory cytokines. The expression levels of circTHBS1, microRNA (miR)-139-5p, and mitofusin 2 (MFN2) were evaluated using quantitative real-time PCR. Cell proliferation and migration were determined using MTT assay, Edu staining, and transwell assay. The protein levels of epithelial-mesenchymal transition (EMT) markers and MFN2 were examined using western blot analysis. The relationship between miR-139-5p and circTHBS1 or MFN2 was confirmed using the dual-luciferase reporter assay and RIP assay. CircTHBS1 was highly repressed in IC tissues and cells, and its expression was positively correlated with the inflammatory response of IC patients. CircTHBS1 could promote the proliferation, migration, EMT process, and inflammation of IC cells, while its knockdown had an opposite effect. CircTHBS1 could serve as a sponge of miR-139-5p, and miR-139-5p could participate in the regulation of circTHBS1 on IC cell progression. In addition, miR-139-5p could target MFN2, and it could inhibit the progression of IC cells by targeting MFN2. Furthermore, circTHBS1 sponged miR-139-5p to positively regulate MFN2. CircTHBS1 promoted IC cell proliferation, migration, EMT process, and inflammation by regulating the miR-139-5p/MFN2 axis indicating that circTHBS1 might be a potential target for IC treatment.

[LOW ENERGY SHOCK WAVE THERAPY ATTENUATES MITOCHONDRIAL DYSFUNCTION AND IMPROVES BLADDER FUNCTION IN HCL INDUCED CYSTITIS IN RATS](#)

Hung-Jen Wang, Pradeep Tyagi, Tsu-Kung Lin, Chao-Cheng Huang, Wei-Chia Lee, Michael B Chancellor, Yao-Chi Chuang. Biomed J. 2021 Jul 2;S2319-4170(21)00072-X. doi: 10.1016/j.bj.2021.06.006. Online ahead of print. PMID: 34224911 DOI: 10.1016/j.bj.2021.06.006

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Wang and colleagues from Taiwan and USA examined the effects of low energy shock wave (LESW) on bladder and mitochondrial function in a rat model of HCl induced cystitis, and the influence of dynamic bladder filling volume on LESW responses. Dysregulation of mitochondria function may impact the urothelial barrier and contribute to bladder dysfunction in patients with Interstitial cystitis/bladder pain syndrome (IC/BPS). Female Sprague-Dawley rats underwent urethral catheterization and intravesical instillation of 0.2 ml of 0.4N HCl (N=32) or 0.2 ml saline (N=8) kept for 90 s. After HCl instillation, the bladder received LESW treatment while filled with 0 ml, 0.2 ml or 0.4 ml saline or no LESW treatment. Continuous cystometry (CMG) was performed on day 8. The bladder was harvested after CMG for histology and Western blotting. HCl provoked bladder overactivity, bladder wall inflammation marked by infiltration of mast cells, increased bax/bcl2 ratio consistent with increased TUNEL staining and increased release of mitochondrial-integrity markers (cleaved caspase 3 and Cytochrome c). LESW treatment suppressed HCl provoked bladder overactivity in association with lower inflammatory reaction, mast cells infiltration, and a lower bax/bcl2 ratio also reflected by reduced TUNEL staining and mitochondrial-integrity markers irrespective of the volume of saline in bladder at the time of LESW. It was concluded that these findings support that anti-inflammatory effect of LESW in chemical cystitis is associated with the reversal of the molecular-cellular perturbations in mitochondrial dependent intrinsic apoptotic pathway.

[THERAPEUTIC EFFECT OF MODULATING THE NLRP3-REGULATED TRANSFORMING GROWTH FACTOR-B SIGNALING PATHWAY ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Hung-Jen Shih, Chao-Yuan Chang, Chung-Howe Lai, Chun-Jen Huang. Biomed Pharmacother. 2021 Jun;138:111522. doi: 10.1016/j.biopha.2021.111522. Epub 2021 Apr 1. PMID: 34311526 DOI: 10.1016/j.biopha.2021.111522

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a disorder with complex pathogenesis and lacks effective treatment. Chronic inflammation is the main pathogenesis of Hunner-type IC/BPS. The NLR family pyrin domain-containing 3 (NLRP3) inflammasome-related transforming growth factor- β (TGF- β)/Smad signalling pathway plays a crucial role in inflammation-related tissue fibrosis. In this study from Taiwan, lipopolysaccharide (LPS) and protamine sulfate (LPS/PS) were instilled into the mouse bladder twice a week for 5 consecutive weeks to establish a chronic inflammation-induced IC/BPS model (LPS/PS model). Following LPS/PS treatment, curcumin (oral, 100 mg/kg; a potent NLRP3 modulator) was administered for 2 weeks in the curcumin treatment group, and normal saline was used for the sham group. Bladder function was evaluated by performing the voiding spot assay and examining the status of urothelial denudation and fibrosis in bladder tissues. The expression of NLRP3 inflammasome, interleukin-1 β , TGF- β , Smad, vimentin, and E-cadherin in bladder tissues was evaluated through immunohistochemistry staining. Results revealed that the repeated instillation of LPS/PS leads to voiding dysfunction, bladder urothelium denudation, and detrusor muscle fibrosis through the upregulation of the NLRP3 inflammasome/IL-1 β -related TGF- β /Smad pathway and the increased epithelial-mesenchymal transition process in bladder tissues. The downregulation of the NLRP3 inflammasome/IL-1 β -related TGF- β /Smad pathway in bladder tissues through curcumin effectively mitigated bladder injury in the LPS/PS model. In conclusion, the NLRP3 inflammasome/IL-1 β -related TGF- β /Smad pathway plays a crucial role in bladder injury in the LPS/PS model, and modulation of this pathway, such as by using curcumin, can effectively mitigate the sequelae of chronic inflammation-induced IC/BPS.

[ANTI-INFLAMMATORY IRON CHELATOR, DIBI, REDUCES LEUKOCYTE-ENDOTHELIAL ADHESION AND CLINICAL SYMPTOMS OF LPS-INDUCED INTERSTITIAL CYSTITIS IN MICE](#)

Georg Hagn, Bruce Holbein, Juan Zhou, Christian Lehmann. *Clin Hemorheol Microcirc.* 2021 Jul 3. doi: 10.3233/CH-201078. Online ahead of print. PMID: 34250933 DOI: 10.3233/CH-201078

Interstitial cystitis (IC) is a prevalent and debilitating chronic inflammatory disease of the urinary bladder. Currently there are no fully effective therapeutic agents available, in part due to the still obscure pathogenesis of IC. Lipopolysaccharide (LPS) also known as endotoxin from Gram negative bacteria elicits IC in mice and has formed the basis of model systems for investigation. Excess free iron plays an important role in inflammation through generation of reactive oxygen species (ROS). The novel iron chelator DIBI has been shown to sequester excess free iron and dampen excess inflammatory responses to systemic LPS administration and also to Gram negative bacterial infections. The overall objective of this study from Canada was to evaluate the effects of DIBI on LPS induced IC in mice. Leukocyte activation, endothelial adhesion and functional capillary density were assessed by intravital microscopy of the bladder microcirculation following a single intravesical LPS administration with or without intravesical DIBI treatment. Clinical IC symptoms were also assessed through behavioral and pain threshold force measurements. Four groups of female BALB/c mice (n = 5-6/group) were randomized in this study: control group, IC group without therapy, IC group with DIBI therapy and control group with DIBI therapy. The groups were examined using intravital microscopy (IVM) of the bladder for leukocyte-endothelial interactions (adherent leukocytes, temporarily interacting leukocytes) and functional capillary density (FCD). A modified behavioral score by Boucher et al. and Von-Frey-Aesthesiometry were used to evaluate key behavioral indices related to pain and visceral pain perception. LPS introduced intravesically induced an early (≤ 2 h) inflammation of the bladder evidenced by leukocyte activation and adhesion to bladder capillary walls. Intravesical DIBI therapy of mice 30min following LPS administration and assessed after 1.5h treatment showed a significant decrease in the number of adherent leukocytes compared to IC animals without DIBI treatment. DIBI treated mice showed a significantly lowered increase in behavioral distress scores compared to IC mice without therapy. Untreated IC mice exhibited a significantly decreased threshold force value for evoked pain response and DIBI treatment improved the threshold pain response. A significant inverse correlation was found for the two pain and suffering evaluation methods results. DIBI reduced inflammatory endothelial leukocyte adhesion and key indices related to pain and suffering over those observed in untreated IC mice. Our findings suggest a potential therapeutic role for DIBI for IC treatment.

[FIRST-LINE TREATMENT POSTERIOR TIBIAL NERVE STIMULATION IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Sahin Kabay, Sibel Canbaz Kabay, Mehmet Sevim. *Cent European J Urol.* 2021;74(2):208-214. doi: 10.5173/cej.2021.0372. Epub 2021 Jun 5. PMID: 34336240 PMCID: PMC8318015 DOI: 10.5173/cej.2021.0372

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The aim of this study from Turkey was to determine the effects of first-line treatment posterior tibial nerve stimulation (PTNS), applied once a week for a 12 week period, as a treatment modality for patients with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). A total of 39 female patients with IC/BPS were enrolled in the study. Patients had one 30-minute session of PTNS per week for 12 weeks and symptoms were assessed before and after the treatment sessions by the use of a voiding diary, visual analog scale (VAS) for pain, O'Leary-Sant interstitial cystitis symptom index (ICSI), and O'Leary-Sant interstitial cystitis problem index (ICPI). The mean age of the patients was 38.9 ± 7.1 years. The improvements in voiding diary parameters after 12 weeks of PTNS treatment were statistically significant compared to baseline but the changes in nocturia, and average voiding volume were not statistically significant. Mean parametric improvements after 12 weeks of PTNS treatment compared to baseline included a daytime frequency decrease by 3.8 voids daily, urgency episodes decrease by 4.7 episodes daily, nocturia decrease by 0.3 voids and voided volume improvement by a mean of 8.4 ml. The difference for ICSI, ICPI and VAS between baseline and the 12th week of PTNS treatment scores demonstrated statistically significant improvements in pain severity, symptom and problem index. The findings in this study demonstrated the improvements of voiding diaries, ICSI, ICPI and VAS scores in patients with IC/BPS after 12 weeks PTNS. PTNS treatment is a beneficial first-line treatment option for IC/BPS symptom amelioration.

HIDROX[®] AND CHRONIC CYSTITIS: BIOCHEMICAL EVALUATION OF INFLAMMATION, OXIDATIVE STRESS, AND PAIN

Ramona D'Amico, Angela Trovato Salinaro, Marika Cordaro, Roberta Fusco, Daniela Impellizzeri, Livia Interdonato, Maria Scuto, Maria Laura Ontario, Roberto Crea, Rosalba Siracusa, Salvatore Cuzzocrea, Rosanna Di Paola, Vittorio Calabrese. Antioxidants (Basel). 2021 Jun 29;10(7):1046. doi: 10.3390/antiox10071046. PMID: 34209690 DOI: 10.3390/antiox10071046

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Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic bladder condition characterized by frequent urination, inflammation, oxidative stress, and pain. The aim of the study was to evaluate the anti-inflammatory and antioxidant effects of an oral administration of Hidrox[®] (10 mg/kg) in the bladder and spinal cord in a rodent model of IC/BPS. The chronic animal model of cystitis was induced by repeated intraperitoneal injections of cyclophosphamide (CYP) for five consecutive days. Treatment with Hidrox[®] began on the third day of the CYP injection and continued until the 10th day. CYP administration caused macroscopic and histological bladder changes, inflammatory infiltrates, increased mast cell numbers, oxidative stress, decreased expression of the tight endothelial junction (e.g., zonula occludens-1 (ZO-1) and occludin), and bladder pain. Treatment with Hidrox[®] was able to improve CYP-induced inflammation and oxidative stress via the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) pathway. It was also able to reduce bladder pain which was aggravated by the activation of neuroinflammation in the central nervous system. In particular, Hidrox[®] reduced the brain-derived neurotrophic factor (BDNF), as well as the activation of astrocytes and microglia, consequently reducing mechanical allodynia. These results indicate that nutritional consumption of Hidrox[®] can be considered as a new therapeutic approach for human cystitis, increasing the conceivable potential of a significant improvement in the quality of life associated with a lowering of symptom intensity in patients with IC/BPS.

[TREATMENT OF BLADDER PAIN SYNDROME. A NETWORK META-ANALYSIS]

[Article in German]

Sebastian Graf. Urologe A. 2021 Aug;60(8):1035-1038. doi: 10.1007/s00120-021-01588-4. Epub 2021 Jul 5. PMID: 34226948 PMCID: PMC8318957 DOI: 10.1007/s00120-021-01588-4

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PERCUTANEOUS TIBIAL NERVE STIMULATION FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PILOT STUDY

Neha T Sudol, Noelani Guaderrama, Emily Adams-Piper, Emily Whitcomb, Felicia Lane. Int Urogynecol J. 2021 Oct;32(10):2757-2764. doi: 10.1007/s00192-020-04481-4. Epub 2020 Aug 13. PMID: 32789810 DOI: 10.1007/s00192-020-04481-4

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain condition that requires multimodal management. The American Urological Association includes sacral neuromodulation in the treatment algorithm for refractory IC/BPS. Sudol and colleagues sought to determine the rate of overall symptom improvement of IC/BPS symptoms, using validated measures, after treatment with percutaneous tibial nerve stimulation (PTNS), a form of peripheral neuromodulation. This was a single-arm, dual-centre, pilot study examining a standard PTNS protocol in subjects with IC/BPS. The primary outcome was subject response of "moderately" or "markedly improved" on the Global Response Assessment (GRA) scale after 12-weekly PTNS sessions. Assuming a 60%

response rate, 24 subjects were needed to detect a response rate between 40 and 80% with 95% confidence. Secondary objectives included change in urinary frequency on a 24-h bladder diary, bladder pain as measured by VAS and responses to validated questionnaires for pelvic pain and IC/BPS. Of 21 subjects enrolled, 16 initiated and 10 completed the PTNS treatment course. The GRA response rate was 40% at week 6 and 30% at week 12. Seventy percent of the cohort had some degree of improvement. There were no adverse events. While only a minority of subjects with IC/BPS were responders to PTNS per GRA criteria, 70% of the cohort had some degree of improvement. Due to low recruitment and loss to follow-up, the authors did not achieve their predetermined significance. However, they believe that their promising findings add to the limited literature on this subject.

HOW DO WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME MAKE TREATMENT CHOICES?

Daisy Hassani, Lorraine Flick, Hareena Sangha, Lily A Brown, Uduak Andy, Lily Arya. Int Urogynecol J. 2021 Oct 2. doi: 10.1007/s00192-021-04994-6. Online ahead of print. PMID: 34599672 DOI: 10.1007/s00192-021-04994-6

There is a relative lack of data regarding how patients weigh various factors when choosing a treatment strategy for interstitial cystitis/bladder pain syndrome (IC/BPS). The aim of Hassani and colleagues from Philadelphia was to describe patient experience with their current and prior treatments and discuss factors they consider when choosing a treatment. Twenty-one women with IC/BPS participated in five focus groups moderated by a psychologist. Focus groups were conducted until thematic saturation was reached. Group discussions were transcribed and independently coded by two reviewers. Emergent themes and concepts were identified using grounded theory methodology. Data on symptoms and beliefs regarding medications were collected using validated questionnaires: Interstitial Cystitis Symptom and Problem Index (ICSI and ICPI) and Beliefs in Medications Questionnaire-Specific (BMQ-S). The median age of participants was 42 years, and all had some college education. Median score (range) for the ICSI was 12 (4, 20) and for the ICPI was 10 (3, 16), indicating moderate symptom burden. Most patients had tried only first- or second-line treatments. The median BMQ-S score was 2, indicating a neutral attitude toward medication. Several themes were identified. Patients expressed interest in self-management of symptoms using a structured care plan that incorporates guided self-care practices and care that can be delivered virtually. Patients desired to minimize treatment side effects by reducing prescription medications and avoiding surgical procedures. Finally, patients had considerable interest in alternative treatments; however, they wanted these treatments to be evidence-based. Women with IC/BPS have a strong interest in guided programs that teach self-care practices and deliver alternative treatments through remote platforms.

YOUTUBE™ AS A SOURCE OF INFORMATION ON BLADDER PAIN SYNDROME: A CONTEMPORARY ANALYSIS

Simone Morra, Claudia Collà Ruvolo, Luigi Napolitano, Roberto La Rocca, Giuseppe Celentano, Gianluigi Califano, Massimiliano Creta, Marco Capece, Carmine Turco, Simone Cilio, Alberto Melchionna, Gerardo Gerundo, Francesco Trama, Francesco Mangiapia, Ferdinando Fusco, Vincenzo Mirone, Nicola Longo. Neurourol Urodyn. 2021 Sep 24. doi: 10.1002/nau.24802. Online ahead of print. PMID: 34559920 DOI: 10.1002/nau.24802

The purpose of this study was to evaluate the quality of YouTube™ videos on bladder pain syndrome (BPS) and to investigate whether they can be used as a reliable source of information. The search term "bladder pain syndrome" was used on YouTube™ platform. The first 100 videos were selected. Patient Education Materials Assessment Tool for audio-visual content (PEMAT A/V), Global Quality Score (GQS), Misinformation tool, and DISCERN score were used to assess videos' quality content. Pearson's test was used to assess potential correlations between variables. Seventy-nine videos were suitable for the analyses. The overall quality of YouTube™ videos on BPS has been evaluated as good according to PEMAT A/V, GQS, Misinformation tool, and DISCERN score. It is possible to assume that YouTube™ may be considered as a reliable source of information on BPS.

A SYSTEMATIC REVIEW OF RACIAL/ETHNIC DISPARITIES IN FEMALE PELVIC FLOOR DISORDERS

Daniel C Gonzalez, Shayan Khorsandi, Megan Mathew, Ekene Enemchukwu, Raveen Syan. Urology. 2021 Oct 7;S0090-4295(21)00907-9. doi: 10.1016/j.urology.2021.09.018. Online ahead of print. PMID: 34627869 DOI: 10.1016/j.urology.2021.09.018

Numerous studies have investigated the influence of health disparities among women with pelvic floor disorders with varied results. Racial/ethnic disparities, in particular, inconsistently indicate differences in prevalence of disease, disease severity, and treatment outcomes. The aim of the authors was to review the body of literature examining racial/ethnic disparities in pelvic floor disorders, including overactive bladder, stress urinary incontinence, pelvic organ prolapse, and interstitial cystitis. A better understanding of these disparities may help

guide clinicians, researchers, and advocates in providing improved education, outreach opportunities, and access to care in minority women with pelvic floor disorders.

MUSIC DURING FLEXIBLE CYSTOSCOPY FOR PAIN AND ANXIETY - A PATIENT-BLINDED RANDOMISED CONTROL TRIAL

George McClintock, Eddy Wong, Pascal Mancuso, Nestor Lalak, Paul Gassner, Kayvan Haghghi, Prem Rathore, Lesley McAulay, Nicola Jeffery. BJU Int. 2021 Oct;128 Suppl 1:27-32. doi: 10.1111/bju.15527. Epub 2021 Jul 30. PMID: 34174137 DOI: 10.1111/bju.15527

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The purpose of this study from Australia was to assess the role of music in reducing the pain and anxiety associated with flexible cystoscopy using a blinded trial design. A patient-blinded randomised control trial of music during flexible cystoscopy was performed comparing the pain, measured by visual analogue scale (VAS), anxiety, measured by the State-Trait Anxiety Inventory (STAI), and vital signs of 109 patients across two public hospitals in New South Wales, Australia. The purpose and hypothesis of the study was concealed from patients until after results had been collected. There were no statistically significant differences detected between the No Music and Music groups in VAS pain score, change in STAI anxiety score or post-procedural vital signs between the two groups. It was concluded that music does not appear to decrease perceived pain or anxiety when used during flexible cystoscopy. These findings may differ from the literature due to several factors, most significantly blinding of participants, but also potentially due to the ethnic composition of the study population or lack of choice of music.

ESTROGEN INHIBITS BLADDER OVERACTIVITY IN RATS WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS VIA DOWNREGULATING THE EXPRESSION OF P2X3 RECEPTORS IN BLADDER EPITHELIUM CELLS

Xin Liu, Yang Yang, Ye Gao, Hengshuai Zhang, Jingzhen Zhu, Xingyou Dong, Jie Xu. NeuroUrol Urodyn. 2021 Oct 7. doi: 10.1002/nau.24811. Online ahead of print. PMID: 34622458 DOI: 10.1002/nau.24811

The therapeutic effect of estrogen on interstitial cystitis/bladder pain syndrome is unclear. In this study, Liu and colleagues from Chongqing, China explored the effect of estrogen on bladder overactivity in rats with cyclophosphamide-induced cystitis and its underlying mechanism. Vivo cystometry was used to determine the effect of estrogen on bladder excitability. The effect of estrogen on the expression of P2X3 receptors in bladder epithelium was detected by real-time polymerase chain reaction and western blot. Effect of P2X3 receptors in bladder urothelium on stretch-released adenosine triphosphate was performed by a Flexcell FX5000 Compression system and an Enzyme-Linked Immunosorbent Assay Kit. Estrogen deprivation significantly increased the urinary frequency, while supplementation with diarylpropionitrile (DPN), an estrogen receptor β (ER β) agonist, alleviated the urinary frequency. 17 β -Estradiol and DPN decreased the expression of P2X3 receptors in urothelium cells which was partially inhibited by ER β antagonist 4-[2-phenyl-5,7-bis(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-3-yl]phenol. Meanwhile, inhibiting the expression of P2X3 receptors by ER β agonist or antagonizing the function of P2X3 receptors by selective P2X3 receptor antagonist AF-353 or A-317491 significantly reduced the stretch-released ATP from urothelium cells. It was concluded that estrogen has a direct effect on the regulation of bladder overactivity in rats with cyclophosphamide-induced cystitis by downregulating the expression of bladder epithelial P2X3 receptors through ER β and reducing the adenosine triphosphate released from urothelium during bladder filling, thereby inhibiting the generation of the micturition reflex.

SYSTEMIC AND INTRATHECAL BACLOFEN PRODUCE BLADDER ANTINOCICEPTION IN RATS

Timothy J Ness, Alan Randich, Xin Su, Cary DeWitte, Keith Hildebrand. BMC Urol. 2021 Oct 4;21(1):139. doi: 10.1186/s12894-021-00899-0. PMID: 34607587 PMCID: PMC8489106 DOI: 10.1186/s12894-021-00899-0

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Baclofen, a clinically available GABAB receptor agonist, produces non-opioid analgesia in multiple models of pain but has not been tested for effects on bladder nociception. In this study from the USA, a series of experiments examined the effects of systemic and spinally administered baclofen on bladder nociception in female anesthetized rats. Models of bladder nociception included those which employed neonatal and adult bladder inflammation to produce bladder hypersensitivity. Cumulative intraperitoneal dosing (1-8 mg/kg IP) and cumulative intrathecal dosing (10-160 ng IT) of baclofen led to dose-dependent inhibition of visceromotor responses (VMRs) to urinary bladder distension (UBD) in all tested models. There were no differences in the magnitude of the analgesic effects of baclofen as a function of inflammation versus no inflammation treatments. Hemodynamic (pressor) responses to UBD were similarly inhibited by IT baclofen as well as UBD-evoked excitatory responses of spinal dorsal horn neurons. The GABAB receptor antagonist, CGP 35,348, antagonized

the antinociceptive effects of IT baclofen on VMRs in all tested models but did not affect the magnitude of the VMRs by itself suggesting no tonic GABAB activity was present in this preparation. Tolerance to a seven day continuous IT infusion of baclofen was not observed. These data provide support for a clinical trial of baclofen as a non-opioid treatment of human bladder pain.

HUNNER LESION

FEATURES OF VARIOUS BLADDER LESIONS AND THEIR IMPACT ON CLINICAL SYMPTOMS AND RECURRENCE IN INTERSTITIAL CYSTITIS

Jung Hyun Shin, Bosik Kang, Myung-Soo Choo. *J Urol.* 2021 Sep;206(3):669-678. doi: 10.1097/JU.0000000000001811. Epub 2021 Apr 23. PMID: 33890486 DOI: 10.1097/JU.0000000000001811

The authors from Korea investigated the impact of various bladder lesions on the clinical symptoms and recurrence of interstitial cystitis (IC). Patients with IC who underwent transurethral resection and cauterization for Hunner lesions (HLs) were enrolled. Features of HLs-noninflamed, inflamed, and gradually inflamed-and associated cystoscopic findings, including waterfall bleeding (none, focal or extensive), submucosal hemorrhage, and mucosal streak, were analyzed to investigate their association with preoperative symptoms and recurrence. They included 272 procedures from 141 patients (male:female ratio 37:104) with a mean±SD age of 61.4±10.5 years. Recurrence was observed in 160 procedures after a mean of 15.6 months (range 0.7-91.7); repeat transurethral resection and cauterization was performed in 131 cases. The number of HLs observed at each procedure was variable, and sufficient bladder filling revealed hidden lesions in 10.7% of cases. Waterfall bleeding was frequently accompanied with inflamed/gradually inflamed HLs. Inflammatory HLs were associated with smaller functional bladder capacity and preoperative urgency. Extensive waterfall bleeding was associated with smaller functional bladder capacity. On multivariate analysis, initially inflamed HLs and gradual inflammatory changes in HLs were found to be risk factors for recurrence. Sufficient bladder filling revealed hidden HLs. The features of HLs were not associated with subjective symptoms; inflamed changes were a predictive factor for IC recurrence and associated with frequent urgency episodes and smaller bladder capacity.

IDENTIFICATION OF NOVEL BIOMARKERS IN HUNNER'S INTERSTITIAL CYSTITIS USING THE CIBERSORT, AN ALGORITHM BASED ON MACHINE LEARNING

Kaining Lu, Shan Wei, Zhengyi Wang, Kerong Wu, Junhui Jiang, Zejun Yan, Yue Cheng. *BMC Urol.* 2021 Aug 16;21(1):109. doi: 10.1186/s12894-021-00875-8. PMID: 34399738 PMCID: PMC8365919 DOI: 10.1186/s12894-021-00875-8

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Hunner's interstitial cystitis (HIC) is a complex disorder characterized by pelvic pain, disrupted urine storage, and Hunner lesions seen on cystoscopy. There are few effective diagnostic biomarkers. In this study from China, the authors used the novel machine learning tool CIBERSORT to measure immune cell subset infiltration and potential novel diagnostic biomarkers for HIC. The GSE11783 and GSE57560 datasets were downloaded from the Gene Expression Omnibus for analysis. Ten HIC and six healthy samples from GSE11783 were analyzed using the CIBERSORT algorithm. Gene Set Enrichment Analysis (GSEA) was performed to identify biological processes that occur during HIC pathogenesis. Finally, expression levels of 11 T cell follicular helper cell (Tfh) markers were compared between three healthy individuals and four patients from GSE57560. Six types of immune cells in HIC from GSE11783 showed significant differences, including resting mast cells, CD4+ memory-activated T cells (CD3+ CD4+ HLA-DR+ cells), M0 and M2 macrophages, Tfh cells, and activated natural killer cells. Except for plasma cells, there were no significant differences between Hunner's lesion and non-Hunner's lesion areas in HIC. The GSEA revealed significantly altered biological processes, including antigen-antibody reactions, autoimmune diseases, and infections of viruses, bacteria, and parasites. There were 11 Tfh cell markers with elevated expression in patients from GSE57560. This was the first demonstration of Tfh cells and CD3+ CD4+ HLA-DR+ cells with elevated expression in HIC. These cells might serve as novel diagnostic biomarkers.

EVIDENCE FOR EARLY CYCLOSPORINE TREATMENT FOR HUNNER LESION INTERSTITIAL CYSTITIS

Annah Vollstedt 1, Lauren Tennyson, Katherine Turner, Deborah Hasenau, Md Saon, Teresa McCartney, Dana Beck, Jason Gilleran, Kenneth Peters. *Female Pelvic Med Reconstr Surg.* 2021 Sep 30. doi: 10.1097/SPV.0000000000001108. Online ahead of print. PMID: 34608034 DOI: 10.1097/SPV.0000000000001108

The objective of this study was to evaluate this team's experience using cyclosporine A (CyA) in the treatment of Hunner lesion interstitial cystitis (HLIC). Retrospective chart review was performed on patients with HLIC treated with CyA from August 2012 to September 2019. Demographic and clinical variables, number of

interstitial cystitis therapies, frequency, nocturia, and bladder pain visual analog scores before and after CyA treatment were collected, as well as the Global Response Assessment (GRA) and the Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index. CyA responders were defined as those with moderately or markedly improved GRA scores. A total of 51 patients with HLIC treated with CyA were identified. Mean follow-up was 3 years (0.36-6.8 years). Seventy-six percent (28 of 37) were female; mean age was 68 years (51-84 years). Before CyA treatment, an average of 8 previous therapies were tried and patients reported an average of 8 of 10 bladder pain. Daytime frequency was 11-20 times per day, and nocturia was 7 times per night. Per the GRA, 84% (31 of 37) were considered CyA responders. Posttherapy Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index scores were lower in responders compared with non-responders. Bladder pain, number of hydrodistentions/fulgurations, nocturia, and daytime frequency improved significantly after CyA treatment. The cyclosporine A response rate was 84%, with most of these patients reporting marked improvement. Bladder pain, daytime frequency, and nocturia were significantly improved after CyA treatment, and the number of interventions after CyA treatment decreased. Cyclosporine A should be considered earlier than fifth-line therapy in HLIC.

UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS)

CLINICAL PRESENTATION OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS) VARIES WITH PRESENTING AGE - IMPLICATION ON PATIENT EVALUATION

James Gross, Joel Vetter, H Henry Lai. *Urology*. 2021 Jul 22;S0090-4295(21)00680-4. doi: 10.1016/j.urology.2021.07.007. Online ahead of print. PMID: 34302833 DOI: 10.1016/j.urology.2021.07.007

This study compared the clinical presentation of UCPPS from a large clinical practice grouped by their presenting age to improve the evaluation of this condition. A total of 223 male and female patients seeking care for their UCPPS were recruited to study their urologic and non-urologic presentation. Their evaluation included cystoscopy and multiple questionnaires to assess their pelvic pain, non-urologic pain, urinary symptoms, somatic symptoms, and psychosocial health. Patients were then grouped by age into the following groups: less than 30 years of age, between the ages of 30 and 60, and older than 60. These groups were then compared on multiple domains. Patients between the ages of 60 and 30 were most likely to have concomitant COPC (such as fibromyalgia or migraine headaches), more widespread distribution of non-urologic pain, higher somatic symptom burden, and depression. Patients 30 years old or younger were more likely to have more severe urologic and non-urologic pain, and urinary pain symptoms that are less typical of IC/BPS (eg, pain worsened during or after urination). Patients older than 60 were more likely to have Hunner lesion. The authors conclude that their findings support the evaluation of non-urologic pain, COPC and psychosocial health in middle-aged patients; Hunner lesion in older patients; and a higher clinical suspicion of other confusable diagnoses when younger patients present with atypical symptoms.

NEUROBIOLOGY BLADDER PAIN

NEUROANATOMY OF BLADDER PAIN

Tyler Sheetz, J. Quentin Clemens & Irene Crescenze. *Curr Bladder Dysfunct Rep* 16, 41–45 (2021). <https://doi.org/10.1007/s11884-021-00629-0>

In this review, the authors summarize the most recent literature on neurobiology of bladder pain in a systematic fashion starting with end organ, peripheral nervous system, the spinal cord, and ending with the brain. Special attention is dedicated to pain processing in patients with spinal cord injury. Chronic bladder pain is not an isolated entity and is in fact a result of a complex interaction between the end organ, surrounding structures, and peripheral and central nervous system. The afferent fibers collecting the information from the bladder urothelium and mucosa are a very diverse population and respond not only to stretch but also to noxious and chemical signalling. Neuroinflammation appears to be central to the process of sensitization. Imaging and molecular evidence is emerging noting actual alterations in signalling pathways and neuroanatomy in patients with chronic pelvic pain beyond the end organ. Tremendous progress has been made to better understand the complex pathophysiology of bladder pain on a molecular and neuroanatomic level. Ideally, this information can be utilized to better identify specific and individualized intervention targets for patients with chronic bladder pain.

CHRONIC CYSTOPATHIES

[**EFFECTIVENESS AND SAFETY OF INTRAVESICAL HYALURONIC ACID FOR SYMPTOM CONTROL IN CHRONIC BLADDER DISEASES**](#) [Article in Spanish]

Juan Boronat Catalá, Ana García Tello, Laura González Montes, Sonia Ruiz Graña, Diego Torres Pérez, Luis Llanes González. *Arch Esp Urol*. 2021 Sep;74(7):639-644. PMID: 34472431

Chronic bladder disorders are a common condition. Endovesical hyaluronic acid is one of the therapeutic options for these patients. It is intended to verify the effectiveness and safety of treatment with intravesical instillations of hyaluronic acid in patients with bladder symptoms. The authors present a series of 32 patients who received intravesical instillations of hyaluronic acid. Demographic characteristics, tolerance, and complications were analyzed, and symptoms before and after treatment were compared. Symptomatic relief achieved with treatment was assessed using the Patient Global Improvement Impression Scale (PGI-I). The median age was 74 years (IQR 60-78) and 65.6% were women. Median follow-up was 10 months (IQR 7-14). Eleven patients were diagnosed with radiotherapy-induced cystitis, 17 with bladder pain syndrome/interstitial cystitis (BPS/IC), and 4 with recurrent cystitis. After treatment, symptoms improved in 81.8% of patients with radical cystitis, 82.3% of patients with BPS/IC, and 75% of the patients with recurrent cystitis. The incidence of hematuria was reduced from 46.9% to 9.4%, filling symptoms from 62.5% to 12.5% and pain from 40.6% to 12.5%. 100% of the patients tolerated the treatment well and only 2 adverse effects were recorded (urinary tract infection and acute urine retention). During follow-up, 65.6% showed total control of symptoms and 15.6% partial control, achieving a greater response in the group of patients with hematuria (73.3%). 61.3% of the patients perceived relief of symptoms after treatment according to the PGI-I scale. 88.9% maintained symptomatic improvement at the end of the follow-up. It was concluded that intravesical hyaluronic acid is a safe and effective treatment for filling symptoms, hematuria, and pain in patients with chronic cystopathies. Patients with radiotherapy-induced cystitis seem to especially benefit from treatment.

LOWER URINARY TRACT

[**SYSTEMATIC REVIEW AND META-ANALYSIS IDENTIFY SIGNIFICANT RELATIONSHIPS BETWEEN CLINICAL ANXIETY AND LOWER URINARY TRACT SYMPTOMS**](#)

Behrang Mahjani, Lotta Renström Koskela, Anita Batuuure, Christina Gustavsson Mahjani, Magdalena Janecka, Christina M Hultman, Abraham Reichenberg, Joseph D Buxbaum, Olof Akre, Dorothy E Grice. *Brain Behav*. 2021 Aug 17. doi: 10.1002/brb3.2268. Online ahead of print. PMID: 34402598 DOI: 10.1002/brb3.2268

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Lower urinary tract symptoms (LUTS), such as voiding symptoms, overactive bladder, and interstitial cystitis, and anxiety disorders are often comorbid conditions in patients. However, the existing evidence regarding the rates and nature of the co-occurrence of these conditions has not been systematically evaluated. The aim of this study from the USA was to examine these relationships. The authors conducted a systematic review and meta-analysis to examine the relationship between LUTS and anxiety. They identified 814 articles, of which 94 fulfilled inclusion criteria, and 23 had sufficient data for meta-analysis. The odds ratio (OR) for clinically significant anxiety among individuals with LUTS was 2.87. The OR for LUTS among individuals with clinically significant anxiety was 2.87, although very few studies examined this relationship. A large value of I² index suggests high heterogeneity between studies. The results demonstrate a significant association between clinically significant anxiety and LUTS in both females and males. There were limited studies on younger individuals and on individuals ascertained for clinically significant anxiety, which should motivate further study in these areas. Understanding the co-occurrence of these conditions will lead to better prevention and interventions to ameliorate the progression of the symptoms and improve the quality of life. A thorough assessment of anxiety may provide more optimal care for LUTS patients.

[**FEMALE CHRONIC POSTERIOR URETHRITIS IS UNDERESTIMATED IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS**](#)

Juanjuan Xie, Xin Li, Yufang Lü, Caisheng Huang, Xinyang Long, Yong Liu, Huaxiang Lu, Jianhua Long, Bo Chen, Zhigang Luo, Zengnan Mo. *Transl Androl Urol*. 2021 Aug;10(8):3456-3464. doi: 10.21037/tau-21-550. PMID: 34532270 PMCID: PMC8421815 DOI: 10.21037/tau-21-550

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As one of the causes of urethral symptoms, female chronic posterior urethritis is a common and distressing disease; however, it is often neglected and misdiagnosed as overactive bladder (OAB) or interstitial cystitis/bladder pain syndrome (IC/BPS). Currently, little is known about the urothelium and lamina propria of the bladder neck and proximal urethra. Thus, identifying urethral lesions is necessary for the diagnosis and

treatment of female chronic posterior urethritis. Transurethral electroresection is an effective and safe approach for treating female chronic posterior urethritis. This study from China sought to determine if urethral lesions are necessary for the diagnosis and treatment of female chronic posterior urethritis and evaluate the efficacy and safety of the transurethral electroresection of mucosa and submucosa in treating female chronic posterior urethritis. A single-center, retrospective, observational study was conducted at a teaching and referral hospital. A total of 147 female patients who had been diagnosed with chronic papillary urethritis underwent transurethral electroresection between 2015 and 2018. Each patient underwent a follow-up examination. A chart review was also performed. Patients had a mean age of 54 years (range, 23-82 years), and the average follow-up period was 54.8 months (range, 6-600 months). Urinary frequency and urgency (51.7%) were the most common clinical manifestations of chronic posterior urethritis. Forty-two-point two percent of patients had positive urine culture results, most commonly with *Mycoplasma genitalium*. The cystoscopic findings revealed that chronic posterior urethritis has tuft-like, pseudopodia-like, finger-like, and follicular-like polyps and villi, and a pebble-like appearance with mucosal hyperemia. The success rate of the transurethral electroresection was 88.6%, and patients showed no apparent or serious complications. This study showed that female chronic posterior urethritis is a cause that contributes to LUT symptoms. Its characteristic cystoscopic appearance and biopsy play a vital role in its diagnosis. The transurethral electroresection of urethral lesions is simple, effective, and minimally invasive without any apparent complications.

FEMALE UROLOGY

[WOMEN DOCTORS IN FEMALE UROLOGY: CURRENT STATUS AND IMPLICATIONS FOR FUTURE WORKFORCE](#)

Athina Pirpiris, Garson Chan, Helen E O'Connell, Johan Gani. *BJU Int.* 2021 Oct;128 Suppl 1:33-39. doi: 10.1111/bju.15546. Epub 2021 Aug 2. PMID: 34258849 DOI: 10.1111/bju.15546

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The purpose of this interesting study from Australia was to objectively determine the percentage of female trainees and consultants who are interested in their career being focused on female urology (FU) in order to facilitate the improved planning for the future of this sub-specialty. This was an international cross-sectional study spanning 1 year, from December 2018 to December 2019. An anonymous, voluntary survey was generated using the online survey generator Survey monkey®. The survey was sent to urology consultants and trainees who were female from Australia, New Zealand, and Canada. The total response rate to the survey was 61%. Up to 50% of female consultants and trainees selected a career in FU due to their gender, but up to 75% of respondents were also interested in FU of their own accord. Common concerns held by a majority of respondents included both the medical community's and the public's lack of awareness of FU as a component of urological expertise. Despite these concerns, most of the trainees were not concerned regarding their future work opportunities in FU, and many had intentions to pursue a fellowship in FU. It was concluded that female urology is an increasingly popular sub-specialisation of urology, given the steady increase in the intake of female trainees. Similar trends were identified internationally. Urology training in this area will need to continue to increase the community's and the primary health care referrer's awareness in order to ensure the continued success and growth of the sub-specialty.

UROBIOME / MICROBIOME

[FORMING CONSENSUS TO ADVANCE UROBIOME RESEARCH](#)

Linda Brubaker, Jean-Philippe F Gourdine, Nazema Y Siddiqui, Amanda Holland, Thomas Halverson, Roberto Limeria, David Pride, Lenore Ackerman, Catherine S Forster, Kristin M Jacobs, Krystal J Thomas-White, Catherine Putonti, Qunfeng Dong, Michael Weinstein, Emily S Lukacz, Lisa Karstens Alan J Wolfe. *mSystems.* 2021 Aug 31;6(4):e0137120. doi: 10.1128/mSystems.01371-20. Epub 2021 Jul 20. PMID: 34282932 PMCID: PMC8409733 DOI: 10.1128/mSystems.01371-20

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Urobiome research has the potential to advance the understanding of a wide range of diseases, including lower urinary tract symptoms and kidney disease. Many scientific areas have benefited from early research method consensus to facilitate the greater, common good. This consensus document, developed by a group of expert investigators currently engaged in urobiome research (UROBIOME 2020 conference participants), aims to promote standardization and advances in this field by the adoption of common core research practices. They propose a standardized nomenclature as well as considerations for specimen collection, preservation, storage, and processing. Best practices for urobiome study design include our proposal for standard metadata elements as part of core metadata collection. Although it is impractical to follow fixed analytical procedures when

analyzing urobiome data, they propose guidelines to document and report data originating from urobiome studies. They offer this first consensus document with every expectation of subsequent revision as this field progresses.

THE HUMAN UROBIOME

L Brubaker, C Putonti, Q Dong, A J Wolfe. Mamm Genome. 2021 Aug;32(4):232-238. doi: 10.1007/s00335-021-09862-8. Epub 2021 Mar 2. PMID: 33651197 DOI: 10.1007/s00335-021-09862-8

Traditionally, the healthy urinary bladder has been considered to be sterile. Several teams have used metagenomic (DNA-dependent) and metaculturomic (culture-dependent) methods to debunk this longstanding dogma. In fact, resident microbial communities (urobiome) have been detected in both adult females and males. Although the field is young, several observations have been made. For example, the urobiome differs between men and women, likely due to anatomical and hormonal differences. Importantly, the urobiome has been associated with a variety of lower urinary tract disorders, including overactive bladder and post-operative urinary tract infection, raising the possibility that clinicians might one day treat symptoms by modifying the urobiome instead of killing the suspected uropathogen. Little is known concerning the relationship between the urobiome and host genetics; so far, only a single paper has reported such a study. However, major efforts have gone into understanding the genomics of the urobiome itself, a process facilitated by the fact that many urobiome studies have used metaculturomic methods to detect and identify microbes. In this narrative review, the authors introduce the urobiome with separate sections on the female and male urobiomes, discuss challenges specific to the urobiome, describe newly discovered associations between the urobiome and lower urinary tract symptoms, and highlight the one study that has attempted to relate host genetics and the urobiome. They finish with a section on how metagenomic surveys and whole genome sequencing of bacterial isolates are improving our understanding of the urobiome and its relationship to lower urinary tract health and disorders.

COMBINED SIGNATURE OF THE URINARY MICROBIOME AND METABOLOME IN PATIENTS WITH INTERSTITIAL CYSTITIS

Hwei Xu, Nebiyu Elias Tamrat, Jie Gao, Jie Xu, Yiduo Zhou, Sicong Zhang, Zhengsen Chen, Yunpeng Shao, Liucheng Ding, Baixin Shen, Zhongqing Wei. Front Cell Infect Microbiol. 2021 Aug 30;11:711746. doi: 10.3389/fcimb.2021.711746. eCollection 2021. PMID: 34527602 PMCID: PMC8436771 DOI: 10.3389/fcimb.2021.711746

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Interstitial cystitis (IC) is a clinical syndrome characterized by frequency, urgency, and bladder pain or pelvic pain; however, the underlying pathophysiological mechanisms and diagnostic markers are unknown. In this study from China, microbiome and metabolome analysis were used to explain the urine signatures of IC patients. Urine samples from 20 IC patients and 22 control groups were analyzed by using 16S rRNA sequence and liquid chromatography coupled with mass spectrometry. Four opportunistic pathogen genera, including *Serratia*, *Brevibacterium*, *Porphyromonas*, and *Citrobacter*, were significantly upregulated in IC group. The altered metabolite signatures of the metabolome may be related to sphingosine metabolism, amino acid metabolism, and fatty acid biosynthesis. Meanwhile, the associations were observed between different metabolites and microbiomes of IC. The present study suggests that the combined signatures of IC in urine microbiome and metabolome may become its prospective diagnostic markers.

THE BLADDER MICROBIOME AND INTERSTITIAL CYSTITIS: IS THERE A CONNECTION?

Melinda G Abernethy, Angie Tsuei. Curr Opin Obstet Gynecol. 2021 Sep 1. doi: 10.1097/GCO.0000000000000747. Online ahead of print. PMID: 34475365 DOI: 10.1097/GCO.0000000000000747

Interstitial cystitis/painful bladder syndrome (PBS) is a debilitating condition, the etiology of which remains unclear and for which there are variable and often unsatisfactory treatment options. Within the last decade, evolving knowledge regarding the presence and role of the urinary microbiome has led to investigations regarding its impact on symptoms and severity of interstitial cystitis/PBS. Since 2017, five studies have investigated differences between the microbiome of female patients with interstitial cystitis/PBS to asymptomatic controls. While varied in methodology, specifically with regard to urine collection processing and microbial detection, the majority of studies (4/5) found no association between urinary microbiota and interstitial cystitis/PBS. Research regarding the role of the urinary microbiome and lower urinary tract function and dysfunction, including interstitial cystitis/BPS, remains in preliminary stages. While data regarding the role of lactobacillus in lower urinary tract homeostasis is inconclusive, further research is warranted.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

[PENTOSAN ASSOCIATED RETINAL PIGMENTARY CHANGES: FDA'S PERSPECTIVE ON AN EMERGING POSTMARKETING SAFETY FINDING](#)

Allison Lardieri, Karen Konkel, Lynda McCulley, S Christopher Jones, David Moeny, Christine Nguyen, Catherine Sewell, Wiley Chambers, Adebola Ajao. *Int Urogynecol J.* 2021 Sep 10. doi: 10.1007/s00192-021-04970-0. Online ahead of print. PMID: 34505923 DOI: 10.1007/s00192-021-04970-0

Recent publications describe pigmentary changes in the retina associated with the use of pentosan polysulfate sodium, the only FDA-approved oral agent for relief of bladder pain or discomfort associated with interstitial cystitis. To evaluate this association, the authors reviewed data from the FDA Adverse Event Reporting System and published case reports and observational studies. They found that the totality of clinical and epidemiology evidence does not resolve the question of causation between pentosan use and retinal pigmentary changes; however, several elements support a potential association. Here, they provide their perspective on the available evidence the agency weighed when retinal pigmentary changes were added to pentosan labelling. It is important for urogynecologists prescribing pentosan to be aware of this potential association and be vigilant about assessing eye health in pentosan users.

[MACULAR FINDINGS OF PATIENTS ON PENTOSAN POLYSULFATE SODIUM](#)

Barton L Blackorby, Himanshu Banda, Bradley T Smith, Gaurav K Shah. *Mil Med.* 2021 Jul 23;usab301. doi: 10.1093/milmed/usab301. Online ahead of print. PMID: 34296258 DOI: 10.1093/milmed/usab301

In 2018, a unique maculopathy associated with chronic pentosan polysulfate sodium (PPS) use for the treatment of interstitial cystitis (IC) was described, where the authors detailed macular retinal pigment epithelial abnormalities in six patients. In this paper from the USA, a retrospective study of a larger patient pool at one large tertiary retina practice was undertaken to evaluate patients taking PPS and their macular findings. A retrospective chart review was performed on all patients presenting to a single large retina practice between 2011 and 2019. Patient's macular diagnosis, findings, optical coherence tomography scans, and macular auto-fluorescent scans were assessed. This project was Institutional Review Board (IRB) approved by the St Luke's Hospital IRB board (St Louis, MO, USA). Fifty-five patients were identified as taking PPS for IC. Fifty-three patients were found to have a diagnosis consistent with changes attributable to known macular diseases to include macular degeneration and pattern dystrophies. Two (4%) of fifty-five patients had macular findings suggestive of PPS toxicity. The first was a 58-year-old female with subtle retinal pigment epithelium (RPE) deposits on optical coherence tomography that exhibited hyper-autofluorescence. The second was a 72-year-old female with 14 years of PPS use who exhibited RPE excrescences and parafoveal areas of atrophy. Pentosan polysulfate sodium may be the cause of macular findings in a small percentage of patients referred to a tertiary retina practice. Although causation of macular changes with PPS use has yet to be elucidated, clinicians should be aware of this possibility when assessing patients with atypical macular findings. Future longitudinal studies are necessary to evaluate a definitive relationship. This paper should remind all clinicians of the importance of a throughout review of the patient's medication list as novel toxicities may become apparent years after initial FDA trials. The strength of this study is the larger patient population compared to earlier studies, and the main weaknesses include the retrospective nature of the study, lack of family and genetic testing, and lack of multimodal imaging for all patients.

[SAFETY AND EFFICACY OF PENTOSAN POLYSULFATE IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY](#)

George Kasyan, Yury Kupriyanov, Alexander Karasev, Kirill Baibarin, Dmitry Pushkar. *Cent European J Urol.* 2021;74(2):201-207. doi: 10.5173/cej.2021.0340.R1. Epub 2021 May 7. PMID: 34336239 PMCID: PMC8318027 DOI: 10.5173/cej.2021.0340.R1

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Bladder pain syndrome/interstitial cystitis (BPS/IC) is a condition characterized by urgency, frequency and/or pelvic pain. The disease occurs mainly in women. BPS/IC can be severe enough to have a significant impact on patients' quality of life, but it can also be associated with moderate symptoms that are equally debilitating. The aim of this article was to evaluate the possibility of the use of pentosan polysulfate sodium in patients in the complex treatment of BPS/IC. A multicenter, double-blind, placebo-controlled, randomized study was conducted in parallel groups in 7 Russian medical centers. Efficacy and safety have been established as the main criteria. A total of 93 patients were screened. Statistical analysis was performed. It has been shown that pentosan therapy

is more effective than in the placebo. Average change in the number of points on the scale O'Leary-Santa Interstitial Cystitis Symptom Index compared to baseline data in the pentosan group 4.93 ± 3.03 , in the placebo group 1.66 ± 3.19 , and the adverse events and safety of pentosan are comparable to the placebo group. The authors concluded that oral glycosaminoglycan (pentosan polysulfate sodium) is an effective and safe drug and should be included in the complex treatment of patients with BPS/IC.

[\[ORAL THERAPY FOR INTERSTITIAL CYSTITIS: PENTOSAN POLYSULFATE SODIUM\]](#)

[Article in German]

Andreas Wiedemann. *Aktuelle Urol.* 2021 Sep 28. doi: 10.1055/a-1629-0199. Online ahead of print. PMID: 34583396 DOI: 10.1055/a-1629-0199

It is currently assumed that interstitial cystitis/bladder pain syndrome is caused by damage to the glycosaminoglycane layer on the urothelium of the urinary bladder. This layer can be repaired by oral therapy with pentosan polysulfate sodium. The focus of this article is on the history of this drug, its efficacy, its valuation in guidelines and especially the possible correlation with maculopathy. PPS has a US and European approval for the therapy of IC characterised by glomerulations or a Hunner lesion detected by endoscopy and bladder distension. Its efficacy was proven in randomised trials. This led to a recommendation as a basic pharmaceutical therapy (in addition to behavioural intervention, dietary therapy or other drug treatments such as pain therapy). After a treatment period of six months, efficacy should be re-evaluated. Side-effects include mild haemodilution, nausea and loss of hair. Two publications of a US eye clinic have recently postulated a correlation between prolonged high-dose therapy with PPS and a special kind of maculopathy. Although this correlation was rejected in a large-scale health service study in Germany, a "red-hand-letter" led to the recommendation to perform an ophthalmologic examination before and during the treatment with PPS. Due to a pending litigation between payers and the distributor, PPS is currently out of trade in Germany. However, PPS can still be prescribed but must be imported from adjacent European countries. Unfortunately, these modalities have led to a significant undersupply of patients with IC/BPS. It is feared that this undersupply will increase further as the litigation is ongoing. Being the only causally acting compound in the therapy of IC/BPS, PPS has an exceptional status. Although an ongoing litigation is pending in Germany and the correlation with maculopathy is still unclear, PPS must remain part of the current and future therapy of IC/BPS.

COVID-19 AND LOWER URINARY TRACT

[LOWER URINARY TRACT SIGNS AND SYMPTOMS IN PATIENTS WITH COVID-19](#)

Aida Javan Balegh Marand, Christian Bach, Dick Janssen, John Heesakkers, Morteza Ghojzadeh, Thomas Alexander Vögeli, Hanieh Salehi-Pourmehr, Hadi Mostafae, Sakineh Hajebrahimi, Mohammad Sajjad Rahnama'i. *BMC Infect Dis.* 2021 Jul 26;21(1):706. doi: 10.1186/s12879-021-06394-z. PMID: 34311703 DOI: 10.1186/s12879-021-06394-z

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The type of pneumonia that is caused by the new coronavirus (SARS-CoV-2) has spread across the world in a pandemic. It is not clear if COVID-19 patients have any lower urinary tract signs or symptoms. The effect of COVID-19 on lower urinary tract function was studied in a prospective multi-centre, observational study including 238 patients who were admitted with symptoms caused by COVID-19 to the university hospital of Aachen in Germany and Tabriz in Iran. None of the patients reported having any lower urinary tract symptoms. SARS-CoV-2 was found in the urine of 19% of the tested patients. The mortality rate in COVID-19 infected patients with microscopic haematuria together with white blood cells in their urine, was significantly increased from 48 to 61% in the Tabriz cohort and from 30 to 35% in the Aachen cohort. Furthermore, in the group of patients with SARS-CoV-2 urine PCR, the mortality rate rose from 30 to 58%. Patients admitted with COVID-19 did not report having any lower urinary tract symptoms, even those patients who had a positive Urine SARS-CoV-2 PCR. In addition, haematuria, WBC in urine as well as SARS-CoV-2 presence in urine, were found to be strong negative prognostic factors in admitted COVID-19 patients.

[IS CORONAVIRUS DISEASE 2019 ASSOCIATED WITH INDICATORS OF LONG-TERM BLADDER DYSFUNCTION?](#)

Blayne Welk, Lucie Richard, Emmanuel Braschi, Marcio A Averbek. *Neurourol Urodyn.* 2021 Jun;40(5):1200-1206. doi: 10.1002/nau.24682. Epub 2021 May 4. PMID: 33942372 PMCID: PMC8242545 DOI: 10.1002/nau.24682

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Early reports have suggested that coronavirus disease 2019 (COVID-19) can present with significant urinary frequency and nocturia, and that these symptoms correlate with markers of inflammation in the urine. The

authors evaluated surrogate markers of chronic urinary symptoms to determine if they were more frequent after COVID-19 infection. Routinely collected data from the province of Ontario was used to conduct a matched, retrospective cohort study. They identified patients 66 years of age or older who had a positive COVID-19 test between February and May 2020 and survived at least 2 months after their diagnosis. They matched them to two similar patients who did not have a positive COVID-19 test during the same time period. They measured the frequency of urology consultation, cystoscopy, and new prescriptions for overactive bladder medications during a subsequent 3-month period. Proportional hazard models were adjusted for any baseline differences between the groups. They matched 5617 patients with COVID-19 to 11,225 people who did not have COVID-19. The groups were similar, aside from a higher proportion of patients having hypertension and diabetes in the CoVID-19 cohort. There was no significantly increased hazard of new receipt of overactive bladder medication, urology consultation, or cystoscopy among patients who had COVID-19, compared to the matched cohort. They concluded that surrogate markers of potential bladder dysfunction were not significantly increased in the 2-5 months after COVID-19 infection.

CENTRAL PAIN SENSITIZATION

[EFFECTIVENESS OF ACCEPTANCE AND COMMITMENT THERAPY IN CENTRAL PAIN SENSITIZATION SYNDROMES: A SYSTEMATIC REVIEW](#)

Carmen M Galvez-Sánchez, Casandra I Montoro, María Moreno-Padilla, Gustavo A Reyes Del Paso, Pablo de la Caba. Review J Clin Med. 2021 Jun 19;10(12):2706. doi: 10.3390/jcm10122706. PMID: 34205244 PMCID: PMC8235706 DOI: 10.3390/jcm10122706

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Acceptance and commitment therapy (ACT) is considered by the American Psychological Association as an evidence-based treatment for a variety of disorders, including chronic pain. The main objective of the present systematic review was to determine the effectiveness of ACT in patients with central pain sensitization syndromes (CPSS). This systematic review was conducted according to the guidelines of the Cochrane Collaboration and PRISMA statements. The protocol was registered in advance in the Prospective Register of Systematic Reviews (PROSPERO) international database. The selected articles were evaluated using the Cochrane risk of bias (ROB) assessment tool. The PubMed, Scopus, and Web of Science databases were searched. The literature search identified 21 studies (including investigations of fibromyalgia syndrome, irritable bowel syndrome, and migraine) eligible for the systematic review. There were no studies regarding the effectiveness of ACT for chronic tension-type headache (CTTH), interstitial cystitis (IC), or temporomandibular disorder (TMD). The evaluation of ROB showed that 12 of the selected studies were of low quality, 5 were of moderate quality, and 4 were high quality. ACT reduces some clinical symptoms, such as anxiety, depression, and pain. This positive effect of ACT might be mediated by pain acceptance, psychological flexibility, optimism, self-efficacy, or adherence to values. ACT showed better results in comparison to non-intervention (e.g., "waiting list") conditions, as well as pharmacological and psychoeducational interventions. It is not entirely clear whether extended ACT treatments are more advantageous than briefer interventions. There are few studies about the effectiveness of ACT on CPSS. However, ACT seems to reduce subjective CPSS symptoms and improve the health-related quality of life of these patients. The absence of studies on the effectiveness of ACT in CTTH, IC, and TMD, indicate the pressing need for further ACT studies in these CPSS.

ORGAN CROSS SENSITIZATION

[ORGAN CROSS-SENSITIZATION MECHANISMS IN CHRONIC DISEASES RELATED TO THE GENITOURINARY TRACT](#)

Tsuyoshi Majima, Naoto Sassa. J Smooth Muscle Res. 2021;57(0):49-52. doi: 10.1540/jsmr.57.49. PMID: 34629366 DOI: 10.1540/jsmr.57.49

There are various refractory chronic inflammatory diseases related to the genitourinary tract, such as interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. It has been reported that in the general population these diseases are related to other chronic illnesses, such as irritable bowel syndrome or vulvodynia. Here, the authors from Japan review papers regarding pelvic organ cross-sensitization, a factor which is considered to contribute to these relationships. Several other researchers have also reported that noxious stimuli from a diseased pelvic organ are transmitted to an adjacent normal structure via shared sensory neural pathways at the prespinal, spinal, and supraspinal levels, resulting in functional changes in the adjacent normal structure. In conclusion, since there are few treatments to cure interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome completely, further studies regarding organ

cross-sensitization may provide new insights into the pathophysiology and treatment strategies for these diseases.

VULVODYNIA

VULVODYNIA - AN EVOLVING DISEASE

F Guidozzi, D Guidozzi. Climacteric. 2021 Aug 17;1-6. doi: 10.1080/13697137.2021.1956454. Online ahead of print. PMID: 34402359 DOI: 10.1080/13697137.2021.1956454

Vulvodynia is a common vulval pain syndrome that occurs most commonly in reproductive women of all ages. It can, in some cases, present for the first time after menopause. Up to about 15% of adult women have had symptoms of vulvodynia, with 4-5% currently symptomatic. Since there are no specific tests for diagnosis, vulvodynia is a diagnosis of exclusion. The condition is commonly associated with other chronic pain disorders and can be exceedingly debilitating, resulting in sexual dysfunction, severe depression and/or anxiety. It can significantly impair quality of life. Goals for long-term team approach management should be discussed with the patient at the commencement of each intervention as effectiveness of therapy is not assured. Currently, there is no intervention that effects cure in all individuals and a combination of pharmacological therapy, psychotherapy and physiotherapy, reserving surgery as a last-line option, is the best option for treatment. There are no long-term data on how long women will have symptoms and, if resolved, what provokes symptoms again in the future, whilst correlation between the etiology of vulvodynia and efficacy of treatment is not known.

VULVODYNIA - IT IS TIME TO ACCEPT A NEW UNDERSTANDING FROM A NEUROBIOLOGICAL PERSPECTIVE

Rafael Torres-Cueco, Francisco Nohales-Alfonso. Int J Environ Res Public Health. 2021 Jun 21;18(12):6639. doi: 10.3390/ijerph18126639. PMID: 34205495 PMCID: PMC8296499 DOI: 10.3390/ijerph18126639

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Vulvodynia is one of the most common causes of pain during sexual intercourse in premenopausal women. The burden of vulvodynia in a woman's life can be devastating due to its consequences in the couple's sexuality and intimacy, in activities of daily living, and psychological well-being. In recent decades, there has been considerable progress in the understanding of vulvar pain. The most significant change has been the differentiation of vulvar pain secondary to pathology or disease from vulvodynia. However, although it is currently proposed that vulvodynia should be considered as a primary chronic pain condition and, therefore, without an obvious identifiable cause, it is still believed that different inflammatory, genetic, hormonal, muscular factors, etc. may be involved in its development. Advances in pain neuroscience and the central sensitization paradigm have led to a new approach to vulvodynia from a neurobiological perspective. In this Spanish study, it is proposed that vulvodynia should be understood as complex pain without relevant nociception. Different clinical identifiers of vulvodynia are presented from a neurobiological and psychosocial perspective. In this case, strategies to modulate altered central pain processing is necessary, changing the patient's erroneous cognitions about their pain, and also reducing fear avoidance-behaviors and the disability of the patient.

PUDENDAL NERVE

INITIAL EXPERIENCE USING A NOVEL NERVE STIMULATOR FOR THE MANAGEMENT OF PUDENDAL NEURALGIA

Ly Hoang Roberts, Annah Vollstedt, Joshua Volin, Teresa McCartney, Kenneth M Peters. NeuroUrol Urodyn. 2021 Aug;40(6):1670-1677. doi: 10.1002/nau.24735. Epub 2021 Jun 30. PMID: 34196055 DOI: 10.1002/nau.24735

In patients with pudendal neuralgia, prior studies have shown efficacy in chronic stimulation with Interstim® (Medtronic, Inc.). This feasibility study reports on the initial experience of using a wireless system to power an implanted lead at the pudendal nerve, StimWave®, to treat pudendal neuralgia. Retrospective chart review identified patients with a lead placed at the pudendal nerve for neuralgia and powered wirelessly. Clinical outcomes were assessed at Postoperative visits and phone calls. Administered non-validated follow-up questionnaire evaluated the Global Response Assessment, percentage of pain improvement, satisfaction with device, and initial and current settings of the device (h/day of stimulation). Thirteen patients had the StimWave® lead placed at the pudendal nerve, 12 (92%) female and 1 (7.6%) male. Mean age was 50 years (range: 20-58). Failed prior therapies include medical therapy (100%), pelvic floor physical therapy (92%), pudendal nerve blocks (85%), pelvic floor muscle trigger point injections (69%), neuromodulation (30.7%), or surgeries for urogenital pain (23.1%). After the trial period, 10/13 (76.9%) had >50% improvement in pain with 6/13 (46.1%) reporting 100% pain improvement. Nine underwent permanent lead placement. At last postoperative visit (range, 6-83 days), 5/9 patients reported >50% pain improvement. Seven patients reached for phone calls (22-759 days) reported symptoms to be "markedly improved" (n = 2), "moderately improved" (n = 4), or "slightly improved" (n

= 1). At follow up, complications included lead migration (n = 2), broken wire (n = 1), or nonfunctioning antenna (n = 2). Complex patients with pudendal neuralgia may benefit from pudendal nerve stimulation via StimWave®.

PILOT STUDY: PUDENDAL NEUROMODULATION COMBINED WITH PUDENDAL NERVE RELEASE IN CASE OF CHRONIC PERINEAL PAIN SYNDROME. THE ENTRAMI TECHNIQUE: EARLY RESULTS

Katleen Jottard, Luc Bruyninx, Pierre Bonnet, Nathalie Mathieu, Stefan De Wachter. Int Urogynecol J. 2021 Oct;32(10):2765-2770. doi: 10.1007/s00192-020-04565-1. Epub 2020 Oct 13. PMID: 33048179 DOI: 10.1007/s00192-020-04565-1

Chronic perineal pain syndrome due to pudendal nerve impingement is difficult to diagnose and to treat. All the known treatment options leave room for improvement considering the outcome. Early neuromodulation of the pudendal nerve after its surgical release could improve outcomes. The aim of this study from Belgium was to evaluate the potential beneficial effect of pudendal neuromodulation combined with release surgery using the ENTRAMI technique (endoscopic transluteal minimally invasive technique). This was a single-center prospective descriptive study. Between March 2019 and March 2020, 16 patients (2 males, 14 females) were included. Data were collected at baseline and 1 month after surgery. Patients eligible for inclusion had chronic perineal pain for at least 3 months in the area served by the pudendal nerve. The authors combined pudendal nerve release with neuromodulation. At 1 month, the numeric pain rating scale (NPRS) dropped from 9.5 at baseline to 3.5 (p = 0.003). Seventy-six percent of patients showed a global impression of change (PGIC) of > 50% at 1 month, and optimal treatment response (PGIC ≥ 90%) was found in 41% of patients. The authors note that the drawback of their study was that it was not randomized or blinded. The peripheral nerve evaluation lead (PNE) used could only be implanted for 1 month because of infection risk and is also prone to dislocations and technical failures. Pudendal nerve liberation by the ENTRAMI technique combined with short-term pudendal neuromodulation seems feasible and promising in treating patients with chronic perineal pain.

PELVIC FLOOR

PELVIC FLOOR FUNCTION, DYSFUNCTION, AND TREATMENT

Jörgen Quaghebeur, Peter Petros, Jean-Jacques Wyndaele, Stefan De Wachter. Eur J Obstet Gynecol Reprod Biol. 2021 Aug 28;265:143-149. doi: 10.1016/j.ejogrb.2021.08.026. Online ahead of print. PMID: 34492609 DOI: 10.1016/j.ejogrb.2021.08.026

The pelvic floor functions as a holistic entity. The organs, bladder, bowel, smooth and striated muscles, nerves, ligaments and other connective tissues are directed cortically and reflexly from various levels of the nervous system. Such holistic integration is essential for the system's multiple functions, for example, pelvic girdle stability, continence, voiding/defecation, and sexuality. Pelvic floor dysfunction (PFD) is related to a variety of pelvic pain syndromes and organ problems of continence and evacuation. Prior to treatment, it is necessary to understand which part(s) of the system may be causing the dysfunction (s) of Chronic Pelvic Pain Syndrome (CPPS), pelvic girdle pain, sexual problems, Lower Urinary Tract Symptoms (LUTS), dysfunctional voiding, constipation, prolapse and incontinence. The interpretation of pelvic floor biomechanics is complex and involves multiple theories. Non-surgical treatment of PFD requires correct diagnosis and correctly supervised pelvic floor training. The aims of this review are to analyze pelvic function and dysfunction. Because it is a holistic and entirely anatomically based system, significant weight has been accorded to the Integral Theory's explanations of function and dysfunction.

THE INNERVATION OF THE BLADDER, THE PELVIC FLOOR, AND EMOTION: A REVIEW

Jörgen Quaghebeur, Peter Petros, Jean-Jacques Wyndaele, Stefan De Wachter. Auton Neurosci. 2021 Nov;235:102868. doi: 10.1016/j.autneu.2021.102868. Epub 2021 Aug 10. PMID: 34391125 DOI: 10.1016/j.autneu.2021.102868

The innervation of the pelvic region is complex and includes extensive neurologic pathways. The higher centres' organisation determining the pelvic floor and organs' function remains a challenge understanding the physiological and pain mechanisms. Psychological and emotional factors have a profound influence on the pelvic floor and organ dysfunction such as LUTS. LUTS are associated with stress, depression, and anxiety. Neuroception is a subconscious neuronal system for detecting threats and safety and might explain the permanent disturbance of higher brain centres maintaining functional urological and gastrointestinal disorders and sphincter dysfunction.

CHRONIC PELVIC PAIN

[A SYSTEMATIC REVIEW OF THE COST OF CHRONIC PELVIC PAIN IN WOMEN](#)

Ghi Huang, Ai-Lien Le, Yvette Goddard, Daniel James, Kednapa Thavorn, Magdalene Payne, Innie Chen. *J Obstet Gynaecol Can.* 2021 Sep 26;S1701-2163(21)00695-2. doi: 10.1016/j.jogc.2021.08.011. Online ahead of print. PMID: 34587539 DOI: 10.1016/j.jogc.2021.08.011

The purpose of this study from Canada was to systematically summarize evidence on the costs related to chronic pelvic pain (CPP) for women. Electronic databases (MEDLINE, EMBASE, PubMed, and Cochrane Library) were searched from 1990 to January 2021 and limited to only English and French studies. Of 1304 papers screened, 67 were screened in full-text, with a total of 13 studies included in final analysis. Studies focused on cost studies that estimated hospital cost or health system cost for pelvic pain, dysmenorrhea, dyspareunia, endometriosis with pain, interstitial cystitis or painful bladder syndrome were included. A standardized data extraction form was created to extract study setting, design, and population, patient demographics, study duration, reported costs of chronic pelvic pain components and amounts. Two independent reviewers completed the data extraction and discrepancies were resolved through discussion with third reviewer available. Estimated healthcare costs ranged from \$1,367 to \$7,043 per woman per year (USD). The prescription costs ranged from \$193 to \$2,457 per woman per year. Indirect costs ranged from \$4,216 to \$12,789 per woman per year. Combined costs ranged from \$1,820 to \$20,898 per woman per year. The yearly costs of CPP varied according to the country; yearly costs were estimated to be \$2.8 billion/year, ¥191,680 to ¥246,488 per woman per year, and \$16,970 to \$20,898 per woman per year in the US, Japan, and Australia respectively. The literature suggests that chronic pelvic pain represents a considerable economic burden on women and healthcare systems internationally, with indirect costs contributing a significant portion of total costs.

[NEUROMUSCULAR TREATMENT APPROACH FOR WOMEN WITH CHRONIC PELVIC PAIN SYNDROME IMPROVING PELVIC PAIN AND FUNCTIONALITY](#)

Soha Patil, Gabrielle Daniel, Rakhi Vyas, Yogita Tailor, Melanie Howell, Tayyaba Ahmed, Christian Reutter, Allyson Shrikhande. *Neurourol Urodyn.* 2021 Sep 16. doi: 10.1002/nau.24799. Online ahead of print. PMID: 34529875 DOI: 10.1002/nau.24799

The purpose of this study from the USA was to report the effects of treating underlying myofascial dysfunction and neuropathic pain in women with chronic pelvic pain syndrome (CPPS). Retrospective longitudinal study of 186 women with CPPS treated with ultrasound-guided peripheral nerve blocks and trigger point injections to pelvic floor muscles alongside pelvic floor physical therapy once weekly for 6 weeks in an outpatient setting. Visual Analogue Scale (VAS) and Functional Pelvic Pain Scale (FPPS) questionnaires quantified pain and function in the pelvis. Working, intercourse, sleeping, walking, running, lifting, bladder, and bowel were the function categories. Statistical significance was established by p value less than .05 in paired two-sample t-test. VAS improved by 2.14 where average VAS before treatment was 6.61 (standard deviation [SD] 2.45; p < .05, 95% confidence interval [CI] = 6.26-6.96) and average VAS after treatment was 4.47 (SD 2.71; p < .05, 95% CI = 4.08-4.86). Total FPPS decreased by 3.38 from 11.26 (SD 6.51; p < .05, 95% CI = 10.32-12.19) before treatment to 7.88 (SD 6.22; p < .05, 95% CI = 6.99-8.78) after treatment. Working, intercourse, and sleeping accounted for the highest statistically significant improvement. Findings support the success of the comprehensive treatment protocol. Patients who had persistent symptoms after a full course of pelvic floor physical therapy experienced improvements in pain levels and function once it was combined with ultrasound-guided nerve blocks and trigger point injections, interactively treating underlying neuromuscular dysfunction.

AUTOIMMUNE DISEASES AND IC/BPS

[RISK OF AUTOIMMUNE DISEASES IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A NATIONWIDE POPULATION-BASED STUDY IN TAIWAN](#)

Hann-Ziong Yueh, Min-Hsin Yang, Jing-Yang Huang, James Cheng-Chung Wei. *Front Med (Lausanne).* 2021 Sep 20;8:747098. doi: 10.3389/fmed.2021.747098. eCollection 2021. PMID: 34616760 PMCID: PMC8488113 DOI: 10.3389/fmed.2021.747098

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While the association between autoimmune diseases (ADs) and interstitial cystitis/bladder pain syndrome (IC/BPS) has long been investigated, the lack of comprehensive descriptions of patients in the literature has made comparison and evaluation impossible. Yueh and colleagues from investigated the risk of systemic ADs in patients with IC/BPS in Taiwan using a population-based administrative database. This study evaluated 1,095 patients newly diagnosed with IC/BPS between 2000 and 2013, using data from Taiwan's National Health Insurance Research Database. These patients were randomly matched by demographic characteristics with a comparison cohort of individuals without IC/BPS at a ratio of 1:20. Cox proportional hazards regression analysis

was used to analyze the risk of ADs, adjusting for age, sex, urbanization, length of hospital stay, and comorbidities adjustment. Sensitivity analysis by propensity score was used to adjust for confounding factors. Results: The adjusted Hazard Ratio (aHR) of ADs for IC/BPS patients was 1.409. The subgroup analysis indicated that female or 45-60 years of age had a greater risk of ADs. Furthermore, the subgroup analysis of primary outcomes indicated that IC/BPS had greater incidence with Hashimoto's thyroiditis, ankylosing spondylitis, rheumatoid arthritis, and Sjogren's syndrome.

FIBROMYALGIA

[CENTRAL SENSITISATION IN CHRONIC FATIGUE SYNDROME AND FIBROMYALGIA; A CASE CONTROL STUDY](#)

Julius H Bourke, Theresa Wodehouse, Lucy V Clark, Elena Constantinou, Bruce L Kidd, Richard Langford, Vivek Mehta, Peter D White. *J Psychosom Res.* 2021 Sep 21;150:110624. doi: 10.1016/j.jpsychores.2021.110624. Online ahead of print. PMID: 34600309 DOI: 10.1016/j.jpsychores.2021.110624

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are both complex conditions that are challenging to treat. This may be related to an incomplete understanding of their pathophysiology, itself obfuscated by their heterogeneity. The symptomatic overlap between them and their common comorbidity suggests a shared vulnerability, which might be explained by central sensitisation. 19 CFS cases, 19 FM cases and 20 age and sex matched healthy controls (HC) were recruited primarily from secondary care clinics in London. Those with other pain disorders, psychiatric diagnoses and those taking centrally acting or opiate medications were excluded. Participants were asked to abstain from alcohol and over the counter analgesia 48 h prior to assessment by static and dynamic quantitative sensory tests, including measures of temporal summation (TS) and conditioned pain modulation (CPM). CS, as defined by the presence of both enhanced TS and inefficient CPM, was present in 16 (84%) CFS cases, 18 (95%) FM cases, and none of the HC. Pressure pain thresholds were lower in CFS and FM cases compared to HC. FM cases differed from HC in cold-induced vs HC = 14.2 °C and heat-induced vs HC = 45.3 °C pain thresholds, where CFS cases did not. Central sensitisation may be a common endophenotype in chronic fatigue syndrome and fibromyalgia. Further research should address whether central sensitisation is a cause or effect of these disorders.

[WHICH SYMPTOMS BEST DISTINGUISH FIBROMYALGIA PATIENTS FROM THOSE WITH OTHER CHRONIC PAIN DISORDERS?](#)

Robert M Bennett, Kim D Jones, Jonathan H Aebischer, Amanda W St John, Ronald Friend. *J Eval Clin Pract.* 2021 Sep 27. doi: 10.1111/jep.13615. Online ahead of print. PMID: 34580965 DOI: 10.1111/jep.13615

The primary purpose of this study from the USA was to test both classic and novel FM pain and non-pain symptoms to determine their practical efficacy in aiding clinicians to distinguish FM pain from other chronic pain disorders. 158 pain patients from two primary care clinics were evaluated with history, physical exam, chart review, and a questionnaire containing 26 exploratory symptoms (10 from the Symptom Impact Questionnaire (SIQR) and 16 from the FM literature)). The symptoms were rated on a 0-10 VAS for severity by those patients reporting pain over the past week. Somers' D and mean severity differences between FM and chronic pain patients without FM were used to rank the discriminatory and diagnostic contributions of symptoms. Fifty patients (14.2%) carried a chart diagnosis of FM, 108 (30.7%) had pain but not FM, and 192 (54.5%) who had neither pain nor FM. Comparing means between the two pain groups, the 5 best differentiating symptoms were: a persistent deep aching over most of my body, poor balance, environmental sensitivity, tenderness to touch and pain after exercise. Notably, VAS pain though significantly higher for FM was least discriminatory. The five best symptoms generated a ROC = 0.85 and Somers' D = 0.69, an accuracy of 81%, and an odd's ratio of 14.4. The authors suggest that clinicians may be well-served to consider symptoms in addition to those contained in current diagnostic criteria when recognizing FM in their chronic pain patients.

SJÖGREN'S SYNDROME

[AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN PRIMARY SJÖGREN'S SYNDROME](#)

Kristen Davies, Wan-Fai Ng. *Front Immunol.* 2021 Jul 26;12:702505. doi: 10.3389/fimmu.2021.702505. eCollection 2021. PMID: 34381453 PMCID: PMC8350514 DOI: 10.3389/fimmu.2021.702505

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Primary Sjögren's syndrome (pSS) is an autoimmune disease which primarily affects the exocrine glands, but can also affect other organs, including the nervous system. Many studies have reported evidence of autonomic nervous system (ANS) dysfunction in pSS which may contribute to a wide range of symptoms and functional burden. Symptoms of ANS dysfunction are common and widespread among patients with pSS and are associated

with other features of the disease, particularly fatigue. Accumulating data on the inter-relationship between the ANS and the immune system via the vagus nerve have been reported. Vagus nerve stimulation (VNS) has also been associated with improvement in fatigue in patients with pSS. Taken together, these data suggest that the ANS may be a potential treatment target for pSS, in particularly those with fatigue being a predominant symptom. Future research to dissect the link between the ANS, immune dysregulation and clinical manifestations in pSS and to evaluate the potential of VNS as a therapy for pSS is warranted.

[A NEW MOLECULAR CLASSIFICATION TO DRIVE PRECISION TREATMENT STRATEGIES IN PRIMARY SJÖGREN'S SYNDROME](#)

Perrine Soret, Christelle Le Dantec, Emiko Desvaux, Nathan Foulquier, Bastien Chassagnol, Sandra Hubert, Christophe Jamin, et al. Nat Commun. 2021 Jun 10;12(1):3523. doi: 10.1038/s41467-021-23472-7. PMID: 34112769 PMCID: PMC8192578 DOI: 10.1038/s41467-021-23472-7

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There is currently no approved treatment for primary Sjögren's syndrome, a disease that primarily affects adult women. The difficulty in developing effective therapies is -in part- because of the heterogeneity in the clinical manifestation and pathophysiology of the disease. Finding common molecular signatures among patient subgroups could improve understanding of disease etiology and facilitate the development of targeted therapeutics. Here, the authors report, in a cross-sectional cohort, a molecular classification scheme for Sjögren's syndrome patients based on the multi-omic profiling of whole blood samples from a European cohort of over 300 patients, and a similar number of age and gender-matched healthy volunteers. Using transcriptomic, genomic, epigenetic, cytokine expression and flow cytometry data, combined with clinical parameters, they identify four groups of patients with distinct patterns of immune dysregulation. The biomarkers they identify can be used by machine learning classifiers to sort future patients into subgroups, allowing the re-evaluation of response to treatments in clinical trials.

[DISTAL RENAL TUBULAR ACIDOSIS: A SYSTEMATIC APPROACH FROM DIAGNOSIS TO TREATMENT](#)

Sabrina Giglio, Giovanni Montini, Francesco Trepiccione, Giovanni Gambaro, Francesco Emma. J Nephrol. 2021 Mar 26. doi: 10.1007/s40620-021-01032-y. Online ahead of print. PMID: 33770395 DOI: 10.1007/s40620-021-01032-y

Renal tubular acidosis (RTA) comprises a group of disorders in which excretion of hydrogen ions or reabsorption of filtered HCO₃ is impaired, leading to chronic metabolic acidosis with normal anion gap. In the current review, the focus is placed on the most common type of RTA, Type 1 RTA or Distal RTA (dRTA), which is a rare chronic genetic disorder characterized by an inability of the distal nephron to secrete hydrogen ions in the presence of metabolic acidosis. Over the years, knowledge of the molecular mechanisms behind acid secretion has improved, thereby greatly helping the diagnosis of dRTA. The primary or inherited form of dRTA is mostly diagnosed in infancy, childhood, or young adulthood, while the acquired secondary form, as a consequence of other disorders or medications, can happen at any age, although it is more commonly seen in adults. dRTA is not as "benign" as previously assumed, and can have several, highly variable long-term consequences. The present review indeed reports and summarizes both clinical symptoms and diagnosis, long-term outcomes, genetic inheritance, epidemiology and current treatment options, with the aim of shedding more light onto this rare disorder. Being a chronic condition, dRTA also deserves attention in the transition between pediatric and adult nephrology care, and as a rare disease it has a place in the European and Italian rare nephrological diseases network.

[EPIDEMIOLOGY OF DISTAL RENAL TUBULAR ACIDOSIS: A STUDY USING LINKED UK PRIMARY CARE AND HOSPITAL DATA](#)

Florence Bianic, Florent Guelfucci, Ludovic Robin, Catherine Martre, David Game, Detlef Bockenhauer. Nephron. 2021 Jul 1;1-10. doi: 10.1159/000516876. Online ahead of print. PMID: 34198293 DOI: 10.1159/000516876

Distal renal tubular acidosis (dRTA), or RTA type 1, a rare inherited or acquired disease, is a disorder of the distal tubule caused by impaired urinary acid secretion. Due to associated conditions and nonspecific symptoms, dRTA may go undetected. This analysis aims to estimate the prevalence of dRTA in the UK Clinical Practice Research Datalink (CPRD) databases and extrapolate it to European Union Five (EU5) populations. A retrospective analysis was conducted using the CPRD GOLD database and linked Hospital Episode Statistics (HES) data to identify diagnosed and potentially undiagnosed or miscoded patients (suspected patients). Patients' records with at least one diagnosis code for dRTA, RTA, specific autoimmune diseases, or renal disorders recorded between January 1987 and November 2017 were obtained and analyzed. An algorithm was developed to detect potentially

undiagnosed/miscoded dRTA, based on associated conditions and prescriptions. A total of 216 patients with diagnosis of RTA or dRTA were identified (with 98 linked to hospital data), and 447 patients were identified as having suspected dRTA. dRTA prevalence for 2017 was estimated between 0.46 (recorded cases, of which 22.1% were considered primary) and 1.60 when including suspected cases (7.6% primary) per 10,000 people. Prescription and clinical records of diagnosed patients revealed a wide range of comorbidities and a need for pharmacological treatment to manage associated symptoms. The study provides new estimates of dRTA prevalence in Europe and suggests that patients may often be unreported or miscoded, potentially confounding appropriate disease management.

Editorial note: dRTA can occur with Sjögren's syndrome and may therefore potentially occur with IC/BPS patients who also have Sjögren's syndrome. Hence the two abstracts above.

MICROBIOTA & IBS

MICROBIOTA AND THE IRRITABLE BOWEL SYNDROME

Cristina M Sabo, Dan L Dumitrascu. Minerva Gastroenterol (Torino). 2021 Sep 13. doi: 10.23736/S2724-5985.21.02923-5. Online ahead of print. PMID: 34515452 DOI: 10.23736/S2724-5985.21.02923-5

Gut microbiota plays a vital role in human health. The number of microorganisms inhabiting the gastrointestinal (GI) tract has been estimated to exceed 10¹³. The dominant genera in the human intestine are Firmicutes (more than 180 species of Lactobacillus), Actinobacteria (among others the Bifidobacteriae), Bacteroidetes (the most important is *B. fragilis*) and Proteobacteria (*E. coli*, Salmonella, Yersinia, Shigella, Vibrio, Haemophilus, etc.), but the composition of the flora varies individually, as well as in relation to factors such as host genetics, stress, diet, antibiotics and early childhood experiences. Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders (FGIDs), which has now been renamed disorders of gut-brain interaction, which affect a large number of people worldwide. It is characterized by abdominal pain and altered bowel habits in the absence of obvious anatomic or physiologic abnormalities. It poses a negative economic impact to the global health care system in addition to reducing the quality of life in patients. The pathophysiology of IBS is not fully understood. In IBS subjects gut microbiota relative to healthy controls was observed with an increase in Enterobacteriaceae, Ruminococcus, Clostridium, Dorea species and a decrease of Lactobacillus, Bifidobacterium, and Faecalibacterium species. IBS with diarrhea predominance (IBS-D) IBS with mixed bowel habits (IBS-M) share similarities in the microbial profile. Recent studies suggest that perturbations within "brain-gut-microbiota" axis may lead to IBS development. The aim of this review from Romania was to highlight the potential role of gut microbiota on pathophysiological mechanisms underlying IBS.

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