

# International Painful Bladder Foundation

*The IPBF is a voluntary non-profit organization for interstitial cystitis/bladder pain syndrome/hypersensitive bladder*  
[www.painful-bladder.org](http://www.painful-bladder.org)

## **IPBF e-Newsletter and Research Update Issue 59, June 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:

- COVID-19 impact continues
- Overview of upcoming events
- Online Meeting of Patient Advocates
- New books, publications
- New Guidelines and Classifications
- Patient resources
- How to use the catheter-replacing adapter for bladder instillations
- Research Consortia
- COVID-19: Information About COVID-19 And Useful Online Resources
- RESEARCH UPDATE
- Donations & Sponsoring

## **COVID-19 IMPACT CONTINUES**

The impact of Covid-19 continues to affect all aspects of our lives. Vaccination has not progressed sufficiently fast in many countries and yet travel rules are being relaxed for the summer holidays. The situation is very unclear with some authorities predicting another wave in the autumn. We therefore have to be prepared for continuing virtual conferences or at best hybrid meetings (part virtual, part face-to-face). Virtual conferences mean that programmes have to be shorter and more compact than those of a face-to-face meeting and this has meant that IC/BPS has unfortunately either been ignored or reduced to a quick 5 minutes or wrapped up invisibly in a framework of chronic pelvic pain! While virtual meeting software has in general improved, conference software has sometimes led to opening day crashes. In addition to numerous webinars, many societies now also have podcasts. All of these developments are good news for those who cannot travel to conferences due to health, work commitments or lack of funds. At least something positive has emerged from the COVID pandemic!

## **OVERVIEW OF UPCOMING EVENTS:**

Many conferences in our field that were rescheduled for this year have now been cancelled as face-to-face meetings and are now virtual, even though some are still optimistically planned as face-to-face or hybrid meetings. They include the following events, but with so much uncertainty regarding the COVID-19 crisis it is wise to keep checking the relevant websites for updates.

### **36<sup>th</sup> EAU ANNUAL CONGRESS 2021 NOW VIRTUAL**

The European Association of Urology (EAU) decided that with too many uncertainties about the current situation, it can best serve members and congress delegates with an online-only EAU21 Virtual Congress. The EAU21 Virtual congress will take place from 8- 12 July 2021. The congress website will be continually updated over the coming weeks.  
[www.eau2021.org](http://www.eau2021.org)

### **AMERICAN UROLOGICAL ASSOCIATION – AUA ANNUAL MEETING 2021**

AUA2021 is offering extended programming this year. Virtual programs will be available from May to August, providing education on timely topics: Summer School: June – August; Las Vegas: September 10 – 13: this is currently planned as a face-to-face meeting. Further information: [www.aa2021.org/](http://www.aa2021.org/)

### 51<sup>st</sup> ICS ANNUAL SCIENTIFIC MEETING 2021 ONLINE

Join ICS 2021 Online, 14-17 October. 12 hours of live streamed content each day – join the sessions no matter where you are based in the world. In addition, there are 40 workshops to watch and participate in and hours of other on-demand sessions available to all participants. Registered participants can re-watch all videos on demand.

[www.ics.org/2021](http://www.ics.org/2021)

### 5<sup>th</sup> WORLD CONGRESS ON ABDOMINAL & PELVIC PAIN AND 7<sup>th</sup> ANNUAL CONGRESS OF CONVERGENCES-PP

10-13 November 2021, Lyons, France. This is currently still planned as a face-to-face meeting. It will include 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. Further details and programme: <http://www.convergencespp.com/medias/files/convergences-pp2021.pdf>

## ONLINE MEETING OF IC/BPS PATIENT ADVOCATES

A great advantage of the current shift to online communication due to the pandemic has been the initiative by Mathilde Scholtes from the Dutch ICP and Balaka Basu from Interstitial Cystitis India to organise virtual international meetings of IC/BPS patient advocates. The virtual meeting recently held on 26 June was the third time that patients from around the globe had the opportunity to meet to discuss the problems they are faced with and how these can be solved. This gives everyone a much better idea of what is happening at the grass roots. Patient representatives participating this time came from the Netherlands, India, France, Hungary, Israel, Spain, and the UK and each spoke about the current situation in their country and the impact of the COVID pandemic.

There was a short presentation on the issue of nomenclature and definitions, explaining what ICD-11 is with a brief look at its new classification concepts for chronic pain, and also taking a look at the new 2021 EAU guidelines on chronic pelvic pain. It was emphasised that is very important for the new generation of patient advocates to have a good knowledge and understanding of guidelines, classifications and criteria so as to be able to participate in projects and studies when required.

If any patient organisations/patient advocates wish to join the online meetings, please contact Balaka Basu at [icindiaorg@gmail.com](mailto:icindiaorg@gmail.com).

## NEW BOOKS/PUBLICATIONS

### STATPEARLS REVIEW [INTERNET] ON INTERSTITIAL CYSTITIS

This open access StatPearls overview of interstitial cystitis from Dublin may be useful. Its objectives are:

- Describe the etiology of interstitial cystitis.
- Outline the management of patients with interstitial cystitis.
- Explain the prognosis of interstitial cystitis.
- Summarize how an interprofessional team can coordinate the care of interstitial cystitis to provide the best outcomes.

Click on the title below to go to the full review.

[INTERSTITIAL CYSTITIS](#). Yizhe Lim, Seanan O'Rourke. In: *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Last Update: 2021 Apr 20. PMID: 34033350 Bookshelf ID: NBK570588*

## NEW GUIDELINES AND CLASSIFICATIONS

### - EAU Guidelines on Chronic Pelvic Pain

The EAU has published a new 2021 version of its Guidelines on Chronic Pelvic Pain with more changes in terminology! It is available online: <https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Chronic-Pelvic-Pain-2021.pdf>

**European Association of Urology: EAU 2021 Guidelines on Chronic Pelvic Pain.** D. Engeler (Chair), A.P. Baranowski, B. Berghmans, J. Borovicka, A.M. Cottrell, P. Dinis-Oliveira, S. Elneil, J. Hughes, E.J. Messelink (Vice-chair), A.C. de C Williams Guidelines Associates: B. Parsons, S. Goonewardene, P. Abreu-Mendes, V. Zumstein

### - World Health Organization International Classification of Diseases, ICD-11

The 11th version of the World Health Organization International Classification of Diseases, ICD-11, has a new chronic pain section compiled by an IASP ICD-11 task force. Articles published about the new chronic pain section of ICD-11 can be found in the Research Update.

Further information about ICD-11 and how to use it can be found at <https://icd.who.int/en>. If you go to the Browser section and type in interstitial cystitis, it will show the options.

## PATIENT RESOURCES

The International Association for the Study of Pain (IASP) has a useful web page with resources for patients for living with pain. <https://www.iasp-pain.org/PatientResources?navItemNumber=678>

## HOW TO USE THE CATHETER-REPLACING ADAPTER FOR BLADDER INSTILLATIONS

There is increasing interest in the catheter-replacing adaptor for bladder instillations known either as the iAluAdapter® or the UroDapter®, but not everyone is entirely sure how to use it, including patients who do self-instillation at home. More information is now available online in several languages. For example:

iAluAdapter® tip sheet for patients

[https://ialuril.co.uk/wp-content/uploads/2020/05/1233\\_iAluradapterTipSheetPatients\\_St03.pdf](https://ialuril.co.uk/wp-content/uploads/2020/05/1233_iAluradapterTipSheetPatients_St03.pdf)

On YouTube: The UroDapter - Revolutionizing bladder pain treatment

[https://www.youtube.com/watch?v=H1rMRKrk0PM&fbclid=IwAR0Y2-](https://www.youtube.com/watch?v=H1rMRKrk0PM&fbclid=IwAR0Y2-sUlgUbG7IbVPJiO8alBKgx9vEMRI84th28fwYLi1bepsU4Sw4hc8g)

[sUlgUbG7IbVPJiO8alBKgx9vEMRI84th28fwYLi1bepsU4Sw4hc8g](https://www.youtube.com/watch?v=H1rMRKrk0PM&fbclid=IwAR0Y2-sUlgUbG7IbVPJiO8alBKgx9vEMRI84th28fwYLi1bepsU4Sw4hc8g) and also at

<https://www.urosystem.com/en/urodapter>

## RESEARCH CONSORTIA

### IMI-PAINCARE RESEARCH CONSORTIUM

The aim of the IMI-PainCare Research Consortium is to improve the care of patients suffering from acute or chronic pain. The subtopic TRiPP concerns Translational Research in Pelvic Pain and particularly focuses on IC/BPS and endometriosis. The 3 patient representatives participating are Judy Birch (chronic pelvic pain), Lone Hummelshoj (endometriosis) and Jane Meijlink (IC/BPS). Read more about this project and latest developments at: <https://www.imi-paincare.eu/>. A new research article from the TRiPP project, currently In Press, can be found in the IPBF Research Update in this Newsletter or go direct to:

[https://journals.lww.com/pain/Abstract/9000/Preclinical\\_models\\_of\\_endometriosis\\_and.98097.aspx](https://journals.lww.com/pain/Abstract/9000/Preclinical_models_of_endometriosis_and.98097.aspx)

### MULTI-DISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP)

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network conducts collaborative research on urological chronic pelvic pain disorders—specifically, interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). [Read more.](#)

## 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.
- Latest information is also available from the National Institutes of Health (NIH) at <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>

## **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](#))*

### **LETTER TO THE EDITOR: COMMENT ON “COMPARISON OF DEEP PHENOTYPING FEATURES OF UCPPS WITH AND WITHOUT HUNNER LESION: A MAPP-II RESEARCH NETWORK STUDY” BY LAI ET AL., DOI:10.1002/NAU.24623**

*Magnus Fall. First published: 16 May 2021 <https://doi.org/10.1002/nau.24697> (open access)*

The umbrella terms bladder pain syndrome/interstitial cystitis (BPS/IC) includes many diagnoses; identification is the key to efficacious treatments. In this connection, there has been a debate for decades on a basic question: Is the classic type of IC with Hunner lesions (HL) a distinct entity? As within the BPS/IC complex symptoms are similar—reason for long-term confusion—some say no (or more recently maybe) while others, incorporating more than symptoms into the equation, for a long time have said no doubt. Although several studies noted various symptom differences, recent surveys found that symptoms alone were not able to pick up diagnostic differences between the two main entities (refs. 10 and 11 in the article). Using a panel of tools to systematically explore symptom patterns, the present study demonstrates that HL symptoms are indeed distinct from non-HL, an important piece of information and incentive to convince all of us to walk in the same direction. Multiple and various observations demonstrate that classic IC with Hunner lesions is a distinct inflammatory condition with a characteristic composition of cell infiltrates. Features such as focal lymphocyte aggregates and mast cell activation, including a unique mast cell migratory capacity, indicating relations to immunology,<sup>2-5</sup> excessive levels of intravesical evaporation of nitric oxide (ref. 29 in the article), elevated urine macrophage migration inhibitory factor (ref. 24 in the article), cytokine expressions (ref. 30 in the article), ultrastructural changes, and various neurobiological characteristics and so forth, make the unique profile of this disease clear. HL disease is a distinct entity, reports are more and more concordant. There are reasons to return to the roots and build on what is already known, to learn what is needed to further explore, using the multidisciplinary approach; invite pathologists, immunologists, pharmacologists, neuroscientists, and other experts to investigate additional aspects of HL inflammation. With the MAPP project active in this arena, the most resourceful UCPPS initiative in the world, rational pharmacological treatment may eventually be within reach.

### **IMI-PAINCARE RESEARCH CONSORTIUM**

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

**PRECLINICAL MODELS OF ENDOMETRIOSIS AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AN INNOVATIVE MEDICINES INITIATIVE-PAINCARE INITIATIVE TO IMPROVE THEIR VALUE FOR TRANSLATIONAL RESEARCH IN PELVIC PAIN**

*Nunez-Badinez, Paulina, De Leo, Bianca, Laux-Biehlmann, Alexis, Hoffmann, Anja, Zollner, Thomas M, Saunders, Philippa T.K, Simitsidellis, Ioannis, Charrua, Ana, Cruz, Francisco, Gomez, Raul, Tejada, Miguel Angel, McMahon, Stephen B, Lo Re, Laure, Barthas, Florent, Vincent, Katy, Birch, Judy, Meijlink, Jane, Hummelshoj, Lone, Sweeney, Patrick J, Armstrong, J. Douglas, Treede, Rolf-Detlef, Nagel, Jens. PAIN: March 3, 2021 - Volume Articles in Press - Issue -doi: 10.1097/j.pain.0000000000002248*

Endometriosis (ENDO) and interstitial cystitis/bladder pain syndrome (IC/BPS) are chronic pain conditions for which better treatments are urgently needed. Development of new therapies with proven clinical benefit has been slow. Nunez-Badinez and colleagues from the IMI-PainCare research project have conducted a review of existing preclinical in vivo models for ENDO and IC/BPS in rodents, discussed to what extent they replicate the phenotype and pain experience of patients, as well as their relevance for translational research. In 1009 publications detailing ENDO models, 41% used autologous, 26% syngeneic, 18% xenograft, and 11% allogeneic tissue in transplantation models. Intraperitoneal injection of endometrial tissue was the subcategory with the highest construct validity score for translational research. From 1055 IC/BPS publications, most interventions were bladder-centric (85%), followed by complex mechanisms (8%) and stress-induced models (7%). Within these categories, the most frequently used models were instillation of irritants (92%), autoimmune (43%), and water avoidance stress (39%), respectively. Notably, although pelvic pain is a hallmark of both conditions and a key endpoint for development of novel therapies, only a small proportion of the studies (models of ENDO: 0.5%-12% and models of IC/BPS: 20%-44%) examined endpoints associated with pain. Moreover, only 2% and 3% of publications using models of ENDO and IC/BPS investigated non-evoked pain endpoints. This analysis highlights the wide variety of models used, limiting reproducibility and translation of results. The authors recommend refining models so that they better reflect clinical reality, sharing protocols, and using standardized endpoints to improve reproducibility. The authors are addressing this in their Innovative Medicines Initiative-PainCare/Translational Research in Pelvic Pain project.

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

**COMPARATIVE SAFETY REVIEW OF CURRENT PHARMACOLOGICAL TREATMENTS FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME**

*Po-Yen Chen, Wei-Chia Lee, Yao-Chi Chuang. Expert Opin Drug Saf. 2021 May 19;1-11. doi: 10.1080/14740338.2021.1921733. Online ahead of print. PMID: 33944647 DOI: 10.1080/14740338.2021.1921733*

Interstitial cystitis/bladder pain syndrome is a frustrating disease of chronic bladder pain associated with lower urinary tract symptoms. Although there are many proposed treatment algorithms, the uncertainty as to their etiology has a negative impact on the therapeutic outcome. Often combination therapy of drugs with different mechanisms of action will be utilized to relieve the symptoms. With the various treatment options available to patients and providers, there is an ever-growing need to implement drug efficacy as well as safety to promote best practice in use of the approved drug. This review from Taiwan focuses on guideline-based pharmacotherapies as described by the AUA and EAU, specifically oral, and intravesical therapies with the most up-to-date published literature. Pharmacotherapies targeting bladder, and/or systemic factors in the overall treatment of IC/BPS are discussed with a particular focus on efficacy and drug safety evaluation. IC/BPS is a syndrome that requires bladder targeting agents to restore the urothelium barrier function and inhibit bladder hypersensitivity as well as various drugs with anti-inflammatory effects, and immune modulation effects. Current pharmacotherapies for IC/BPS have various therapeutic effects and adverse effects depending on the dose and individual response.

**VOIDING DYSFUNCTIONS IN PATIENTS WITH NON-HUNNER'S ULCER INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME DO NOT AFFECT LONG-TERM TREATMENT OUTCOME**

*Wan-Ru Yu, Wei-Chuan Chang, Hann-Chorng Kuo. Int J Clin Pract. 2021 May 17;e14372. doi: 10.1111/ijcp.14372. Online ahead of print. PMID: 33998747 DOI: 10.1111/ijcp.14372*

The role of urodynamic study in the diagnosis and prognostication of interstitial cystitis/bladder pain syndrome (IC/BPS) is still controversial. This study from Taiwan evaluated the correlation of the baseline voiding dysfunctions and long-term treatment outcome in patients with non-Hunner's ulcer IC (NHIC). A total of 211 NHIC patients were enrolled. All patients underwent videourodynamic (VUDS) examination at baseline to identify their voiding conditions and received subsequent treatments. The duration, comorbidities, treatments,

changes in OSS and VAS, maximum bladder capacity (MBC), glomerulations, GRA, and flare-up rate showed no significant difference among different subgroups. When the authors divided patients by their storage and voiding conditions, patients with non-hypersensitivity bladder (HSB) had significantly greater MBC whereas those with HSB with or without voiding dysfunction had higher glomerulation. When they analyzed voiding dysfunction subgroups by GRA, patients with a  $GRA \geq 2$  had a significantly shorter duration of disease. There were also significant associations between GRA and the changes of OSS and VAS. It was concluded that VUDS can disclose voiding dysfunction in 39.3% of NHIC patients. With adequate therapy, the voiding dysfunctions in NHIC patients do not affect long-term treatment outcome.

#### **COMPARISON OF INTRAVESICAL HYALURONIC ACID, CHONDROITIN SULFATE, AND COMBINATION OF HYALURONIC ACID-CHONDROITIN SULFATE THERAPIES IN ANIMAL MODEL OF INTERSTITIAL CYSTITIS**

*Yavuz Onur Danacioglu, Bulent Erol, Seyma Ozkanli, Asif Yildirim, Ramazan Gokhan Atis, Mesrur Selcuk Silay, Turhan Caskurlu. Int Neurourol J. 2021 Mar;25(1):42-50. doi: 10.5213/inj.1938176.088. Epub 2021 Jan 19. PMID: 33504136 PMCID: PMC8022172 DOI: 10.5213/inj.1938176.088*

[Free full article, click on title.](#)

In this study from Turkey, three intravesical treatment agents were compared in an interstitial cystitis rat model: chondroitin sulfate, hyaluronic acid, and combined hyaluronic acid-chondroitin sulfate. Thirty-five female rats were divided into 5 groups: control (group I), isotonic (group II), chondroitin sulfate (group III), hyaluronic acid (group IV), and hyaluronic acid-chondroitin sulfate (group V). Chemical cystitis was induced in all experimental groups by intravesical instillation of 1 mL of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) for 15 minutes via the transurethral route. Significant between-group differences were found in vascular congestion. The grade of submucosal edema in groups II and IV was significantly higher than in group I. In group I, the grade of granulation tissue was lower than the other 4 groups, but no significant difference was found between the remaining groups. Neutrophil cell infiltration was more intense in groups II and IV than in group I. Significant differences in the leukocyte and mast cell count were detected between groups II and IV. Abnormal zonula occludens-1 and uroplakin-III immunoreactivity in group II was higher than in groups I, III, or V. Interleukin-8 expression was lower in group V than in group II. A single treatment of chondroitin sulfate and combined hyaluronic acid-chondroitin sulfate treatment demonstrated efficacy by suppressing inflammation and achieving improvements in the urothelium.

#### **[CYSTOSCOPY IN THE ASSESSMENT OF PATIENTS WITH BLADDER PAIN SYNDROME: RESULTS OF A NATIONAL MULTICENTER OBSERVATIONAL STUDY]**

[Article in Spanish]

*Salvador Arlandis, Miguel Ángel Bonillo, Agustín Franco, Lluís Peri, Raquel González-López, Esther Martínez-Cuenca, Antonio Romero, Carlos Müller-Arteaga, María Justa García-Matres. Arch Esp Urol. 2021 Jun;74(5):459-469. PMID: 34080565*

The object of this study from Spain was to observe the use and results of cystoscopy and bladder hydrodistension in the objective assessment of patients with Bladder Pain Syndrome (BPS), in routine clinical practice. Observational, non-interventional, national, multicenter study carried out in Functional Urology and Urodynamic Units of Spain belonging to the IFU Group. 273 women with BPS who underwent cystoscopy at baseline as a diagnostic tool according to clinical criteria and following the routine clinical practice of each center, were studied. The pre and post hydrodistension findings and the scores of the symptom and Health-Related Quality of Life (HRQoL) questionnaires were described: BPIC-SS, PPBC, PGI-S and EQ-5D-5L. The mean age (SD) was 59 (14) years with a high presence of bladder symptoms: increased voiding frequency (81.7%), nocturia (74%) and urgency (60.4%). 40.7% of cystoscopies were performed under anesthesia and 73.7% uses a standard rigid cystoscope. Hunner lesions were observed in 9.9% of the patients, hypervascularizations (46.2%), glomerulations (23.4%), mild bleeding (6.6%) and scars (2.2%). After hydrodistension, a greater number of grade 1 and 2 lesions were observed. In 51.6% of the patients there were no changes, but in 27.5% slight changes were observed and in 11.4% moderate or severe changes. Symptom and HRQoL questionnaire scores showed no association with cystoscopy findings before and after hydrodistension. The value of the cystoscopic findings in the SDV has yet to be defined, although it plays a fundamental role in the differential diagnosis. In this observational study, they did not find correlation of the cystoscopic findings with the symptoms of the patients, measured by validated questionnaires, nor with the HRQoL.

#### **NOVEL APPLICATIONS OF NON-INVASIVE INTRAVESICAL BOTULINUM TOXIN A DELIVERY IN THE TREATMENT OF FUNCTIONAL BLADDER DISORDERS**

Jia-Fong Jhang, Hann-Chorng Kuo. *Toxins (Basel)*. 2021 May 18;13(5):359. doi: 10.3390/toxins13050359. PMID: 34069951 DOI: 10.3390/toxins13050359

[Free full article, click on title.](#)

Although intravesical botulinum toxin type A (BoNT-A) injection for functional bladder disorders is effective, the injection-related problems-such as bladder pain and urinary tract infection-make the procedure invasive and inconvenient. Several vehicles have recently been developed to deliver BoNT-A without injection, thereby making the treatment less or non-invasive. Laboratory evidence revealed that liposome can carry BoNT-A across the uroepithelium and act on sub-urothelial nerve endings. A randomized placebo controlled study revealed that intravesical administration of liposome-encapsulated BoNT-A and TC-3 hydrogel embedded BoNT-A can improve urinary frequency, urgency, and reduce incontinence in patients with overactive bladders. A single-arm prospective study also revealed that intravesical administration of TC-3 hydrogel embedded BoNT-A can relieve bladder pain in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). The authors from Taiwan recently administered suprapubic energy shock wave (ESW) after BoNT-A intravesical administration in six patients with IC/BPS. Although pain reduction and symptom improvement were not significant, immunochemical staining showed cleaved synaptosome-associated protein 25 in the bladder after the procedure. This suggests that ESW can promote passage of BoNT-A across the uroepithelium. In conclusion, using vehicles to intra-vesically deliver BoNT-A for functional bladder disorders is promising. Further studies are necessary to confirm the efficacy and explore novel applications.

#### [TRANSCRANIAL DIRECT CURRENT ELECTRICAL STIMULATION FOR THE TREATMENT OF INTERSTITIAL CYSTITIS: A STUDY PROTOCOL](#)

Larissa Ramalho Dantas Varella Dutra, Edson Silva-Filho, Maiara Costa Oliveira, Brenda Nayara Paiva Tavares, Rodrigo Pegado, Maria Thereza Babosa Albuquerque Cabral Micussi. *Eur J Obstet Gynecol Reprod Biol*. 2021 May 24;262:198-202. doi: 10.1016/j.ejogrb.2021.05.038. Online ahead of print. PMID: 34062307 DOI: 10.1016/j.ejogrb.2021.05.038

Interstitial cystitis or painful bladder syndrome is a chronic disorder that presents an unknown etiology, with no generally accepted treatment. Although there is no gold standard treatment, transcranial direct current stimulation (tDCS) has shown efficacy in several chronic pain syndromes with decrease in pain, and improved functionality and mood. tDCS could be a safe, ease to use, and low-cost complementary intervention for patients with interstitial cystitis. This study from Brazil investigated the effects of a tDCS protocol on pain, functionality, and mood in patients with interstitial cystitis. A randomized controlled clinical trial with two arms. Women will be randomized into two groups: active or sham. Anodal tDCS over the primary motor cortex will be performed for 5 consecutive days with an intensity of 2 mA for 20 min. Participants will be evaluated five times: 1 week before intervention; on the 5th day of tDCS; and 1, 6, and 12 months after the last day of tDCS. The outcomes will be assessed using the numeric rating scale, McGill pain questionnaire, positive and negative affect scale, international consultation on incontinence questionnaire for female lower urinary tract symptoms, Hamilton anxiety scale, six-minute walk test, patient global impression of change, and voiding diary. Only the active group will be expected to show decreased pain. The results of this trial will be the first step in the use of neuromodulation in interstitial cystitis and will provide additional data to support new studies with tDCS.

#### [INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME'S CORRELATIONS WITH PREGNANCY AND NEONATAL OUTCOMES: A STUDY OF A POPULATION DATABASE](#)

Mohammad I Khojah, Ahmad M Badeghiesh, Sara Ismail, Haitham A Baghlaf, Noor Almamlouk, Michael H Dahan. *J Urol*. 2021 May 25;101097JU0000000000001875. doi: 10.1097/JU.0000000000001875. Online ahead of print. PMID: 34032499 DOI: 10.1097/JU.0000000000001875

The purpose of this study from Montreal, Canada was to evaluate the associations with interstitial cystitis during pregnancy using a United States inpatient database. Khojah and colleagues conducted a retrospective cohort study utilizing the Nationwide Inpatient Sample database from the Healthcare Cost and Utilization Project (HCUP-NIS). ICD-9 code number 595.1 was used to extract cases of Chronic Interstitial Cystitis and these pregnancies were compared to pregnancies without chronic interstitial cystitis, using the Chi-squared test to evaluate nominal variables. A multivariate logistic regression model was subsequently used to adjust for statistically significant confounders. There were 9,095,995 deliveries during the study period. 793 pregnant women were found to have chronic interstitial cystitis. Results from this database study indicated that interstitial cystitis diagnosis is associated with an increased risk of preeclampsia, preterm birth and other adverse pregnancy outcomes. Prospective studies are required to confirm the findings of the correlation between interstitial cystitis and adverse pregnancy outcomes.

### [CURRENT STANDARD OF CARE IN TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS](#)

Sabela Rodriguez Lopez, Naşide Mangır. *Ther Adv Urol.* 2021 Jun 12;13:17562872211022478. doi: 10.1177/17562872211022478. eCollection Jan-Dec 2021. PMID: 34178118 PMCID: PMC8202321 DOI: 10.1177/17562872211022478

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Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating, systemic pain syndrome with a cardinal symptom of bladder related pain with associated systemic symptoms. It is characterized by an inflammation that partially or completely destroys the mucus membrane and can extend into the muscle layer; however, the etiology and pathogenesis is still enigmatic. It has been suggested that mast cell activation, defects in the glycosaminoglycan layer, non-functional proliferation of bladder epithelial cells, neurogenic inflammation, microvascular abnormalities in the submucosal layer, autoimmunity and infectious causes may cause BPS/IC. Available treatment options include general relaxation techniques, patient education, behavioral treatments, physical therapy, multimodal pain therapy, oral (amitriptyline, cimetidine, hydroxyzine) and intravesical treatments (heparin, lidocaine, hyaluronic acid and chondroitin sulfate), hydrodistension and other more invasive treatments. Available treatments are mostly not based on a high level of evidence. Lack of understanding of disease mechanisms has resulted in lack of targeted therapies on this area and a wealth of empirical approaches with usually inadequate efficacy. The aim of this article from Spain and Turkey is to review the available evidence on the pathophysiological mechanisms of BPS/IC as they relate to available treatment options.

### [RELATIONSHIP OF PAIN CATASTROPHIZING WITH URINARY BIOMARKERS IN WOMEN WITH BLADDER PAIN SYNDROME](#)

Alex Soriano, Antoinette Allen, Anna P Malykhina, Uduak Andy, Heidi Harvie, Lily Arya. *Female Pelvic Med Reconstr Surg.* 2021 Mar 19. doi: 10.1097/SPV.0000000000001041. Online ahead of print. PMID: 33787562 DOI: 10.1097/SPV.0000000000001041

Brain-derived neurotrophic factor (BDNF) has been implicated in central neurological processes. Soriano and colleagues hypothesized that greater pain catastrophizing is associated with higher urinary BDNF levels in women with bladder pain syndrome. A secondary analysis of a database of women with urinary urgency was conducted. They identified women who met AUA criteria of bladder pain syndrome. Urinary symptoms, pain catastrophizing, and neuropathic pain were measured using the Female Genitourinary Pain Index, Pain Catastrophizing Scale and painDETECT questionnaires respectively. The relationship of the catastrophizing score with urinary BDNF (primary outcome) and other urinary biomarkers, including nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and osteopontin, was evaluated using univariable and multivariable analyses. In 62 women with bladder pain syndrome, 15 (24%) reported pain catastrophizing symptoms. Higher catastrophizing scores were associated with worse urinary symptoms, greater pelvic pain, greater neuropathic pain, and worse quality of life scores. On multivariable analysis, after controlling for age, body mass index and urinary symptoms, a higher pain catastrophizing score was associated with lower BDNF and lower VEGF levels. Urinary urgency was associated with a higher NGF level while bladder pain was associated with higher levels of NGF and VEGF. Neuroinflammatory mechanisms contribute to the central processing of pain in women with bladder pain syndrome. Worse urinary symptoms are associated with higher NGF and VEGF levels, but worse pain catastrophizing is associated with lower BDNF and VEGF levels. Urinary BDNF levels may be useful in phenotyping women who have central augmentation of pain processing.

### [APPLICATIONS OF ELECTROMOTIVE DRUG ADMINISTRATION IN UROLOGY](#)

Safiya Hashemi, Arun Sahai, Sachin Malde. *Urol Ann.* Oct-Dec 2020;12(4):301-308. doi: 10.4103/UA.UA\_152\_19. Epub 2020 Oct 15. PMID: 33776323 PMCID: PMC7992521 DOI: 10.4103/UA.UA\_152\_19

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The aim of this study from London was to review all published evidence regarding the use of Electromotive Drug Administration (EMDA) for the management of urological conditions, focusing on efficacy and safety, and highlighting areas that require further study. The PubMed and Medline databases were searched up to July 23, 2019. All studies reporting the use of EMDA to enhance the intravesical administration of therapeutic drugs for urological conditions were included. Two reviewers independently screened all articles, searched the reference lists of retrieved articles, and performed the data extraction. Thirty-two studies were included. The use of EMDA has been reported in the following urological conditions: (1) nonmuscle-invasive bladder cancer (NMIBC); (2) overactive bladder; (3) bladder pain syndrome; (4) radiation cystitis; (5) detrusor acontractility; and (6) for analgesia prior to transurethral procedures. Overall, most studies are nonrandomized trials with small numbers of patients. The use of EMDA is reported to be safe and effective in all these conditions, with the highest level

of evidence in NMIBC in the neoadjuvant and adjuvant setting. However, the low overall quality of evidence limits the conclusions that can be reached. The use of EMDA to improve the efficacy of intravesical treatments is promising, but the low overall quality of the evidence base has limited its widespread use. Future studies should compare EMDA to passive diffusion and current standard of care in large, randomized, and long-term studies to determine the efficacy, safety, and cost-effectiveness of this modality.

**FACTORS ASSOCIATED WITH TREATMENT OUTCOMES AFTER INTRAVESICAL HYALURONIC ACID THERAPY IN WOMEN WITH REFRACTORY INTERSTITIAL CYSTITIS: A PROSPECTIVE, MULTICENTER STUDY**

*Ching-Pei Tsai, Jenn-Ming Yang, So-Jung Liang, Yi-Hao Lin, Wen-Chu Huang, Tzu-Yin Lin, Chun-Shuo Hsu, Fei-Chi Chuang, Man-Jung Hung. J Chin Med Assoc. 2021 Apr 1;84(4):418-422. doi: 10.1097/JCMA.000000000000498. PMID: 33784267 DOI: 10.1097/JCMA.000000000000498*

Bladder instillation of hyaluronic acid (HA) is an acceptable treatment for bladder pain syndrome/interstitial cystitis (BPS/IC). The treatment is limited by a high proportion of non-responders (~30%-40%). Here, the authors aimed to evaluate predisposing factors associated with treatment outcomes. This is a prospective multicenter study from Taiwan. The authors enrolled a total of 137 (out of 140) women with refractory IC. They all underwent a standard protocol of 6-month intravesical HA therapy (initial 4 weeks, once weekly, followed by once monthly). To assess the outcomes, they used the pain Visual Analog Scale (Pain-VAS), Interstitial Cystitis Symptom and Problem Index (ICSI & ICPI), and a scaled Global Response Assessment (GRA). The age of patients was  $47.6 \pm 27.5$  (range 24-77) years. The authors found statistically significant improvement in the Pain-VAS and the ICSI & ICPI scores both after the initial 4-weekly instillations and at the end of 6-month treatment. Those who reported moderate/marked improvement on GRA at the 2 follow-up visits were considered responders: 39.4% at the first follow-up, and 59.9% at the second follow-up. No remarkable side effect was noted. After statistical analyses, treatment outcomes on GRA were positively associated with baseline functional bladder capacity and with Pain-VAS scores. The initial treatment responses optimally predicted final treatment outcomes (McNemar). It was concluded that Intravesical HA therapy is safe and effective for most (~60%) of our patients with refractory IC. Functional bladder capacity and Pain-VAS scores before treatment, and the early treatment responses are helpful predictors of treatment outcomes.

**IMPROVES SYMPTOMS AND URINARY BIOMARKERS IN REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS RANDOMIZED TO EXTRACORPOREAL SHOCK WAVE THERAPY VERSUS PLACEBO**

*Yuan-Chi Shen, Pradeep Tyagi, Wei-Chia Lee, Michael Chancellor, Yao-Chi Chuang. Sci Rep. 2021 Apr 6;11(1):7558. doi: 10.1038/s41598-021-87040-1. PMID: 33824389 DOI: 10.1038/s41598-021-87040-1*

Extracorporeal shock wave therapy (ESWT) has been shown to improve symptoms in patients with interstitial cystitis/bladder pain syndrome (IC/BPS); however, there is a lack of objective evidence. Shen and colleagues from the USA and Taiwan measured change of urinary biomarker levels in 25 patients with IC/BPS who received ESWT or placebo once a week for 4 weeks. Urines were collected from participants at baseline, 4 and 12 weeks post treatment. A representative 41 inflammatory growth factors, cytokines, and chemokines in urine were measured using a MILLIPLEX immunoassay kit. Symptom bother was assessed by O'Leary-Sant symptom scores (OSS), and visual analog scale (VAS) for pain. The ESWT group exhibited a significant reduction in the OSS and VAS compared to the placebo group 4 weeks post-treatment, and the effects were persistent at 12 weeks. The difference in urinary markers change in ESWT versus placebo was  $P = 0.054$  for IL4,  $P = 0.013$  for VEGF, and  $P = 0.039$  for IL9 at 4 weeks. The change of urine biomarker was not significant in other biomarkers or all the measured proteins at 12 weeks. The current data suggest that IL4, IL9, and VEGF mediation may be involved in its pathophysiologic mechanisms and response to LESW treatment.

**BLADDER INSTILLATIONS WITH TRIAMCINOLONE ACETONIDE FOR INTERSTITIAL CYSTITIS-BLADDER PAIN SYNDROME: A RANDOMIZED CONTROLLED TRIAL**

*Olivia O Cardenas-Trowers, Alyce G Abraham, Thomas K Dotson, Brooke A Houlette, Jeremy T Gaskins, Sean L Francis. Obstet Gynecol. 2021 Apr 8. doi: 10.1097/AOG.0000000000004348. Online ahead of print. PMID: 33831942 DOI: 10.1097/AOG.0000000000004348.*

The purpose of this study was to evaluate the utility of adding triamcinolone acetonide to a standard bladder instillation solution for treatment of interstitial cystitis-bladder pain syndrome (IC/BPS). This was a single-center, randomized, double-blind trial that compared symptom response in women with IC/BPS who underwent six bladder instillations with triamcinolone acetonide or six instillations without. All instillation solutions contained heparin, viscous lidocaine, sodium bicarbonate, and bupivacaine. The primary outcome was the change in IC/BPS symptoms from the first to sixth bladder instillation between groups based on the total OLS (O'Leary-Sant Questionnaire) score. Assuming a 4.03-point or larger difference in the mean total OLS score from the first to

sixth bladder instillation as compared between the groups, 64 participants were needed to show a significant difference with 80% power at the 0.05 significance level. From January 2019 to October 2020, 90 women were enrolled—45 per group; 71 (79%) completed all six bladder instillations. Randomization resulted in groups with similar characteristics. There was no difference between groups in the primary outcome. Women in both groups had improvement in their IC/BPS symptoms as indicated by a decrease in the total OLS score from the first to sixth bladder instillation. The addition of triamcinolone acetonide to a standard bladder instillation solution does not improve symptoms associated with IC/BPS.

#### **[\[EFFECT OF ELECTROACUPUNCTURE ON EXPRESSION OF P-ERK1/2 AND C-FOS IN SPINAL DORSAL HORN IN RATS WITH INTERSTITIAL CYSTITIS\]](#)**

[Article in Chinese]

Wen Li 1, Zhu Jin, Jian-Dang Liu, Ji-Wei Feng, Zhi-Hao Li, Xue-Dan Zhao, Jun-Wei Hu, Yue-Lai Chen. *Zhen Ci Yan Jiu*. 2021 May 25;46(5):375-9. doi: 10.13702/j.1000-0607.200713. PMID: 34085459 DOI: 10.13702/j.1000-0607.200713

The purpose of this study from China was to observe the effect of electroacupuncture (EA) at "Ciliao" (BL32) and "Huiyang" (BL35) on the expression of extracellular signal-regulated kinase 1/2 (p-ERK1/2) and cellular oncogene fos (c-fos) phosphorylated of spinal dorsal horn in rats with interstitial cystitis (IC). Eighteen female Wistar rats were randomly divided into control, model and EA groups, with 6 rats in each group. The IC model was established by intraperitoneal injection of cyclophosphamide (150 mg/kg). EA (30 Hz, 1 mA) was applied to bilateral BL32 and BL35 for 20 min, once daily for 3 consecutive days. The bladder pain was measured by using a Von Frey at 48 h after modelling and 24 h after EA. The expression levels of p-ERK1/2 and c-fos protein in L6-S1 segment of spinal cord were detected by Western blot, and the expression of p-ERK1/2 and c-fos in the right spinal dorsal horn were displayed by immunofluorescence staining. After modelling, the bladder mechanical pain threshold (PT) was significantly decreased, the protein expression of p-ERK1/2 and c-fos in the spinal cord was increased ( $P < 0.05$ ) and the immunofluorescence surface density of p-ERK1/2 and c-fos in the right dorsal horn of spinal cord was increased in the model group relevant to the control group. After EA intervention, IC-induced reduction of PT, and increases of the expression of p-ERK1/2 and c-fos as well as immunofluorescence surface density of p-ERK1/2 and c-fos were reversed in the EA group relevant to the model group. EA at BL 32 and BL 35 has an analgesic effect in IC rats, which may be related to its effect in down-regulating the expression of p-ERK1/2 and c-fos in spinal dorsal horn.

#### **[INTERSTITIAL CYSTITIS: DIAGNOSIS AND TREATMENT IN A PREGNANT PATIENT](#)**

Sofía Argüelles Rojas, José G Oviedo Ortega, Roberto Velasco Sordo. *Cureus*. 2021 Apr 18;13(4):e14549. doi: 10.7759/cureus.14549. PMID: 34017664 PMCID: PMC8130645 DOI: 10.7759/cureus.14549

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Interstitial cystitis or painful bladder syndrome is a chronic condition characterized by severe and acyclic pelvic pain lasting for a period of at least six weeks. Although this condition is not accompanied by urinary infection, the patient's daily activities are impeded. The most common symptoms are urinary frequency, dysuria, suprapubic pain, nycturia, and dyspareunia. The etiology of interstitial cystitis is unclear, and its diagnosis is infrequent because of the low number of cases. A definitive diagnosis is based on cystoscopic findings and typical histopathological evidence, such as Hunner's ulcers. Here, the authors describe the diagnosis and treatment of a clinical case of interstitial cystitis in a patient who started presenting symptoms during pregnancy. A 42-year-old woman at 27.2 weeks of pregnancy began showing symptoms at 10 weeks of gestation. She presented with dysuria and hypogastric pain with an intensity of 9/10, which hindered her daily activities. Physical examination revealed tenderness to deep and superficial hypogastric palpation. Routine urinalysis and urine culture test yielded negative results. She was started on symptomatic treatment from 10 weeks of gestation, but it did not result in any improvement. Therefore, intraoperative diagnostic cystoscopy was performed to obtain biopsy samples. Histopathological analysis of the samples showed evidence of interstitial cystitis. Accordingly, she was started on intravesical instillation of hyaluronic acid, which improved her condition. On the basis of the case findings, the authors recommend that interstitial cystitis should be considered a differential diagnosis in patients with pelvic pain and urinary symptoms unrelated to a urinary infection.

#### **[TRIGONE AS A DIAGNOSTIC AND THERAPEUTIC TARGET FOR BLADDER-CENTRIC INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)**

Amy D Dobberfuhr, Stefanie van Uem, Eboo Versi. *Int Urogynecol J*. 2021 Jun 22. doi: 10.1007/s00192-021-04878-9. Online ahead of print. PMID: 34156506 DOI: 10.1007/s00192-021-04878-9

The pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) may be bladder-centric, with afferent nerve hyperexcitability and/or due to neural central sensitization. In bladder-centric disease, the trigone's unmyelinated nociceptive C-fibers are thought to be upregulated, suggesting this as a potential target for diagnostic modalities and for treatment with local anesthetics and chemodenervation. Dobberfuhl and colleagues from the USA propose that the transvaginal trigone treatment (T3) route of administration of such treatments should be considered in women with IC/BPS, as this approach is easier and less invasive than cystoscopy. For T3, or other bladder-centric treatments to be successful, patient selection should attempt to exclude patients with predominantly neural central sensitization.

#### **BIOPSYCHOSOCIAL PREDICTORS OF SUICIDE RISK IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME**

*Dean A Tripp, Joel Dueck, Ronald R Holden, Julia Moreau, R Christopher Doiron, J Curtis Nickel. Can Urol Assoc J. 2021 Jun 22. doi: 10.5489/cuaj.7337. Online ahead of print. PMID: 34171215 DOI: 10.5489/cuaj.7337*

The impact of interstitial cystitis/bladder pain syndrome (IC/BPS) is prevalent and severe. Studies examining the IC/BPS prevalence and predictors of suicide risk are limited by their lack of theoretically relevant suicide research variables. This research from Canada reports suicide risk prevalence its biopsychosocial predictors for a community IC/BPS sample. Self-identified female patients suffering from IC/BPS recruited from online IC/BPS support groups completed measures of demographic, pain, symptoms, and psychosocial variables. Descriptive statistics, correlations, and multivariable logistic regressions examined prevalence, variable associations, and suicide risk prediction. Suicide risk prevalence was 38.1%. Suicide risk was associated with greater odds for exposure to suicide, psychache, hopelessness, and perceived burdensomeness to others. Further, examining suicide risk by levels of pain showed that exposure to suicide and hopelessness were consistent suicide risk predictors across pain levels; psychache for lower levels of pain, perceived burdensomeness in moderate and severe pain levels, and depression in moderate levels of pain. It was concluded that the high prevalence of suicide risk is alarming and signifies an imperative for recognizing this risk within the IC/BPS population. The identified psychosocial risk factors may be used in refining screening and treatment and in directing future IC/BPS research.

#### **DIAGNOSTIC UTILITY OF SERUM AND URINARY METABOLITE ANALYSIS IN PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME**

*Jayoung Kim, Amanda De Hoedt, Emily Wiggins, Kelsey Haywood, Peng Jin, Bennett Greenwood, Niven R Narain, Vladimir Tolstikov, Valerie Bussberg, Kamil E Barbour, Michael A Kiebish, Stephen Freedland, Jennifer T Anger. Urology. 2021 May 16;S0090-4295(21)00395-2. doi: 10.1016/j.urology.2021.05.005. Online ahead of print. PMID: 34010675 DOI: 10.1016/j.urology.2021.05.005*

The purpose of this US study was to identify the potential biomarkers of interstitial cystitis/painful bladder syndrome (IC), a chronic syndrome of bladder-centric pain with unknown etiology that has an adverse impact on quality of life. The authors analyzed the urine and serum metabolomes of a cohort of IC patients and non-disease controls (NC). Home collection of serum and urine samples was obtained from 19 IC and 20 NC females in the Veterans Affairs (VA) Health Care System. IC was diagnosed independently by thorough review of medical records using established criteria. Biostatistics and bioinformatics analyses, including univariate analysis, unsupervised clustering, random forest analysis, and metabolite set enrichment analysis (MSEA), were then utilized to identify potential IC biomarkers. Metabolomics profiling revealed distinct expression patterns between NC and IC. Random forest analysis of urine samples suggested discriminators specific to IC; these include phenylalanine, purine, 5-oxoproline, and 5-hydroxyindoleacetic acid. When these urinary metabolomics-based analytes were combined into a single model, the AUC was 0.92, suggesting strong potential clinical value as a diagnostic signature. Serum-based metabolomics did not provide potential IC discriminators. Analysis of serum and urine revealed that women with IC have distinct metabolomes, highlighting key metabolic pathways that may provide insight into the pathophysiology of IC. The findings from this pilot study suggest that integrated analyses of urinary metabolites, purine, phenylalanine, 5-oxoproline, and 5-HIAA, can lead to promising IC biomarkers for pathophysiology of IC. Validation of these results using a larger dataset is currently underway.

#### **HYDRODISTENTION DOES NOT ALTER BLADDER GENE EXPRESSION PROFILES IN PATIENTS WITH NON-HUNNER LESION INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME**

*Raymond Xu, Jeffrey Schachar, Robert J Evans, Catherine A Matthews, Gopal Badlani, Stephen J Walker. NeuroUrol Urodyn. 2021 May 4. doi: 10.1002/nau.24680. Online ahead of print. PMID: 33942362 DOI: 10.1002/nau.24680*

Gene expression profiling of bladder biopsies in patients with interstitial cystitis/bladder pain syndrome (IC/BPS), typically obtained following therapeutic bladder hydrodistention (HOD), is used to improve our understanding of molecular phenotypes. The objective of this study from the USA was to determine if the HOD procedure itself impacts the biopsy gene expression profile and, by extension, whether biopsies from non-HOD bladders are appropriate controls. Bladder biopsies were obtained just before HOD and immediately following HOD from 10 consecutively recruited IC/BPS patients undergoing therapeutic HOD. Biopsies were also obtained from four non-IC/BPS patients who did not undergo HOD (controls). Total RNA was isolated from each of the 24 samples and used to query whole-genome microarrays. Differential gene expression analysis was performed to compare expression profiles of IC/BPS biopsies before and after HOD, and between IC/BPS and control biopsies. Principal component analysis revealed complete separation between gene expression profiles from IC/BPS and control samples and while IC/BPS samples before and after HOD showed no significant differences in expressed genes, 68 transcripts were found to be significantly different between IC/BPS and control samples. It was concluded that the bladder HOD procedure itself does not significantly change gene expression within the IC/BPS patient bladder, a finding that provides evidence to support the use of biopsies from non-IC/BPS patients who have not undergone HOD as controls for gene expression studies.

#### **[CLINICAL REMISSION USING PERSONALIZED LOW-DOSE INTRAVENOUS INFUSIONS OF N-ACETYLCYSTEINE WITH MINIMAL TOXICITIES FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)**

*Dipnarine Maharaj, Gayathri Srinivasan, Sarah Makepeace, Christopher J Hickey, Jacqueline Gouvea. J Pers Med. 2021 Apr 24;11(5):342. doi: 10.3390/jpm11050342. PMID: 33923265 DOI: 10.3390/jpm11050342*

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Interstitial Cystitis or Bladder Pain Syndrome (IC/BPS) is a heterogeneous condition characterized by elevated levels of inflammatory cytokines, IL-1 $\beta$ , IL-6, IL-8, IL-10, TNF- $\alpha$ , and is associated with debilitating symptoms of pelvic pain and frequent urination. A standard of care for IC/BPS has not been established, and most patients must undergo a series of different treatment options, with potential for severe adverse events. Here, the authors from the USA report a patient with a 26-year history of IC/BPS following treatment with multiple therapies, including low doses of etodolac, amitriptyline and gabapentin, which she was unable to tolerate because of adverse effects, including headaches, blurred vision and cognitive impairment. The patient achieved a complete clinical remission with minimal adverse events after 16 cycles of N-acetylcysteine (NAC) intravenous (IV) infusions over a period of 5 months, and pro-inflammatory cytokine levels were reduced when compared to measurements taken at presentation. Personalized low dose NAC IV infusion therapy represents an effective, safe, anti-inflammatory therapy administered in the outpatient setting for IC/BPS and warrants further investigation.

#### **[ABNORMAL FUNCTIONAL CONNECTIVITY WITHIN THE PREFRONTAL CORTEX IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME \(IC/BPS\): A PILOT STUDY USING RESTING STATE FUNCTIONAL NEAR-INFRARED SPECTROSCOPY \(RS-FNIRS\)](#)**

*Dongqing Pang, Limin Liao. Neurourol Urodyn. 2021 Jun 15. doi: 10.1002/nau.24729. Online ahead of print. PMID: 34130350 DOI: 10.1002/nau.24729*

The purpose of this study from China was to investigate the abnormalities of functional connectivity (FC) within the prefrontal cortex (PFC) of patients with interstitial cystitis/bladder pain syndrome (IC/BPS) based on resting state functional near-infrared spectroscopy (rs-fNIRS) data using FC matrix analysis. Ten patients with IC/BPS and 15 age- and gender-matched healthy controls (HC) participated. Two rs-fNIRS scans were performed (when the bladder was empty and when the desire to void was strong). The Pearson's correlation coefficient between the time series of the 22 channels was calculated to obtain a 22  $\times$  22 FC matrix for each subject. A two-sample t-test was performed to compare group differences in the FC matrix between patients with IC/BPS and HC. FC was significantly decreased within the PFC in the IC/BPS group based on a two-sample t-test compared with HC. FC decreased in a wider range of brain regions during the strong desire to void state (4 brain regions and 28 edges) when compared with the empty bladder state (3 brain regions and 18 edges). It was concluded that FC abnormalities in IC/BPS patients may lead to frontal lobe disorders involved in processing sensory integration, motivation drive, emotional control, and decision-making whether to urinate, leading to urinary control dysfunction manifested as typical clinical IC/BPS symptoms.

#### **[CURRENT STATUS OF INTRAVESICAL THERAPIES FOR BLADDER PAIN SYNDROME \(BPS\): A NARRATIVE REVIEW OF EMERGING EVIDENCE](#)**

*Dr Patrick Jones 1, Dr Karin M Hjelle 2, Specialist Nurse Jannike Mohn 3, Consultant Urological Surgeon Gigja Guðbrandsdóttir 4, Consultant Urological Surgeon Ingunn Roth 3, Consultant Urological Surgeon Adeel Asghar*

Chaudhry 3, Consultant Urological Surgeon Anne Kvåle Bergesen 3, Professor Christian Beisland. *Urology*. 2021 Jun 9;S0090-4295(21)00466-0. doi: 10.1016/j.urology.2021.05.042. Online ahead of print. PMID: 34118230 DOI: 10.1016/j.urology.2021.05.042

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Bladder pain syndrome (BPS) is a complex condition, which can have debilitating sequelae for patients. Many elements of BPS remain poorly understood including pathophysiology, diagnosis and treatment. Navigating patient care can therefore be challenging for the clinician. Management mandates a multidisciplinary and symptom-based approach. Intravesical treatments such as instillation therapies remain a cornerstone of most treatment algorithms and there are a range of agents that can be selected. This review from Norway offers an up-to-date evaluation of the evidence for these intravesical treatments.

#### [COMORBIDITIES IN A NATIONWIDE, HETEROGENOUS POPULATION OF VETERANS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Bethany F Laden, Catherine Bresee, Amanda De Hoedt, Kai B Dallas, April Scharfenberg, Roopali Saxena, Justin F Senechal, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. *Urology*. 2021 Apr 23;S0090-4295(21)00343-5. doi: 10.1016/j.urology.2021.04.015. Online ahead of print. PMID: 33901534 DOI: 10.1016/j.urology.2021.04.015

The purpose of this study was to examine the prevalence of comorbid conditions in a nationwide population of men and women with IC/BPS utilizing a more heterogeneous sample than most studies to date. Using the Veterans Affairs Informatics and Computing Infrastructure, Laden and colleagues identified random samples of male and female patients with and without an ICD-9/ICD-10 diagnosis of IC/BPS. Presence of comorbidities (NUAS [chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, migraines], back pain, diabetes, and smoking) and psychosocial factors (alcohol abuse, post-traumatic stress disorder, sexual trauma, and history of depression) were determined using ICD-9 and ICD-10 codes. Associations between these variables and IC/BPS status were evaluated while adjusting for the potential confounding impact of race/ethnicity, age, and gender. Data was analyzed from 872 IC/BPS patients (355 [41%] men, 517 [59%] women) and 558 non-IC/BPS patients (291 [52%] men, 267 [48%] women). IC/BPS patients were more likely than non-IC/BPS patients to have a greater number of comorbidities, experience one or more NUAS (chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and migraines) and had a higher prevalence of at least one psychosocial factor. Differences in the frequencies of comorbidities between patients with and without IC/BPS were more pronounced in female patients. It was concluded that these findings validate the findings of previous comorbidity studies of IC/BPS in a more diverse population.

#### [PULSED ELECTROMAGNETIC FIELD \(PEMF\) AS AN ADJUNCT THERAPY FOR PAIN MANAGEMENT IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Christina Ross, Tyler Overholt, Raymond Xu, Gopal Badlani, Robert J Evans, Catherine A Matthews, Stephen J Walker. *Int Urogynecol J*. 2021 Jun 8. doi: 10.1007/s00192-021-04862-3. Online ahead of print. PMID: 34100976 DOI: 10.1007/s00192-021-04862-3

Patients with interstitial cystitis/bladder pain syndrome (IC/BPS) often experience chronic pelvic and even systemic pain that can be difficult to clinically manage. Pulsed electromagnetic field (PEMF) therapy, a non-invasive strategy that has shown significant efficacy for pain reduction in other chronic pain conditions, may provide benefit for pain management in patients with IC/BPS. PEMF delivery to patients occurs via a bio-electromagnetic-energy device which consists of a flexible mat (180 × 50 cm) that the patient lies on for systemic, full-body delivery and/or a flexible pad (50 × 15 cm) for targeted delivery to a specific body region (e.g., pelvic area). The duration of individual sessions, number of sessions per day, total number of sessions, and follow-up observation period vary between previously published studies. Positive outcomes are typically reported as a significant reduction in visual analog scale (VAS) pain score and functional improvement assessed using validated questionnaires specific to the condition under study. The use of PEMF has been evaluated as a therapeutic strategy for pain management in several clinical scenarios. Randomized, double-blinded, placebo-controlled trials have reported positive efficacy and safety profiles when PEMF was used to treat non-specific low back pain, patellofemoral pain syndrome, chronic post-operative pain, osteoarthritis-related pain, rheumatoid arthritis-related pain, and fibromyalgia-related pain. Based on these positive outcomes in a variety of pain conditions, clinical trials to evaluate whether PEMF can provide a safe, non-invasive therapeutic approach to improve symptoms of chronic pain and fatigue in patients with IC/BPS are warranted.

#### [THE EFFECT OF A DIAGNOSIS ON PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A QUALITATIVE APPROACH](#)

*Katherine A Volpe, Emi Komatsu, Larissa V Rodriguez, Christina E Dancz, Avita K Pahwa. Female Pelvic Med Reconstr Surg. 2021 May 1;27(5):e533-e537. doi: 10.1097/SPV.0000000000000985. PMID: 33208655 DOI: 10.1097/SPV.0000000000000985*

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain condition that significantly affects patient quality of life. The authors investigated whether receiving a formal medical diagnosis of IC/BPS was perceived by patients to improve symptoms and disease-specific quality of life. Participants with self-reported IC/BPS completed publicly available online surveys. Surveys included demographic information, validated questionnaires, and a free-text response. Participants were asked to comment on the utility of obtaining a diagnosis. Investigators coded the responses and analyzed the results using grounded theory methodology. Six hundred seventy-three participants who responded to the free-text were analyzed. The mean age of respondents was 52 years, with an average of 10 years since IC/BPS diagnosis. The IC/BPS diagnosis had wide ranging effects on both symptoms and coping. These effects were often mediated by improvements in perceived control and empowerment after diagnosis. Although most participants noted benefit after diagnosis of IC/BPS, some reported harmful effects ranging from stigmatization by providers to desperation when told that there was not a cure. A formal medical diagnosis of IC/BPS has a significant effect on patients who experience the condition. Although diagnosis usually improves symptoms and coping, a universal experience was not described by all IC/BPS patients. Given that most patients report improvement, more work is needed to expedite diagnosis. In addition, we must better understand factors associated with lack of symptom and quality of life improvement after an IC/BPS diagnosis has been made by medical providers.

#### **DOES OBTAINING A DIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IMPROVE SYMPTOMS OR QUALITY OF LIFE? A CROSS-SECTIONAL QUESTIONNAIRE-BASED STUDY**

*Katherine A Volpe, Rachel Mandelbaum, Larissa V Rodriguez, Begüm Z Özel, Renee Rolston, Christina E Dancz. Female Pelvic Med Reconstr Surg. 2021 May 1;27(5):328-333. doi: 10.1097/SPV.0000000000000840. PMID: 32304396 DOI: 10.1097/SPV.0000000000000840*

The aim of this study was to investigate whether receiving a clinical diagnosis of interstitial cystitis (IC) or bladder pain syndrome (BPS) improves patients' symptoms, health-related quality of life (HRQOL), or ability to cope with their symptoms. In this cross-sectional study, participants with self-reported IC/BPS completed an online questionnaire recalling their perceived change in symptoms after diagnosis and treatment. The questionnaire included demographic information, overall HRQOL measured on a visual analog scale (VAS), O'Leary-Sant Interstitial Cystitis Problem Index, the Urinary Impact Questionnaire, and questions regarding patient beliefs about diagnosis. HRQOL and symptom impact scales were compared before and after diagnosis and treatment. Demographic data, symptom data, and beliefs were examined for correlation with improvement in quality of life after diagnosis. A total of 1052 participants initiated the survey and were included in the analysis; most of them identified as female, non-Hispanic, and white (90%). Before symptom onset, median VAS HRQOL score was 87. Median scores nadired at 34 after symptom onset before diagnosis but improved to 61 after diagnosis and treatment. Scores remained stable after diagnosis and initiation of treatment with a median score of 65 at the time of survey. Age, insurance type, and improvement in scores on the symptom impact scale predicted improvement in HRQOL after diagnosis and treatment in the multivariable model. Participants reported improvements on global and symptom-specific quality of life measures after diagnosis and treatment for IC/BPS.

#### **[UPOINT PHENOTYPIC CLASSIFICATION OF A SAMPLE OF FEMALE PATIENTS WITH BLADDER PAIN SYNDROME: RESULTS OF A NATIONAL MULTICENTRIC OBSERVATIONAL STUDY]**

[Article in Spanish]

*Cristina Gutiérrez-Ruiz, Agustín Franco-de-Castro, Rodrigo Gil-Ugarteburu, Javier Casado-Varela, Virginia Martínez-Barea, Eva M<sup>a</sup> Valero-Fernández, Salvador Arlandis-Guzmán. Observational Study Arch Esp Urol. 2021 May;74(4):369-382. PMID: 33942728*

The purpose of this study was to study the possibility of classifying patients with BPS by UPOINT phenotypes and their correlation with the results of different BPS diagnostic tools. Epidemiological, observational, longitudinal and multicentric study performed according to clinical practice. A total of 319 women with BPS were included, 79 with new diagnosis and 240 in follow-up. Sociodemographic and clinical data were collected together with results of cystoscopy, biopsy and physical examination. Patients completed a 3-day Bladder Diary (3dBD) and Patient Reported Outcomes (PROs). All the patients were classified according to the 6 UPOINT domains and their distribution was described according to the clinical history, diagnostic tests, urinary symptoms and PROs' scores. 92.8% of the patients had affectation in more than one phenotype, however, there were no remarkable differences in the clinical and sociodemographic variables according to the number of affected domains. The percentage of patients with 3C classification was higher in the urinary (8.2%), organ-specific (9.0%) and

neurological (10.9%) phenotypes. Around 90% had high voiding frequency, regardless of the phenotype. The improvement reported by the PROs was superior in the neurological and tenderness phenotypes. The worst scores were associated with a greater number of affected domains. The present study is the first one carried out in Spain on a phenotypic classification of women with BPS, with data from routine clinical practice. The results point out that patients with several domains affected present more affectation on the BPS, worse HRQoL and higher anxiety.

#### **NEURONAL DUAL LEUCINE ZIPPER KINASE MEDIATES INFLAMMATORY AND NOCICEPTIVE RESPONSES IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS**

*Chen Jiang, Weilin Fang, Tingting Lv, Yinjun Gu, Jianwei Lv. J Innate Immun. 2021 Jun 25;1-10. doi: 10.1159/000514545. Online ahead of print. PMID: 34175846 DOI: 10.1159/000514545*

Interstitial cystitis is associated with neurogenic inflammation and neuropathic bladder pain. Dual leucine zipper kinase (DLK) expressed in sensory neurons is implicated in neuropathic pain. Jiang and colleagues from Shanghai, China hypothesized that neuronal DLK is involved in the regulation of inflammation and nociceptive behavior in cystitis. Mice deficient in DLK in sensory neurons (cKO) were generated by crossing DLK floxed mice with mice expressing Cre recombinase under Advillin promoter. Cystitis was induced by cyclophosphamide (CYP) administration in mice. Nociceptive behavior, bladder inflammation, and pathology were assessed following cystitis induction in control and cKO mice. The role of DLK in CYP-induced cystitis was further determined by pharmacological inhibition of DLK with GNE-3511. Deletion of neuronal DLK attenuated CYP-induced pain-like nociceptive behavior and suppressed histamine release from mast cells, neuronal activation in the spinal cord, and bladder pathology. Mice deficient in neuronal DLK also showed reduced inflammation induced by CYP and reduced c-Jun activation in the dorsal root ganglia (DRG). Pharmacological inhibition of DLK with GNE-3511 recapitulated the effects of neuronal DLK depletion in CYP treatment mice. The authors are of the opinion that their study suggests that DLK is a potential target for the treatment of neuropathic pain and bladder pathology associated with cystitis.

#### **HUNNER LESION**

#### **THE BACTERIAL MICROBIOTA OF HUNNER LESION INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME**

*J Curtis Nickel, Garth D Ehrlich, Jaroslaw E Krol, Azad Ahmed, Bhaswati Sen, Archana Bhat, Joshua C Mell, R Christopher Doiron, Kerri-Lynn Kelly, Joshua P Earl. BJU Int. 2021 Jun 18. doi: 10.1111/bju.15519. Online ahead of print. PMID: 34143561 DOI: 10.1111/bju.15519*

The purpose of this study from Canada and the USA was to undertake the first comprehensive evaluation of the urinary microbiota associated with Hunner lesion interstitial cystitis/bladder pain syndrome (HL IC/BPS). Despite no previous identification of a distinct IC/BPS microbial urotype, HL IC/BPS, an inflammatory subtype of IC/BPS, was hypothesized most likely to be associated with a specific bacterial species or microbial pattern. The bacterial microbiota of mid-stream urine specimens from HL IC/BPS and age and gender-matched IC/BPS patients without HL (non-HL IC/BPS) were examined using the pan-bacterial domain clinical-level molecular diagnostic Pacific Biosciences full-length 16S gene sequencing protocol, informatics pipeline and database. The authors were not able to identify a unique pathogenic urinary microbiota that differentiates all HL from all non-HL IC/BPS. It is likely that the male-specific differences resulted from colonization/contamination remote from the bladder. They could not show that bacteria play an important role in HL IC/BPS patients.

#### **DECREASED UROTHELIAL CYTOSKELETON AND CELL PROLIFERATION PROTEIN EXPRESSION SUGGEST INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS WITH HUNNER'S LESION AND GRADE 3 GLOMERULATION MIGHT BE DIFFERENT FROM OTHER TYPES OF PATIENTS**

*Jia-Fong Jhang, Yuan-Hong Jiang, Yung-Hsiang Hsu, Han-Chen Ho, Hann-Chorng Kuo. Int J Urol. 2021 May 8. doi: 10.1111/iju.14585. Online ahead of print. PMID: 33966299 DOI: 10.1111/iju.14585*

The purpose of this study from Taiwan was to explore the expression of cytoskeletal and cell proliferation proteins in urothelial cells of patients diagnosed with various clinical subtypes of interstitial cystitis/bladder pain syndrome. Biopsy specimens from 85 IC/BPS patients were classified according to findings on cystoscopy. Cytokeratins and cell proliferation proteins detected in the specimens were evaluated with immunofluorescence staining and quantified with western blotting. A total of 22 patients diagnosed with pure stress urinary incontinence were enrolled as controls. IC/BPS patients with Hunner's lesion and with grade 3 glomerulation hemorrhage had smaller bladder capacities than the other IC/BPS patients without Hunner's lesion. Diminished expression of CK14, CK20, cell proliferation protein tumor protein 63, sonic hedgehog, and fibroblast growth factor receptors 3 and 4, and increased expression of CK5 and BCL2-associated X protein were observed in biopsy

specimens from patients with Hunner's lesion compared with those from patients without Hunner's lesion and controls. In the patients with grade 3 glomerulation hemorrhage, lower expression levels of urothelial CK20, tumor protein 63 and fibroblast growth factor receptor 4, and lower expression of CK5 and BCL2-associated X protein were detected compared with other types of NHIC. A diminished expression of proliferation proteins tumor protein 63 and the mature urothelium marker CK20, and increased expression of the immature marker CK5 in specimens from both Hunner's lesion and grade 3 glomerulation hemorrhage patients can be observed. The urothelium of patients with IC/BPS might be in a state of persistent or chronic injury that could relate to the limited expression of cell proliferation proteins.

**[EDITORIAL COMMENT FROM DR AKIYAMA TO DECREASED UROTHELIAL CYTOSKELETON AND CELL PROLIFERATION PROTEIN EXPRESSION SUGGEST INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS WITH HUNNER'S LESION AND GRADE 3 GLOMERULATION MIGHT BE DIFFERENT FROM OTHER TYPES OF PATIENTS](#)**

Yoshiyuki Akiyama. *Int J Urol.* 2021 May 28. doi: 10.1111/iju.14613. Online ahead of print. PMID: 34050563 DOI: 10.1111/iju.14613

**[EDITORIAL COMMENT FROM DR UEDA TO DECREASED UROTHELIAL CYTOSKELETON AND CELL PROLIFERATION PROTEIN EXPRESSION SUGGEST INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS WITH HUNNER'S LESION AND GRADE 3 GLOMERULATION MIGHT BE DIFFERENT FROM OTHER TYPES OF PATIENTS](#)**

Tomohiro Ueda. *Int J Urol.* 2021 Jun 24. doi: 10.1111/iju.14621. Online ahead of print. PMID: 34169591 DOI: 10.1111/iju.14621

**[EDITORIAL COMMENT FROM DR CHANCELLOR TO DECREASED UROTHELIAL CYTOSKELETON AND CELL PROLIFERATION PROTEIN EXPRESSION SUGGEST INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS WITH HUNNER'S LESION AND GRADE 3 GLOMERULATION MIGHT BE DIFFERENT FROM OTHER TYPES OF PATIENTS](#)**

Michael Chancellor. *Int J Urol.* 2021 Jun 24. doi: 10.1111/iju.14629. Online ahead of print. PMID: 34169577. DOI: [10.1111/iju.14629](https://doi.org/10.1111/iju.14629)

**[CURE OF INTERSTITIAL CYSTITIS AND NON-ULCERATING HUNNER'S ULCER BY CARDINAL/UTEROSACRAL LIGAMENT REPAIR](#)**

Kay Scheffler, Oliver W Hakenberg, Peter Petros. *Urol Int.* 2021 May 21;1-4. doi: 10.1159/000515647. Online ahead of print. PMID: 34023828 DOI: 10.1159/000515647

A serendipitous cure in a 73-year-old woman of Hunner's ulcer, urge, nocturia, apical prolapse by a tissue fixation system tensioned minisling (TFS) which reinforced the cardinal, and uterosacral ligaments (USLs) led us to analyse the relationship between Hunner's ulcer and known pain conditions associated with USL laxity. The original intention was to cure the "posterior fornix syndrome" (PFS), uterine prolapse, and associated pain and bladder symptoms by USL repair. A speculum inserted preoperatively into the posterior fornix alleviated pain and urge symptoms, by mechanically supporting USLs. Hunner's ulcer, along with pain and other PFS symptoms were cured by USL repair. The concept of USL laxity causing chronic pelvic pain and bladder problems is not new. It was published in the German literature by Heinrich Martius in 1938 and by Petros in the English literature in 1993. These findings raise important questions. As PFS symptoms are identical with those of interstitial cystitis (IC), are PFS and IC similar conditions? If so, then patients with IC who have a positive speculum test are at least theoretically, potentially curable by USL repair. These questions need to be explored.

**[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 Apr 23;101097JU0000000000001811. doi: 10.1097/JU.0000000000001811. Online ahead of print. PMID: 33890486 DOI: 10.1097/JU.0000000000001811

The authors from Seoul, Korea aimed to investigate the impact of various bladder lesions on the clinical symptoms and recurrence of interstitial cystitis (IC). IC patients who underwent transurethral resection and cauterization (TURC) for Hunner lesions (HLs) were enrolled. Features of HLs-non-inflamed, 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 with mean age of 61.4±10.5 years. Recurrence was observed in 160 procedures after mean of 15.6 months; repeat TURC 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 (FBC) and preoperative urgency. Extensive waterfall bleeding was associated with smaller FBC ( $p=0.006$ ). 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.

#### [EXPLORATION OF THE CORE GENES IN ULCERATIVE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Hao Wu, Quan-Xin Su, Zi-Yi Zhang, Ze Zhang, Sheng-Lin Gao, Chao Lu, Li Zuo, Li-Feng Zhang. *Int Braz J Urol.* Jul-Aug 2021;47(4):843-855. doi: 10.1590/S1677-5538.IBJU.2020.1104. PMID: 33848079 DOI: 10.1590/S1677-5538.IBJU.2020.1104

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Interstitial cystitis (IC)/bladder pain syndrome (BPS) is a chronic inflammatory disease that can cause bladder pain and accompanying symptoms, such as long-term urinary frequency and urgency. IC/BPS can be ulcerative or non-ulcerative. The aim of this study from China was to explore the core genes involved in the pathogenesis of ulcerative IC, and thus the potential biomarkers for clinical treatment. First, the gene expression dataset GSE11783 was downloaded using the Gene Expression Omnibus (GEO) database and analyzed using the limma package in R to identify differentially expressed genes (DEGs). Then, the Database for Annotation, Visualization and Integrated Discovery (DAVID) was used for Gene Ontology (GO) functional analysis, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) was used for pathway enrichment analysis. Finally, the protein-protein interaction (PPI) network was constructed, and key modules and hub genes were determined using the STRING and Cytoscape software. The resulting key modules were then analyzed for tissue-specific gene expression using BioGPS. A total of 216 up-regulated DEGs and 267 down-regulated genes were identified, and three key modules and nine hub genes were obtained. It was concluded that the core genes (CXCL8, CXCL1, IL6) obtained in this study may be potential biomarkers of interstitial cystitis with guiding significance for clinical treatment.

#### COVID AND IC/BPS

#### [WEB-MEDIATED COUNSELING TO COUNTERACT THE EMOTIONAL IMPACT OF COVID-19 FOR WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

G Marano, E Gaetani, M Marturano, G Sani, A Gasbarrini, G Scambia, M Mazza. *Eur Rev Med Pharmacol Sci.* 2021 Feb;25(4):2109-2113. doi: 10.26355/eurrev\_202102\_25116. PMID: 33660824 DOI: 10.26355/eurrev\_202102\_25116

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Interstitial Cystitis (IC) is a chronic and rare disease, more frequent in women. Symptoms of continuous pain can produce psychological disorders, such as anxiety and depression. The spread of COVID-19 pandemic added to distress experienced by patients with IC emotions, such as fear, sadness, boredom, frustration and anger. Research into very recent literature outlines the necessity for patients facing the complexity of IC during the COVID-19 outbreak to prevent the temporary crisis, to broaden perspectives, to deal with confusion, to support in struggling with unpleasant and unexpected events. People affected by IC have a psychological vulnerability that needs tailored support interventions, particularly in the COVID era. A multidisciplinary approach offers a personalized treatment through a web-mediated counselling intervention for patients and their caregivers: a space for continuous discussion and reflection can favour a relationship-based process of change aimed at an improvement in quality of life.

#### KETAMINE CYSTITIS

#### [AUTOPHAGY ALTERS BLADDER ANGIOGENESIS AND IMPROVES BLADDER HYPERACTIVITY IN THE PATHOGENESIS OF KETAMINE-INDUCED CYSTITIS IN A RAT MODEL](#)

Jian-He Lu, Yi-Hsuan Wu, Tai-Jui Juan, Hung-Yu Lin, Rong-Jyh Lin, Kuang-Shun Chueh, Yi-Chen Lee, Chao-Yuan Chang, Yung-Shun Juan. *Biology (Basel).* 2021 May 30;10(6):488. doi: 10.3390/biology10060488. PMID: 34070854 DOI: 10.3390/biology10060488

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This study from Taiwan into ketamine-induced cystitis in a rat model attempts to elucidate whether autophagy alters bladder angiogenesis, decreases inflammatory response, and ameliorates bladder hyperactivity-thereby influencing bladder function in ketamine-induced cystitis (KIC). The authors report that in their methodology, female Sprague-Dawley (S-D) rats were randomly divided into the control group, the ketamine group, the ketamine+rapamycin group, and the ketamine+wortmannin group. The bladder function, contractile activity of detrusor smooth muscle, distribution of autophagosome and autolysosome, total white blood cells (WBCs) and leukocyte differential counts, the expressions of autophagy-associated protein, angiogenesis markers, and signaling pathway molecules involved in KIC were tested, respectively. The data revealed that treatment with ketamine significantly results in bladder overactivity, enhanced interstitial fibrosis, impaired endothelium, induced eosinophil-mediated inflammation, swelling, and degraded mitochondria and organelles, inhibited angiogenesis, and elevated the phosphorylation of Akt. However, treatment with rapamycin caused an inhibitory effect on vascular formation, removed ketamine metabolites, decreased the eosinophil-mediated inflammation, and ameliorated bladder hyperactivity, leading to improve bladder function in KIC. Moreover, wortmannin treatment reduced basophil-mediated inflammatory response, improved bladder angiogenesis by increasing capillary density and VEGF expression, to reverse antiangiogenic effect to repair KIC. In conclusion, these findings suggested that autophagy could modulate inflammatory responses and angiogenesis, which improved bladder function in KIC.

## UROBIOME - MICROBIOTA

### [URINARY MICROBIOME AND ITS CORRELATION WITH DISORDERS OF THE GENITOURINARY SYSTEM](#)

*Aida Javan Balegh Marand, Gommert A Van Koeveringe, Dick Janssen, Nafiseh Vahed, Thomas-Alexander Vögeli, John Heesakkers, Sakineh Hajebrahimi, Mohammad Sajjad Rahnama'i. Urol J.. 2021 Feb 6. doi: 10.22037/uj.v16i7.5976. Online ahead of print. PMID: 33550579 DOI: 10.22037/uj.v16i7.5976*

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Until recently, the urine of healthy individuals was assumed to be sterile. However, improvement of bacterial detection methods has debunked this assumption. Recent studies have shown that the bladder contains microbiomes, which are not detectable under standard conditions. In this review, the authors aimed to present an overview of the published literature regarding the relationship between urinary microbiota and functional disorders of the genitourinary system. A search was made of Medline, PubMed, Embase, The Cochrane library and Scopus to identify RCTs published, with MeSH and free keywords including microbiota, bladder pain syndrome, prostatitis, kidney stone disease, and bladder cancer until September 2020. Randomized controlled trials investigating microbiome and lower urinary tract symptoms were included. Non-randomized trials, cross-over trials and pooled studies were excluded. The articles were critically appraised by two reviewers. The urine microbiome is a newly introduced concept, which has attracted the attention of medical researchers. Since its recent introduction, researchers have conducted many fruitful studies on this phenomenon, changing our perspective toward the role of bacteria in the urinary tract and our perception of the genitourinary system health.

**Patient Summary:** A deeper understanding of the urinary microbiome can help us to develop more efficient methods for restoring the microbiota to a healthy composition and providing symptom relief. Modification of the urinary microbiome without antibiotic use can be a possible venue for future research.

### [\[THE ROLE OF THE MICROBIOME IN UROLOGICAL DISEASES\]](#)

[Article in German]

*Michael Atzler, Thilo Westhofen, Alexander Tamalunas, Melanie Schott, Patrick Keller, Benedikt Ebner, Christian Stief, Giuseppe Magistro. Aktuelle Urol. 2021 Jun 8. doi: 10.1055/a-1478-2960. Online ahead of print. PMID: 34102684 DOI: 10.1055/a-1478-2960*

*Abstract in English, German*

The use of modern molecular technologies in the last decade has given us new insights into the complex interactions of the human microbiome in health and in the pathogenesis of diseases. Among other things, the sterility concept of the urinary tract has been discarded and the goal is now to identify the different microbial signatures associated with various diseases. Dysbalances of the microbiome are increasingly suspected of causing negative effects on various malignant and benign diseases. Recently, such associations have also been shown for prostate carcinoma, renal cell carcinoma and urinary bladder carcinoma. This may lead to the discovery of new potential biomarkers for the diagnosis and as a therapeutic target of the diseases mentioned. For the diagnosis of some benign diseases such as interstitial cystitis, urge incontinence and chronic prostatitis or chronic pelvic pain syndrome, microbial involvement was previously considered an exclusion criterion.

However, current studies show that the individual patient's microbiome can have an influence on the development and severity of the respective disease.

#### **CULTIVABLE BACTERIA IN URINE OF WOMEN WITH INTERSTITIAL CYSTITIS: (NOT) WHAT WE EXPECTED**

Jacobs, Kristin M, Price, Travis K, Thomas-White, Krystal, Halverson, Thomas, Davies, Abigail, Myers, Deborah L, Wolfe, Alan J. *Female Pelvic Medicine & Reconstructive Surgery: May 2021 - Volume 27 - Issue 5 - p 322-327. doi: 10.1097/SPV.0000000000000854*

[Free full article, click on title.](#)

Multiple studies show cultivatable bacteria in urine of most women. The existence of these bacteria challenges interstitial cystitis (IC)/painful bladder syndrome (PBS) diagnosis, which presumes a sterile bladder. The aims of this study were (1) to compare the female bladder microbiomes in women with IC/PBS and unaffected controls and (2) to correlate baseline bladder microbiome composition with symptoms.

#### **GENOME INVESTIGATION OF URINARY GARDNERELLA STRAINS AND THEIR RELATIONSHIP TO ISOLATES OF THE VAGINAL MICROBIOTA**

Catherine Putonti, Krystal Thomas-White, Elias Crum, Evann E Hilt, Travis K Price, Alan J Wolfe. *mSphere*. 2021 May 12;6(3):e00154-21. doi: 10.1128/mSphere.00154-21. PMID: 33980674 PMCID: PMC8125048 DOI: 10.1128/mSphere.00154-21

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Gardnerella is a frequent member of the urogenital microbiota. Given the association between Gardnerella vaginalis and bacterial vaginosis (BV), significant efforts have been focused on characterizing this species in the vaginal microbiota. However, Gardnerella also is a frequent member of the urinary microbiota. In an effort to characterize the bacterial species of the urinary microbiota, the authors from the USA present here 10 genomes of urinary Gardnerella isolates from women with and without lower urinary tract symptoms. These genomes complement those of 22 urinary Gardnerella strains previously isolated and sequenced by their team. They included these genomes in a comparative genome analysis of all publicly available Gardnerella genomes, which include 33 urinary isolates, 78 vaginal isolates, and 2 other isolates. While once this genus was thought to consist of a single species, recent comparative genome analyses have revealed 3 new species and an additional 9 groups within Gardnerella. Based upon their analysis, they suggest a new group for the species. They also find that distinction between these Gardnerella species/groups is possible only when considering the core or whole-genome sequence, as neither the sialidase nor vaginolysin genes are sufficient for distinguishing between species/groups despite their clinical importance. In contrast to the vaginal microbiota, they found that only five Gardnerella species/groups have been detected within the lower urinary tract. Although they found no association between a particular Gardnerella species/group(s) and urinary symptoms, further sequencing of urinary Gardnerella isolates is needed for both comprehensive taxonomic characterization and etiological classification of Gardnerella in the urinary tract. Prior research into the bacterium Gardnerella vaginalis has largely focused on its association with bacterial vaginosis (BV). However, G. vaginalis is also frequently found within the urinary microbiota of women with and without lower urinary tract symptoms as well as individuals with chronic kidney disease, interstitial cystitis, and BV. This prompted their investigation into Gardnerella from the urinary microbiota and all publicly available Gardnerella genomes from the urogenital tract. The authors believe that their work suggests that while some Gardnerella species can survive in both the urinary tract and vagina, others likely cannot. This study provides the foundation for future studies of Gardnerella within the urinary tract and its possible contribution to lower urinary tract symptoms.

#### **THE EFFECT OF MINDFULNESS-BASED STRESS REDUCTION ON THE URINARY MICROBIOME IN INTERSTITIAL CYSTITIS**

Abigail Shatkin-Margolis, James White, Anne E Jedlicka, Tiffanie Tam, Austin Hill, Jennifer Yeung, Catrina C Crisp, Rachel N Pauls. *Int Urogynecol J*. 2021 May 15. doi: 10.1007/s00192-021-04812-z. Online ahead of print. PMID: 33991218 DOI: 10.1007/s00192-021-04812-z

The objective was to investigate the impact of mindfulness-based stress reduction therapy on the urinary microbiome of patients with interstitial cystitis/bladder pain syndrome. In this Institutional Review Board-approved prospective cohort study from the USA, patients with IC/BPS were recruited to attend an 8-week mindfulness-based stress reduction course involving yoga and meditation. Eligible participants were English-speaking women aged 18 or older with interstitial cystitis/bladder pain syndrome. All participants had a negative urinalysis within 2 months of enrollment and were currently undergoing first- or second-line treatment at the time of recruitment. The mindfulness-based stress reduction course met weekly for 1 h. A straight-catheter urine sample was obtained prior to and following the mindfulness-based stress reduction series. DNA from urine

samples underwent bacterial 16S ribosomal gene sequencing at Johns Hopkins University Laboratories followed by taxonomic abundance and diversity analysis by Resphera Biosciences Laboratory. Participants completed validated symptom questionnaires pre- and post-intervention. A total of 12 participants completed the 8-week course and were included in the analysis. The average age was 59 and the majority identified as white. Patient symptoms, measured by the Urogenital Distress Inventory Short Form and Interstitial Cystitis Symptom and Pain Indices, improved significantly. Overall composition of the urinary microbiome changed significantly and demonstrated an increase in diversity following the intervention. It was concluded that mindfulness-based stress reduction therapy improves patient symptoms and was associated with significant changes in the urinary microbiome in patients with IC/BPS.

#### **THE MICROBIOME AND UROLOGY**

*Young Sam Cho. Int Neurourol J. 2021;25 (1): 1-2. Publication Date (Web): 2021 March 31 (Editorial). doi:<https://doi.org/10.5213/inj.2121edi.001>*

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Research on the microbiome is currently in the spotlight, and researchers are actively exploring the role of the microbiome in a wide variety of urological diseases. The complex microbial communities colonizing the human body have been recognized as major factors with a very close relationship to the pathogenesis of various diseases. In the past, healthy human urine was originally considered to be a sterile body fluid based on routine urine culture techniques. With the advent of modern DNA sequencing technology, such as 16S ribosomal RNA (rRNA) gene or whole-metagenome sequencing, slowly or fastidiously growing bacteria were detected as unique commensal flora in the urinary tract.

*See also Nickel et al under Hunner Lesion*

#### **OVERACTIVE BLADDER VERSUS INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME**

##### **CLUSTERING OF PATIENTS WITH OVERACTIVE BLADDER SYNDROME**

*James Gross, Joel M Vetter, H Henry Lai. BMC Urol. 2021 Mar 19;21(1):41. doi: 10.1186/s12894-021-00812-9. PMID: 33740925 PMCID: PMC7980623 DOI: 10.1186/s12894-021-00812-9*

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Overactive bladder is a heterogeneous condition with poorly characterized clinical phenotypes. To discover potential patient subtypes in patients with overactive bladder (OAB), Gross and colleagues used consensus clustering of their urinary symptoms and other non-urologic factors. Clinical variables included in the k-means consensus clustering included OAB symptoms, urinary incontinence, anxiety, depression, psychological stress, somatic symptom burden, reported childhood traumatic exposure, and bladder pain. 48 OAB patients seeking care of their symptoms were included. k-means consensus clustering identified two clusters of OAB patients: a urinary cluster and a systemic cluster. The systemic cluster, which consisted of about half of the cohort (48%), was characterized by significantly higher psychosocial burden of anxiety, depression, psychological stress, somatic symptom burden, and reported exposure to traumatic stress as a child, compared to the urinary cluster. The systemic cluster also reported more intense bladder pain, more widespread distribution of pain. The systemic cluster had worse urinary incontinence and quality of life. The two clusters were indistinguishable by their urgency symptoms. The two OAB clusters were different from patients with IC/BPS (worse urgency incontinence and less pain). It was concluded that the OAB population is heterogeneous and symptom-based clustering has identified two clusters of OAB patients (a systemic cluster vs. a bladder cluster). Understanding the pathophysiology of OAB subtypes may facilitate treatments. The authors compared the bladder pain and urinary incontinence scores of our two identified OAB clusters to a known IC/BPS cohort to verify that their OAB population was not an IC/BPS population that was misclassified as patients with OAB. Results showed that the systemic cluster had significantly less bladder pain and more urinary incontinence compared to IC/BPS patients. They are of the opinion that the systemic cluster was not simply an IC/BPS population mimicking OAB. Even though the systemic cluster had higher pain and psychosocial symptoms compared to the urinary cluster, the systemic cluster had significantly less bladder pain and more urinary incontinence compared to IC/BPS. Furthermore, the patients in both clusters were classified as OAB using a previously described independent nomogram, which had a diagnostic accuracy of 94% in their validation cohort. These findings make it unlikely that patients in the systemic cluster had IC/BPS, which further supports this previously unrecognized cluster as a subtype of OAB.

#### **CYSTOSCOPES**

**MARKET READINESS FOR SINGLE-USE CYSTOSCOPES ACCORDING TO UROLOGISTS AND PROCUREMENT MANAGERS WORLDWIDE**

*Dinah Rindorf, Sara Larsen, Lotte Ockert, Helene Jung, Claus Dahl. Res Rep Urol. 2021 May 6;13:221-226. doi: 10.2147/RRU.S309602. eCollection 2021. PMID: 33987109 PMCID: PMC8110249 DOI: 10.2147/RRU.S309602*

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Single-use endoscopes have been subjected to increased awareness in recent years, and several new single-use cystoscopes (eg Ambu® aScope 4 Cysto) have entered the market. However, the market readiness for such single-use cystoscopes remains unknown. This study from Denmark investigates the worldwide market readiness for single-use cystoscopes among urologists and procurement managers (PMs) from Europe, Japan, and the US. An online survey using QuestionPro® was distributed to urologists and PMs in France, Germany, Italy, Japan, Spain, the UK, and the US between March 10, 2020 and July 14, 2020. All surveys were translated into the respective local language. Statistical analyses were performed using the software package Stata/SE version 16.1, StataCorp. Fisher's exact test was used to analyze categorical variables and simple linear regression was applied to continuous variables. A total of 415 urologists and PMs completed the survey (343 [82.7%] urologists and 72 [17.3%] PMs). Seventy (16.9%) were from Japan, 100 (24.1%) were from the US, and 245 (59.0%) were evenly distributed across the following European countries: France, Germany, Italy, Spain, and the UK. On average, respondents indicated that they would consider converting to single-use in 44.5% of their cystoscopy procedures. Respondents anticipated significantly higher conversion when they (1) used single-use ureteroscopes in their department, (2) were concerned about cystoscopy-related infection as a result of contaminated cystoscopes, (3) were members of their institution's value committee, or (4) considered cost-transparency to be important when purchasing cystoscopes. This study investigated the marked readiness for single-use cystoscopes according to urologists and PMs worldwide. Respondents indicated a willingness to convert to single-use cystoscopes in nearly half (44.5%) of their cystoscopy procedures. Respondents that were concerned about cystoscopy-related infections as a result of contaminated cystoscopes indicated a significantly higher anticipated conversion rate.

**OMICS**

**OMICS IN UROLOGY: AN OVERVIEW ON CONCEPTS, CURRENT STATUS AND FUTURE PERSPECTIVES**

*Andrea Panunzio, Alessandro Tafuri, Alessandro Princiotta, Ilaria Gentile, Giovanni Mazzucato, Nicolò Trabacchin, Alessandro Antonelli, Maria Angela Cerruto. Urologia. 2021 Jun 25;3915603211022960. doi: 10.1177/03915603211022960. Online ahead of print. PMID: 34169788 DOI: 10.1177/03915603211022960.*

Recent technological advances in molecular biology have led to great progress in the knowledge of structure and function of cells and their main constituents. In this setting, 'omics' is standing out in order to significantly improve the understanding of etiopathogenetic mechanisms of disease and contribute to the development of new biochemical diagnostics and therapeutic tools. 'Omics' indicates the scientific branches investigating every aspect of cell's biology, including structures, functions and dynamics pathways. The main 'omics' are genomics, epigenomics, proteomics, transcriptomics, metabolomics and radiomics. Their diffusion, success and proliferation, addressed to many research fields, has led to many important acquisitions, even in Urology. The aim of this narrative review is to define the state of art of 'omics' application in Urology, describing the most recent and relevant findings, in both oncological and non-oncological diseases, focusing the attention on urinary tract infections, interstitial cystitis, urolithiasis, prostate cancer, bladder cancer and renal cell carcinoma. In Urology the majority of 'omics' applications regard the pathogenesis and diagnosis of the investigated diseases. In future, its role should be implemented in order to develop specific predictors and tailored treatments.

**CLASSIFICATION AND GUIDELINES: CHRONIC PAIN – ICD-11, NICE**

**CLASSIFICATION OF CHRONIC PAIN FOR THE INTERNATIONAL CLASSIFICATION OF DISEASES (ICD-11): RESULTS OF THE 2017 INTERNATIONAL WHO FIELD TESTING**

*Antonia Barke, Beatrice Korwisi, Robert Jakob, Nenad Konstanjsek, Winfried Rief, Rolf-Detlef Treede. Pain. 2021 Apr 8. doi: 10.1097/j.pain.0000000000002287. Online ahead of print. PMID: 33863861 DOI: 10.1097/j.pain.0000000000002287*

Because chronic chronic pain has been poorly represented in the International statistical classification of diseases and related health problems (ICD) despite its significant contribution to the burden of disease worldwide, the International Association for the Study of Pain (IASP) developed a classification of chronic pain that was included in the ICD-11 version as 'MG30' and approved by the World Health Assembly in 2019. The

objective of this field test was to determine its properties. A web-based survey using the WHO-FiT platform recruited 177 health-care professionals from all WHO regions. Following a training on coding chronic pain hosted by the IASP website, participants evaluated 18 diagnostic codes (lines) of the 2017 frozen version of the ICD-11 and 12 vignettes (cases) describing chronic pain conditions. Correctness, ambiguity and perceived difficulty of the coding were compared between the ICD-11 and the ICD-10 and the applicability of the morbidity rules for the ICD-11 verified. In the line coding, 43.0% of correct chronic pain diagnoses assigned with the ICD-10 contrasted with 63.2% with the ICD-11. Especially in cases in which the chronic pain is regarded as the symptom of an underlying disease, the ICD-11 (63.5%) commanded more correct diagnoses than the ICD-10 (26.8%). The case coding was on average 83.9% accurate, only in 1.6% of cases any difficulty was perceived. The morbidity rules were applied correctly in 74.1% of cases. From a coding perspective, the ICD-11 is superior to the ICD-10 in every respect, offering better accuracy, difficulty and ambiguity in coding chronic pain conditions.

#### **CLASSIFICATION ALGORITHM FOR THE INTERNATIONAL CLASSIFICATION OF DISEASES-11 CHRONIC PAIN CLASSIFICATION: DEVELOPMENT AND RESULTS FROM A PRELIMINARY PILOT EVALUATION**

*Beatrice Korwisi, Ginea Hay, Nadine Attal, Qasim Aziz, Michael I Bennett, Rafael Benoliel, Milton Cohen, Stefan Evers, Maria Adele Giamberardino, Stein Kaasa, Eva Kosek, Patricia Lavand'homme, Michael Nicholas, Serge Perrot, Stephan Schug, Blair H Smith, Peter Svensson, Johan W S Vlaeyen, Shuu-Jiun Wang, Rolf-Detlef Treede, Winfried Rief, Antonia Barke. Pain. 2021 Jul 1;162(7):2087-2096. doi: 10.1097/j.pain.0000000000002208. PMID: 33492033 DOI: 10.1097/j.pain.0000000000002208*

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The International Classification of Diseases-11 (ICD-11) chronic pain classification includes about 100 chronic pain diagnoses on different diagnostic levels. Each of these diagnoses requires specific operationalized diagnostic criteria to be present. The classification comprises more than 200 diagnostic criteria. The aim of the Classification Algorithm for Chronic Pain in ICD-11 (CAL-CP) is to facilitate the use of the classification by guiding users through these diagnostic criteria. The diagnostic criteria were ordered hierarchically and visualized in accordance with the standards defined by the Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. The resulting linear decision tree underwent several rounds of iterative checks and feedback by its developers, as well as other pain experts. A preliminary pilot evaluation was conducted in the context of an ecological implementation field study of the classification itself. The resulting algorithm consists of a linear decision tree, an introduction form, and an appendix. The initial decision trunk can be used as a standalone algorithm in primary care. Each diagnostic criterion is represented in a decision box. The user needs to decide for each criterion whether it is present or not, and then follow the respective yes or no arrows to arrive at the corresponding ICD-11 diagnosis. The results of the pilot evaluation showed good clinical utility of the algorithm. The CAL-CP can contribute to reliable diagnoses by structuring a way through the classification and by increasing adherence to the criteria. Future studies need to evaluate its utility further and analyze its impact on the accuracy of the assigned diagnoses.

#### **COMPARING THE ICD-11 CHRONIC PAIN CLASSIFICATION WITH ICD-10: HOW CAN THE NEW CODING SYSTEM MAKE CHRONIC PAIN VISIBLE? A STUDY IN A TERTIARY CARE PAIN CLINIC SETTING**

*Nantthasorn Zinboonyahgoon, Choopong Luansritisakul, Sarasate Eiamtanasate, Sirikan Duangburong, Virachat Sanansilp, Beatrice Korwisi, Antonia Barke, Winfried Rief, Rolf-Detlef Treede. Pain. 2021 Jul 1;162(7):1995-2001. doi: 10.1097/j.pain.0000000000002196. PMID: 33449507 DOI: 10.1097/j.pain.0000000000002196*

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Pain is a frequent reason for patients to ask for medical services. However, systematic information about the extent and impact of pain, especially in developing countries, has not been available up to now. The authors evaluated whether the 11th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD) can fill this gap by coding all electronic out-patient medical records of the pain clinic at Siriraj Hospital in Thailand in 2019 (8714 visits), using the ICD-10 and ICD-11 browsers referenced on the WHO websites. The 3 most frequent pain-related codes in ICD-10 were R52.2 "other chronic pain" (29%), M54.5 "low back pain" (18%), and M79.6 "pain in limb" (13%). In ICD-11, the 3 most frequent codes were MG30.31 "chronic secondary musculoskeletal pain associated with structural changes" (28%), MG30.51 "chronic peripheral neuropathic pain" (26%), and MG30.10 "chronic cancer pain" (23%). Thus, using the currently valid ICD-10 system, roughly one-third of patient encounters were coded as "other chronic pain," and the next 2 were specifying the pain region rather than any underlying cause. By contrast, ICD-11 coding of the same patients identified underlying causes (bones and joints, somatosensory nervous system, cancer, or surgery), which provide guidance towards differential patient management. In their pain clinic, most patients suffered from chronic cancer pain, chronic neuropathic pain, and chronic secondary musculoskeletal pain, which were poorly

defined or nonexistent in the current ICD-10 coding system. Compared with the ICD-10, the ICD-11 provides more detailed diagnostic categories and is more informative for clinical use, research, and resource allocation for pain-related conditions.

#### **PRAGMATIC BUT FLAWED: THE NICE GUIDELINE ON CHRONIC PAIN**

*Christopher Eccleston, Dominic Aldington, Andrew Moore, Amanda C de C Williams. Lancet. 2021 May 29;397(10289):2029-2031. doi: 10.1016/S0140-6736(21)01058-8. PMID: 34062133 DOI: 10.1016/S0140-6736(21)01058-8*

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The 2021 UK National Institute for Health and Care Excellence (NICE) guidance on chronic pain<sup>1</sup> (chronic primary pain, chronic secondary pain, or both) and the management of chronic primary pain among people older than 16 years has prompted debate among clinicians. The NICE recommendations on assessment of chronic pain, with person-centred assessment at its heart, make good sense and are to be welcomed. But the recommendations on chronic primary pain are more controversial. Chronic primary pain is a public health problem: globally, low back pain ranks highest for the health metric of estimated years lived with disability. The International Classification of Diseases 11th Revision (ICD-11) classifies many conditions in which persistent unremitting pain is the primary problem as chronic primary pain.<sup>3</sup> This group of pain disorders includes fibromyalgia, complex regional pain syndrome, chronic primary headache, and orofacial pain, as well as visceral pain and musculoskeletal pain, each of which contains heterogeneous conditions that require individual approaches to treatment. Clinical guidelines need to recognise this variety in chronic primary pain. In the opinion of the authors, the NICE guideline takes an oversimplified approach and presents chronic primary pain as a diagnosis of exclusion: “Think about a diagnosis of chronic primary pain if there is no clear underlying (secondary) cause, or the pain or its impact is out of proportion to any observable injury or disease, particularly when the pain is causing significant distress and disability.” They share the concerns of the UK Faculty of Pain Medicine and others about this misreading of chronic primary pain.

See also:

#### **CHRONIC PAIN (PRIMARY AND SECONDARY) IN OVER 16S: ASSESSMENT OF ALL CHRONIC PAIN AND MANAGEMENT OF CHRONIC PRIMARY PAIN**

*National Institute for Health and Care Excellence (UK); 2021 Apr 7. National Institute for Health and Care Excellence: Clinical Guidelines. PMID: 33939353 Bookshelf ID: NBK569960 Free Books & Documents*

This NICE guideline covers assessing all chronic pain (chronic primary pain, chronic secondary pain, or both) and managing chronic primary pain in people aged 16 years and over. Chronic primary pain is pain with no clear underlying cause, or pain (or its impact) that is out of proportion to any observable injury or disease.

#### **PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE**

##### **PENTOSAN POLYSULFATE MACULOPATHY**

*Aaron Lindeke-Myers, Adam M Hanif, Nieraj Jain. Surv Ophthalmol. 2021 May 14;S0039-6257(21)00123-5. doi: 10.1016/j.survophthal.2021.05.005. Online ahead of print. PMID: 34000253.*

*DOI:10.1016/j.survophthal.2021.05.005*

Pentosan polysulfate sodium (PPS), a semisynthetic sulfated polysaccharide, is the only FDA-approved oral therapy for interstitial cystitis. Recent studies have described a progressive, vision-threatening macular condition associated with long-term PPS use. The authors reviewed all publications concerning PPS maculopathy to consolidate known clinical features and to evaluate the strength of this association. Current literature supports a strong dose-dependent association between PPS exposure and a progressive maculopathy impacting the retinal pigment epithelium (RPE) and RPE-photoreceptor interface that may worsen even after drug cessation. Initial symptoms may include prolonged dark adaptation and difficulty reading with relative visual acuity preservation. Fundus examination often shows macular pigment clumps corresponding to lesions of focal RPE thickening. Fundus autofluorescence most clearly depicts the condition, with a distinctive pattern of hypo- and hyperautofluorescent spots in the posterior pole that sometimes extend to the retinal periphery. Many cases also show a characteristic peripapillary hypoautofluorescent halo. Near infrared reflectance may aid in early detection. RPE atrophy, cystoid macular edema, and macular neovascularization may also occur, potentially resulting in loss of central acuity. This newly described association implies significant public health risk. Ophthalmologists should screen PPS users with multimodal retinal imaging, and prescribers should minimize dose and duration of PPS use.

**CASE REPORT: PENTOSAN POLYSULFATE SODIUM MACULOPATHY ORIGINALLY DIAGNOSED AS PATTERN MACULAR DYSTROPHY**

Aaron W Case, Matthew J Anderson, Lovelee E Sayomac. *Optom Vis Sci.* 2021 May 25. doi: 10.1097/OPX.0000000000001702. Online ahead of print. PMID: 34039907 DOI: 10.1097/OPX.0000000000001702

Pentosan polysulfate sodium (PPS) maculopathy is a clinical entity characterized by a pigmented maculopathy in the setting of chronic exposure to PPS. Pentosan polysulfate sodium is indicated for discomfort related to interstitial cystitis/painful bladder syndrome. Given a reported interstitial cystitis/painful bladder syndrome prevalence up to 2%, recognition is critical to mitigate visual sequelae. The authors present an observational case report demonstrating typical findings of PPS maculopathy in a patient originally diagnosed with a pattern macular dystrophy. They demonstrate the importance of medical history, medication profile review, and multimodal imaging in the diagnosis and management. The patient provided written informed consent for medical information and images to be published. A 55-year-old White woman presented with a painless, bilateral loss of vision and bilateral pigmented maculopathy that was initially diagnosed as pattern macular dystrophy. Detailed review of medical history, medication profile, and subsequent studies, including optical coherence tomography, near-infrared reflectance imaging, fundus autofluorescence, fluorescein angiography, and genetic studies, ultimately led to the diagnosis of PPS maculopathy. Pentosan polysulfate sodium was discontinued, and ongoing surveillance with multimodal imaging was encouraged. Because toxic maculopathies are an uncommon diagnosis, screening and recognition of PPS maculopathy are critical in the primary eye care setting. Discontinuation of the insulting agent may be necessary to prevent potentially severe and irreversible vision loss in the at-risk population.

**PAIN/CHRONIC PELVIC PAIN**

**NOCIPLASTIC PAIN: TOWARDS AN UNDERSTANDING OF PREVALENT PAIN CONDITIONS**

Mary-Ann Fitzcharles 1, Steven P Cohen 2, Daniel J Clauw 3, Geoffrey Littlejohn 4, Chie Usui 5, Winfried Häuser 6. *Lancet.* 2021 May 29;397(10289):2098-2110. doi: 10.1016/S0140-6736(21)00392-5. PMID: 34062144 DOI: 10.1016/S0140-6736(21)00392-5

Nociplastic pain is the semantic term suggested by the international community of pain researchers to describe a third category of pain that is mechanistically distinct from nociceptive pain, which is caused by ongoing inflammation and damage of tissues, and neuropathic pain, which is caused by nerve damage. The mechanisms that underlie this type of pain are not entirely understood, but it is thought that augmented CNS pain and sensory processing and altered pain modulation play prominent roles. The symptoms observed in nociplastic pain include multifocal pain that is more widespread or intense, or both, than would be expected given the amount of identifiable tissue or nerve damage, as well as other CNS-derived symptoms, such as fatigue, sleep, memory, and mood problems. This type of pain can occur in isolation, as often occurs in conditions such as fibromyalgia or tension-type headache, or as part of a mixed-pain state in combination with ongoing nociceptive or neuropathic pain, as might occur in chronic low back pain. It is important to recognise this type of pain, since it will respond to different therapies than nociceptive pain, with a decreased responsiveness to peripherally directed therapies such as anti-inflammatory drugs and opioids, surgery, or injections.

**AN UPDATE ON THE MANAGEMENT OF CHRONIC PELVIC PAIN IN WOMEN**

K Vincent, E Evans. *Anaesthesia.* 2021 Apr;76 Suppl 4:96-107. doi: 10.1111/anae.15421. PMID: 33682093 DOI: 10.1111/anae.15421

Chronic pelvic pain represents a major public health problem for women and impacts significantly on their quality of life. Yet it is under-researched and a challenge to manage. Women who suffer from chronic pelvic pain frequently describe their healthcare journey as long, via a variety of specialists and frustrating, with their pain often dismissed. Aetiological factors and associations are best conceptualised using the 'three P's' model of predisposing, precipitating and perpetuating factors. This integrates the numerous biological, psychological and social contributors to the complex, multifactorial nature of chronic pelvic pain. Overall management involves analgesia, hormonal therapies, physiotherapy, psychological approaches and lifestyle advice, which like other chronic pain conditions relies on a multidisciplinary team approach delivered by professionals experienced and trained in managing chronic pelvic pain.

**CLINICAL OUTCOMES OF A MULTIDISCIPLINARY FEMALE CHRONIC PELVIC PAIN PROGRAM**

Lauren C Westbay, William Adams, Margaret Kistner, Cynthia Brincat, Larissa Bresler, Linda C Yang, Colleen M Fitzgerald. *Female Pelvic Med Reconstr Surg.* 2021 Mar 24. doi: 10.1097/SPV.0000000000001045. Online ahead of print. PMID: 34009830 DOI: 10.1097/SPV.0000000000001045

The aim of this study was to describe patient-reported longitudinal outcomes in a multidisciplinary female chronic pelvic pain (CPP) program. The authors conducted a retrospective cohort study for women cared for in a tertiary, multidisciplinary, female (CPP) program between 2012 and 2017. Patient demographics were collected from electronic medical records. Patients completed the numerical rating scale for pain, Pain Disability Index (PDI), and Patient Global Impression of Improvement scale at each visit. Mixed-effects models were used to assess change in patient responses over time. Patients with a mean age of 44.3 years (SD, 14.6) and median duration of symptoms of 3 years (interquartile range, 1.0-7.0) were assessed in this analysis. The primary diagnosis was pelvic floor myofascial pain (67%). On multivariable analysis, numerical rating scale scores decreased by -0.11 point [95% confidence interval (CI), -0.20 to -0.01] every 3 months. On multivariable analysis, total PDI score decreased by -0.88 point, and PDI sexual subscores decreased by -0.29 point every 3 months. A higher (worse) Patient Global Impression of Improvement score was associated with a higher (worse) PDI score at follow-up. Patients in a multidisciplinary CPP program demonstrated improvement over time in pain disability that was associated with an overall global impression of improvement.

#### **EFFICACY AND SAFETY OF DRUG COMBINATIONS FOR CHRONIC PELVIC PAIN: PROTOCOL FOR A SYSTEMATIC REVIEW**

Mohammed Mohiuddin, Rex Park, Ursula Wesselmann, Caroline Pukall, Keith Jarvi, Curtis Nickel, Christopher Doiron, Ian Gilron. *JMIR Res Protoc.* 2021 May 17;10(5):e21909. doi: 10.2196/21909. PMID: 33999006 DOI: 10.2196/21909

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Chronic pelvic pain with various etiologies and mechanisms affects men and women and is a major challenge. Monotherapy is often unsuccessful for chronic pelvic pain, and combinations of different classes of medications are frequently prescribed, with the expectation of improved outcomes. Although a number of combination trials for chronic pelvic pain have been reported, the authors from Canada and USA are not aware of any systematic reviews of the available evidence on combination drug therapy for chronic pelvic pain. They have developed a protocol for a systematic review to evaluate available evidence of the efficacy and safety of drug combinations for chronic pelvic pain. This systematic review will involve a detailed search of randomized controlled trials investigating drug combinations to treat chronic pelvic pain in adults. The databases searched will include the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from their inception until the date the searches are run to identify relevant studies. The primary outcome will be pain relief measured using validated scoring tools. Secondary outcomes, where reported, will include the following: adverse events, serious adverse events, sexual function, quality of life, and depression and anxiety. Methodological quality of each included study will be assessed using the Cochrane Risk of Bias Tool. The systematic review defined by this protocol is expected to synthesize available good quality evidence on combination drug therapy in chronic pelvic pain, which may help guide future research and treatment choices for patients and their health care providers. This review will provide a clearer understanding of the efficacy and safety of combination pharmacological therapy for chronic pelvic pain.

#### **CHRONIC PELVIC PAIN EDUCATIONAL EXPERIENCE AMONG MINIMALLY INVASIVE GYNECOLOGIC SURGERY FELLOWS AND RECENT GRADUATES: A NEEDS ASSESSMENT**

Megan S Orlando, Janelle K Moulder, Jorge F Carrillo, Erin T Carey, Austin D Findley, Diana Atashroo, Mark Dassel. *J Minim Invasive Gynecol.* 2021 May 4;S1553-4650(21)00199-0. doi: 10.1016/j.jmig.2021.04.021. Online ahead of print. PMID: 33962024 DOI: 10.1016/j.jmig.2021.04.021

Learning to evaluate and treat chronic pelvic pain (CPP) is an established curriculum objective within the Fellowship in Minimally Invasive Gynecologic Surgery (FMIGS). The authors' aim was to investigate current educational experiences related to the evaluation and management of CPP and the impacts of those experiences on FMIGS fellows and recent fellowship graduates, including satisfaction, confidence in management, and clinical interest in CPP. The AAGL-Elevating Gynecologic Surgery Special Interest Group for pelvic pain developed a 33-item survey tool to investigate the following topics: 1) current educational experiences with the assessment and management of patients with CPP, 2) satisfaction with fellowship training in CPP, 3) perceived preparedness to treat patients with CPP, 4) plans to incorporate management of CPP into clinical practice, and 5) perceived desires to expand CPP exposure. Composite scores were created to examine experiences related to diseases associated with CPP and pharmaceutical and procedural treatment options. The survey was distributed via AAGL email lists and offered on FMIGS social media sites August 2017 to November 2017 to all active FMIGS fellows

and individuals who graduated the fellowship during the preceding five years. Fifty-three of 82 (65%) current FMIGS fellows and 104 of 169 (62%) recent fellowship graduates completed the survey. Only, 66% of current fellows endorsed working with a fellowship faculty member whose clinical work focused on CPP. Most current fellows reported having a "good amount" or "extensive" experience with superficial endometriosis (39/53, 74%) and deeply infiltrative endometriosis (34/53, 64%), while the majority reported having "no" or "little" experience with frequently comorbid conditions like irritable bowel syndrome (68%), pelvic floor tension myalgia (55%), and interstitial cystitis/painful bladder syndrome (51%). For both current fellows and recent graduates, increased CPP Disease Experience composite scores were associated with satisfaction with CPP training, perceived preparedness to treat patients with CPP, and the desire to incorporate the treatment of CPP into future clinical practice of current fellows indicated that they believed an expanded pelvic pain curriculum should be part of the FMIGS fellowship. This needs assessment of FMIGS fellows and recent graduates suggests that there are gaps between FMIGS curriculum objectives and current educational experiences, and that fellows desire increased CPP exposure. Expansion and standardization of the CPP educational experience is needed and could lead to increased focus on this disease process among subspecialty benign gynecologic surgeons.

#### **PELVIC FLOOR PHYSICAL THERAPY FOR PELVIC FLOOR HYPERTONICITY: A SYSTEMATIC REVIEW OF TREATMENT EFFICACY**

*Daniëlle A van Reijn-Baggen, Ingrid J M Han-Geurts, Petra J Voorham-van der Zalm, Rob C M Pelger, Caroline H A C Hagens-van Miert, Ellen T M Laan. Sex Med Rev. 2021 Jun 11;S2050-0521(21)00012-3. doi: 10.1016/j.sxmr.2021.03.002. Online ahead of print. PMID: 34127429 DOI: 10.1016/j.sxmr.2021.03.002*

Hypertonicity of the pelvic floor (PFH) is a disabling condition with urological, gynecological and gastrointestinal symptoms, sexual problems and chronic pelvic pain, impacting quality of life. Pelvic floor physical therapy (PFPT) is a first-line intervention, yet no systematic review on the efficacy of PFPT for the treatment of PFH has been conducted. This study from the Netherlands systematically appraised the current literature on efficacy of PFPT modalities related to PFH. The literature search resulted in 10 eligible studies including 4 RCTs, 5 prospective studies, and 1 case study published between 2000 and 2019. Most studies had a high risk of bias associated with the lack of a comparison group, insufficient sample sizes and non-standardized interventions. Six studies were of low and 4 of medium quality. All studies were narratively reviewed. Three of 4 RCTs found positive effects of PFPT compared to controls on five out of 6 outcome measures. The prospective studies found significant improvements in all outcome measures that were assessed. PFPT seems to be efficacious in patients with chronic prostatitis, chronic pelvic pain syndrome, vulvodynia, and dyspareunia. Smallest effects were seen in patients with interstitial cystitis and painful bladder syndrome.

#### **IRRITABLE BOWEL SYNDROME**

##### **POST-INFECTION IRRITABLE BOWEL SYNDROME**

*Antonio Berumen, Adam L Edwinston, Madhusudan Grover. Gastroenterol Clin North Am. 2021 Jun;50(2):445-461. doi: 10.1016/j.gtc.2021.02.007. Epub 2021 Apr 23. PMID: 34024451 DOI: 10.1016/j.gtc.2021.02.007*

Epidemiologic data support the concept that acute gastrointestinal infection is one of the strongest risk factors for development of irritable bowel syndrome (IBS). Risk of post-infection IBS (PI-IBS) seems to be greater with bacterial and protozoal than viral enterocolitis. Younger individuals, women, and those with severe enterocolitis are more likely to develop PI-IBS. Disease mechanisms in animal models and humans involve chronic perturbation of intestinal microbiome, epithelial and neuronal remodeling, and immune activation. These mechanisms can lead to luminal (increased proteolytic activity, altered bile acid composition) and physiologic (increased permeability, transit changes, and visceral hypersensitivity) alterations that can mediate PI-IBS symptoms.

#### **FIBROMYALGIA AND CHRONIC FATIGUE SYNDROME**

##### **CHRONIC FATIGUE SYNDROME: ABNORMALLY FAST MUSCLE FIBER CONDUCTION IN THE MEMBRANES OF MOTOR UNITS AT LOW STATIC FORCE LOAD**

*E G Klaver-Krol, H J Hermens, R C Vermeulen, M M Klaver 4, H Luyten, N R Henriquez, M J Zwarts. Clin Neurophysiol. 2021 Apr;132(4):967-974. doi: 10.1016/j.clinph.2020.11.043. Epub 2021 Jan 29. PMID: 33639451 DOI: 10.1016/j.clinph.2020.11.043*

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are disorders of unknown etiology and unclear pathophysiology, with overlapping symptoms of - especially muscular -fatigue and pain. Studies have shown

increased muscle fiber conduction velocity (CV) in the non-painful muscles of FM patients. The authors investigated whether CFS patients also show CV abnormalities. Females with CFS, with FM, and healthy controls underwent surface electromyography of the biceps brachii, loaded up to 20% of maximum strength, during short static contractions. The mean CV and motor unit potential (MUP) velocities with their statistical distribution were measured. The CV changes with force differed between CFS-group and both FM-group and controls. The CV of the CFS-group increased excessively with force ( $P < 0.001$ ), whereas that of the controls increased only slightly and non-significantly, and that of the FM-group did not increase at all. In the CFS-group, the number of MUPs conveying very high conduction velocities increased abundantly with force and the MUPs narrowed. The authors are of the opinion that their results suggest disturbed muscle membrane function in CFS patients, in their motor units involved in low force generation. Central neural deregulation may contribute to this disturbance. These findings MAY help to detangle the underlying mechanisms of CFS.

#### **FIBROMYALGIA AS A HETEROGENEOUS CONDITION: SUBGROUPS OF PATIENTS BASED ON PHYSICAL SYMPTOMS AND COGNITIVE-AFFECTIVE VARIABLES RELATED TO PAIN**

*M Pilar Martínez, Ana I Sánchez, Germán Prados, María J Lami, Beatriz Villar, Elena Miró. Span J Psychol. 2021 May 18;24:e33. doi: 10.1017/SJP.2021.30. PMID: 34002687 DOI: 10.1017/SJP.2021.30*

Fibromyalgia (FM) is a chronic syndrome characterized by heterogeneous clinical manifestations and knowing this variability can help to develop tailored treatments. To understand better the heterogeneity of FM the present cross-sectional study analyzed the role of several physical symptoms (pain, fatigue and poor sleep quality) and cognitive-affective variables related to pain (pain catastrophizing, pain vigilance, self-efficacy in pain management, and pain acceptance) in the configuration of clinical profiles. A sample of 161 women with FM fulfilled an interview and several self-report measures to explore physical symptoms, cognitive-affective variables, disability and psychopathology. To establish FM groups a hierarchical cluster analysis was performed. The findings revealed three clusters that differed in the grouping variables, Wilks'  $\lambda = .17$ ,  $F(14, 304) = 31.50$ ,  $p < .001$ ,  $\eta^2 = .59$ . Group 1 ( $n = 72$ ) was characterized by high physical and psychological affectation, Group 2 ( $n = 19$ ) by low physical affectation and high pain self-efficacy, and Group 3 ( $n = 70$ ) by moderate physical affectation and low pain catastrophizing. The external validation of the clusters was confirmed, Wilks'  $\lambda = .72$ ,  $F(4, 314) = 14.09$ ,  $p < .001$ ,  $\eta^2 = .15$ , showing Group 1 the highest levels of FM impact and psychopathological distress. Considering the distinctive clinical characteristics of each subgroup therapeutic strategies addressed to the specific needs of each group were suggested. Assessing FM profiles may be key for a better understanding and approach of this syndrome.

#### **LUPUS CYSTITIS**

#### **SUCCESSFUL TREATMENT OF REFRACTORY CYSTITIS ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITH BELIMUMAB**

*Liping Xu, Xinwei Song, Qiaoding Dai, Tianrong Guan, Yan Zhang, Na Lin, Ji-An Wang. Int Immunopharmacol. 2021 Apr 6;96:107574. doi: 10.1016/j.intimp.2021.107574. Online ahead of print. PMID: 33836367 DOI: 10.1016/j.intimp.2021.107574*

Lupus cystitis (LC) is a rare manifestation of SLE, the diagnosis of LC is challenging, especially in the absence of other systemic manifestations or the obvious disease activity index of SLE, further cystoscopy and bladder biopsy are crucial. The symptoms of cystitis could be controlled with high-dose GC, but in the process of GC reduction, the condition repeated. Here the authors report one case of refractory LC treated with Belimumab. The case is a 45-year-old female patient who had SLE and presented with urinary urgency, frequency and pain for more than 3 years. Laboratory assays revealed high ANA, reduced complement 3 level, proteinuria, significantly elevated Leukocyte esterase and leukocyte in urine, with the negative urinary culture of bacteria and mycoplasma, meanwhile, the cystoscopy and bladder biopsy showed interstitial inflammation. Confirming the diagnosis of refractory SLE-LC, recommended-dose Belimumab (10 mg/kg fortnightly for 3 times, monthly for 6 times) was administered, resulting in the normalization of urinary activity and significant reductions in leukocyte counts and protein levels of urine. No lupus cystitis relapse or SLE activity occurred during 10 months of follow-up. The authors suggest that their case confirms the efficacy and good follow-up outcomes of Belimumab treatment for refractory SLE-LC.

#### **VERY SEVERE AND REFRACTORY NONINFECTIOUS CYSTITIS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: POTENTIAL ROLE OF RITUXIMAB THERAPY**

*Vanessa Ocampo-Piraquive, Inés Mondragón-Lenis, Juan G De Los Rios, Carlos A Cañas. Case Rep Rheumatol. 2021 Feb 27;2021:6610111. doi: 10.1155/2021/6610111. eCollection 2021. PMID: 33728086 PMCID: PMC7936892 DOI: 10.1155/2021/6610111*

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Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with various clinical manifestations, including, rarely, a form of interstitial cystitis (lupus cystitis, LC). LC can be asymptomatic and usually has discrete symptoms that improve with conventional therapies available for SLE and/or typical interstitial cystitis. A very severe and refractory form is rarely described. In this study, the authors present four patients with SLE and a very severe form of non-infectious cystitis refractory to the different forms of treatment described. The clinical descriptions of the cases, demographic factors, manifestations associated with SLE, and clinical and paraclinical manifestations related to cystitis, treatments, and outcomes are provided. A proposal for the pathogenesis of this condition is based on the common findings of these patients, including the fact that three were in SLE remission and all four receiving rituximab as induction and/or maintenance therapy.

## **SJÖGREN'S SYNDROME**

### **SJÖGREN'S SYNDROME: A SYSTEMIC AUTOIMMUNE DISEASE**

*Simone Negrini, Giacomo Emmi, Monica Greco, Matteo Borro, Federica Sardanelli, Giuseppe Murdaca, Francesco Indiveri, Francesco Puppo. Clin Exp Med. 2021 Jun 7. doi: 10.1007/s10238-021-00728-6. Online ahead of print. PMID: 34100160 DOI: 10.1007/s10238-021-00728-6*

Sjögren's syndrome is a chronic autoimmune disease characterized by ocular and oral dryness resulting from lacrimal and salivary gland dysfunction. Besides, a variety of systemic manifestations may occur, involving virtually any organ system. As a result, the disease is characterized by pleomorphic clinical manifestations whose characteristics and severity may vary greatly from one patient to another. Sjögren's syndrome can be defined as primary or secondary, depending on whether it occurs alone or in association with other systemic autoimmune diseases, respectively. The pathogenesis of Sjögren's syndrome is still elusive, nevertheless, different, not mutually exclusive, models involving genetic and environmental factors have been proposed to explain its development. The emergence of aberrant autoreactive B-lymphocytes, conducting to autoantibody production and immune complex formation, seems to be crucial in the development of the disease. The diagnosis of Sjögren's syndrome is based on characteristic clinical signs and symptoms, as well as on specific tests including salivary gland histopathology and autoantibodies. Recently, new classification criteria and disease activity scores have been developed primarily for research purposes and they can also be useful tools in everyday clinical practice. Treatment of Sjögren's syndrome ranges from local and symptomatic therapies aimed to control dryness to systemic medications, including disease-modifying agents and biological drugs. The objective of this review paper from Italy is to summarize the recent literature on Sjögren's syndrome, starting from its pathogenesis to current therapeutic options.

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