

International Painful Bladder Foundation

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

IPBF e-Newsletter and Research Update Issue 57, December 2020

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 impact continues
- Virtual Meetings
- Pan-European Pain Project IMI-Paincare – Review of 2020 and Engagement of Patient Organisations
- The Virtual Global Meeting of IC/BPS Patient Advocates Held on 5 December 2020
- Information Sought on Doctors/Clinics Treating IC/BPS Patients in African Countries
- EUPATI: Patient Engagement Through Education
- Calls to Rename “Pain Catastrophizing” Backed by International Patient-Researcher Partnership
- Keeping Track of Your Own Medical History
- New Books
- COVID-19: Information About COVID-19 And Useful Online Resources
- Overview of rescheduled upcoming events
- Research Update
- Donations & Sponsoring

COVID-19 IMPACT CONTINUES

With the challenging COVID-19 crisis continuing, conferences that had already been rescheduled had to be rescheduled yet again, and many 2020 meetings were transformed into virtual meetings, conferences and masterclasses. Meetings now scheduled for the latter half of 2021 are likely to be so-called “hybrid” meetings, in other words both physical and virtual.

This year, we have had great opportunities to participate in many online presentations and to peruse at our leisure abstracts and posters in the field of IC/BPS and the wider field of pelvic pain through virtual conferences, masterclasses and webinar training sessions which have remained available online. There has also been a considerable volume of literature published. However, one cannot help but notice the continuing lack of global consensus, particularly in relation to the different names for the same condition which is very confusing for new patients. This has been particularly noticeable in new abstracts, although published literature seems to show a possible trend towards IC/BPS. The issue of glomerulations also seems to be an area of confusion. Internationally accepted standard terminology, definitions and criteria for diagnosis and research would provide a sounder basis for meaningful progress in research, better treatment for patients and might go some way towards persuading all-important authorities to approve and reimburse treatment.

Recent online meetings and webinars have included the following virtual events:

50th ICS ANNUAL MEETING WENT VIRTUAL IN 2020

Like so many other organisations, the International Continence Society (ICS) had to cancel its planned 50th annual scientific meeting, replacing it with a virtual meeting 19-22 November 2020. This included a number of abstracts and posters on IC/BPS.

The presentations are available on demand on the platform for 3 months for those who registered and after that ICS 2020 delegates and ICS members will be able to access them on the ICS website indefinitely!

<https://www.ics.org/2020/programme> platform: <https://www.ics.org/news/1179>

ESSIC 2020 IC/BPS MASTERCLASS ONLINE

With the planned conference cancelled, the International Society for the Study of Bladder Pain Syndrome (ESSIC) organized a 2020 online Masterclass on IC/BPS comprising educational video presentations on many aspects of IC/BPS by leading experts together with 6 live discussion webinars.

You can find more information and the programme at <https://www.essic.org/masterclass-2020>. This masterclass will be available online until 31 December.

UROWEBINAR: LOCAL INTRAVESICAL INSTILLATION THERAPY OF IC/BPS (PRESENT AND FUTURE)

This webinar on 5 November was presented by IC/BPS experts Dr Dick Janssen from the Netherlands and Dr Sandor Lovasz from Hungary and organized by the European School of Urology. It is available online, see <https://uroweb.org/education/online-education/webinars/> under Recorded Webinars.

THE VIRTUAL ANNUAL MEETING OF THE GLOBAL INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SOCIETY (GIBS), INDIA, 5 & 6 SEPTEMBER 2020

The Indian GIBS society has been producing training webinars on IC/BPS for urologists and gynaecologists in India and surrounding countries throughout the year in collaboration with urology and gynaecology societies. The annual GIBS conference also had to be moved online. With more than 500 participants from 37 countries worldwide, it was a global virtual event and an ideal way of educating a maximum number of people, including patient advocates. It was also multidisciplinary with urologists, gynaecologists and other specialists and therapists speaking, including a number of well-known international experts from ESSIC. Participants were able to submit written questions both in advance and during the meeting online and this led to lively panel discussions. Our review on the IPBF website looks at just a few highlights of this 2-day virtual meeting. [Read more](#) or go to http://www.painful-bladder.org/pdf-2/2020-09_GIBS_India.pdf

PAN-EUROPEAN PAIN PROJECT IMI-PAINCARE – REVIEW OF 2020 AND ENGAGEMENT OF PATIENT ORGANISATIONS

IMI-PainCare is an international consortium of 40 partners from academia, biotech companies, pharmaceutical industry, pain societies, and the three patient organisations International Painful Bladder Foundation (IPBF), Pelvic Pain Support Network (PPSN), and Endometriosis.org Ltd (EOL). The lead is shared by Prof. Rolf-Detlef Treede, University of Heidelberg, and Dr Marcel Froehlich, Grünenthal.

Set within the framework of the European Innovative Medicine Initiative (IMI) (www.imi.europa.eu), the largest public-private partnership for health research worldwide, it was launched on April 01, 2018 to improve the care of patients with acute or chronic pain (www.imi-paincare.eu). The consortium strives to streamline the research and development process for novel analgesic drugs and improve treatment quality in clinical practice.

The main interest of the IPBF is in the subproject TRiPP - "Translational research in pelvic pain" which has a special focus on improving the management of pain related to endometriosis (EAP) and interstitial cystitis/bladder pain syndrome (IC/BPS).

[Click here](#) to access the full article by Petra Bloms-Funke, IMI-PainCare consultant and Karin Schubart, ConsulTech GmbH, or via the IPBF home page www.painful-bladder.org, where you can read much more about this project and the work of the three patient organisations within the IMI-PainCare research consortium.

REVIEW OF THE VIRTUAL GLOBAL MEETING OF IC/BPS PATIENT ADVOCATES HELD ON 5 DECEMBER 2020, ORGANIZED BY THE DUTCH ICP AND IC INDIA

In 2019 the Dutch IC/BPS patient association (ICP) organized a first global patient advocacy meeting following the annual ESSIC meeting in Amsterdam. This year, because of COVID, it was decided to hold a virtual meeting on 5 December 2020 in collaboration with the ICI patient association from India. This was kindly organized by Mathilde Scholtes (ICP) and Balaka Basu (IC India). Around 19 patient advocates took part. The aim was to catch up on developments in the different countries, exchange information between the IC/BPS patient associations and obtain feedback on the impact of COVID-19 on the IC/BPS patients. Many thanks are due to Mathilde and Balaka for getting this off the ground.

[Click here](#) or go to the IPBF home page www.painful-bladder.org to read the full review.

INFORMATION SOUGHT ON DOCTORS/CLINICS TREATING IC/BPS PATIENTS IN AFRICAN COUNTRIES

We often receive requests from patients for information about doctors/clinics treating IC/BPS in different African countries. If any of our newsletter readers can provide potential contacts, we would be most grateful since it will help us to assist these patients.

EUPATI: PATIENT ENGAGEMENT THROUGH EDUCATION

EUPATI, the European Patients' Academy on Therapeutic Innovation, is a European organisation providing patients and support groups with accessible and reliable information and training on medicines research and development and other therapeutic innovations. After operating as a special project hosted by the European Patients' Forum (EPF) for 8 years (a leading patient umbrella organisation in Europe), EUPATI has now become an independent Foundation registered in The Netherlands. This change opens up new and exciting avenues of development for the leading non-profit organisation in education for patients and on patient engagement in Europe. While a European organisation, EUPATI may nevertheless be of interest to support groups worldwide. For further information: <https://eupati.eu/>

CALLS TO RENAME "PAIN CATASTROPHIZING" BACKED BY INTERNATIONAL PATIENT-RESEARCHER PARTNERSHIP

The IASP Pain e-Monthly included an article by Jayden O'Brien (17 Sep 2020) regarding an ongoing initiative which is investigating different perspectives on the controversial term "pain catastrophizing", an anathema to patients. This study is canvassing opinions on replacements for the term "pain catastrophizing," following concerns from some patients with intractable pain that the term is stigmatizing and poses a barrier to quality care. [Read more...](#)

KEEPING TRACK OF YOUR OWN MEDICAL HISTORY

The importance of a complete medical history should not be underestimated. However, in today's world, people move around nationally and internationally and it may therefore be difficult for healthcare providers to track down a patient's medical history. Even in these electronic times, medical information is often not passed on and paper records may have been destroyed. Everyone should therefore endeavour to keep as complete a personal medical record as possible with dates (years) of important illnesses, surgery, accidents, trauma, diagnosed diseases and disorders, prescribed medication, allergies & adverse reactions, etc. A methodical record of symptoms, diagnoses and treatment will not only help the next healthcare provider but also benefit the patient.

NEW BOOKS

FACING PELVIC PAIN - A Guide for Patients and Their Families

EDITORS: Elise J.B. De, MD Theodore A. Stern, MD

ISBN-13: 978-1-951166-22-9 (Print)

ISBN-13: 978-1-951166-24-3 (Ebook)

Published 2021 by The Massachusetts General Hospital Psychiatry Academy.

Facing Pelvic Pain is a new comprehensive resource for anyone affected by this diagnosis and deals with all aspects, including causes of pelvic pain and its different types of care.

This new book will shortly be available on Amazon.

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.
- Useful information is also available at <https://www.coronavirus.gov>.

- Latest research information is available from the National Institutes of Health (NIH) at <https://www.nih.gov/coronavirus>.
- WHO Coronavirus disease (COVID-19) https://www.who.int/health-topics/coronavirus#tab=tab_1
- 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>

OVERVIEW OF RESCHEDULED UPCOMING EVENTS:

With conferences this year cancelled due to COVID-19, many have been rescheduled for the second half of 2021 and some 2021 meetings are likely to be hybrid events, in other words a combination of physical and virtual meetings. These include the following events, but with so much uncertainty regarding the Covid-19 crisis it is wise to keep checking the website for updates.

SUFU 2021 WINTER MEETING

This meeting has been changed to a virtual meeting.

25-27 February 2021

<https://sufuorg.com/meetings/upcoming-sufu/meeting-information.aspx>

EULAR 2021 CONGRESS EUROPEAN CONGRESS OF RHEUMATOLOGY

2-5 June 2021, Paris, France. This is planned as a hybrid event: virtual congress plus physical congress

<https://congress.eular.org/>

IASP WORLD CONGRESS ON PAIN

The International Association for the Study of Pain (IASP) Council has decided to move the IASP World Congress on Pain in Amsterdam, 27 June – 1 July 2021 to a virtual experience, due to the COVID-19 pandemic. For further information, [click here](#) or go to

<https://www.iaspworldcongress.org/>

36th EAU ANNUAL CONGRESS 2021 MILAN, ITALY

The European Association of Urology (EAU) is planning to hold its rescheduled annual congress 9-13 July 2021, in Milan, Italy as both a physical and virtual meeting. The venue is: MiCo – Milano Convention Centre, Viale Eginardo, Gate 2, 20149 Milan, Italy. For further information: <https://eaucongress.uroweb.org/>

AUA 2021 ANNUAL MEETING, LAS VEGAS, UNITED STATES OF AMERICA

The American Urological Association (AUA) is planning to hold its rescheduled annual meeting Friday, September 10 – Monday, September 13, 2021 in Las Vegas, Nevada, United States. For 2021, the AUA is reviewing plans to make a limited number of sessions from the Annual Meeting available online via a mix of livestream and recorded webcasts. Further information about any virtual options will be posted to AUA2021.org once they become available. For further information, [click here](#) or go to <https://www.aua2021.org/>

51st ICS ANNUAL SCIENTIFIC MEETING 2021

The 51st annual scientific meeting of the International Continence society (ICS) will be held 12-15 October 2021 at the Melbourne

Convention and Exhibition Centre (MCEC) in Melbourne, Australia. For further information, [click here](#) or go to <https://www.ics.org/2021>

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, 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 generally use the terminology used by the authors.

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

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

ASSOCIATION OF LONGITUDINAL CHANGES IN SYMPTOMS AND URINARY BIOMARKERS IN PATIENTS WITH UROLOGICAL CHRONIC PELVIC PAIN SYNDROME: A MAPP RESEARCH NETWORK STUDY

Roopali Roy, Alisa J Stephens, Cassandra Daisy, Lauren Merritt, Craig W Newcomb, Jiang Yang, Adelle Dagher, Adam Curatolo, Monisha Sachdev, Brenden McNeish, Richard Landis, Adrie van Bokhoven, Andrew El-Hayek, John Froehlich, Michel A Pontari, David Zurakowski, Richard S Lee, Marsha A Moses. *J Urol.* 2020 Oct 7;101097JU0000000000001391. doi: 10.1097/JU.0000000000001391. Online ahead of print. PMID: 33026902.

The purpose of this study was to analyze a series of novel non-invasive urinary biomarkers for their ability to objectively monitor the longitudinal clinical status of UCPPS patients. Baseline, 6- and 12-month urine samples were collected and used to quantify vascular endothelial growth factor (VEGF), VEGF receptor 1 (VEGF-R1), neutrophil gelatinase-associated lipocalin (NGAL), matrix metalloproteinase (MMP)-2, MMP-9, and MMP-9/NGAL complex by enzyme-linked immunosorbent assays (ELISA). Patients' symptom changes were classified as improved, stable, or worse using a functional clustering algorithm. Proportional odds models were used to evaluate the association between symptom change and urinary biomarkers. Across all sampled participants, longitudinal decreases in normalized VEGF concentration (pg/ug) were associated with pain severity improvement, and decreases in MMP-9, NGAL, and VEGF-R1 concentration (pg/mL) as well as NGAL normalized concentration were associated with improved urinary symptoms. Longitudinal decreases in normalized VEGF-R1 were associated with pain improvement in patients with moderate widespreadness, no bladder symptoms and no painful filling. Lower baseline normalized VEGF-R1 concentration was associated with pain improvement in patients with pelvic pain only. Higher baseline MMP-9/NGAL levels were associated with pain and urinary improvement across all participants. Moreover, longitudinal increases in MMP-2 concentration was associated with improved pain in men and patients with painful filling. The authors suggest that these urinary biomarkers may be useful in monitoring UCPPS symptom changes with respect to both urinary severity and pain severity. With further testing, they may represent objective biologic measures of UCPPS progression and/or resolution while also providing insight into the pathophysiology of UCPPS.

AOAH REMODELS ARACHIDONIC ACID-CONTAINING PHOSPHOLIPID POOLS IN A MODEL OF INTERSTITIAL CYSTITIS PAIN: A MAPP NETWORK STUDY

Wenbin Yang, Ryan E Yaggie, Anthony J Schaeffer, David J Klumpp. *PLoS One.* 2020 Sep 14;15(9):e0235384. doi: 10.1371/journal.pone.0235384. eCollection 2020. PMID: 32925915 DOI: 10.1371/journal.pone.0235384

Free full article, click on title

Interstitial cystitis/bladder pain syndrome (IC) is a debilitating condition of chronic pelvic pain with unknown etiology. Recently, the authors used a genetic approach in a murine model of IC to identify the lipase acyloxyacyl hydrolase (AOAH) as a modulator of pelvic pain. They found that AOAH-deficient mice have elevated pelvic pain responses, and AOAH immunoreactivity was detected along the bladder-brain axis. Lipidomic analyses identified arachidonic acid (AA) and its metabolite PGE2 as significantly elevated in the sacral spinal cord of AOAH-deficient mice, suggesting AA is a substrate for AOAH. Here, they quantified the effects of AOAH on phospholipids containing AA. Spinal cord lipidomics revealed increased AA-containing phosphatidylcholine in AOAH-deficient mice and concomitantly decreased AA-phosphatidylethanolamine, consistent with decreased CoA-independent transferase activity (CoIT). Overexpression of AOAH in cell cultures similarly altered distribution of AA in phospholipid pools, promoted AA incorporation, and resulted in decreased membrane fluidity. Finally, administration of a PGE2 receptor antagonist reduced pelvic pain in AOAH-deficient mice. Together, these findings suggest that AOAH represents a potential CoA-independent AA transferase that modulates CNS pain pathways at the level of phospholipid metabolism.

SENSITIVITY OF FUNCTIONAL CONNECTIVITY TO PERIAQUEDUCTAL GRAY LOCALIZATION, WITH IMPLICATIONS FOR IDENTIFYING DISEASE-RELATED CHANGES IN CHRONIC VISCERAL PAIN: A MAPP RESEARCH NETWORK NEUROIMAGING STUDY

Sonja J Fenske, Douglas Bierer, Gisela Chelimsky, Lisa Conant, Candida Ustine, Ke Yan, Thomas Chelimsky, Jason J Kutch. *Neuroimage Clin.* 2020 Sep 20;28:102443. doi: 10.1016/j.nicl.2020.102443. Online ahead of print. PMID: 33027702 PMCID: PMC7548991 DOI: 10.1016/j.nicl.2020.102443

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

Previous studies examining the resting-state functional connectivity of the periaqueductal gray (PAG) in chronic visceral pain have localized PAG coordinates derived from BOLD responses to provoked acute pain. These coordinates appear to be several millimeters anterior of the anatomical location of the PAG. Therefore, the authors aimed to determine whether measures of PAG functional connectivity are sensitive to the localization technique, and if the localization approach has an impact on detecting disease-related differences in chronic visceral pain patients. First, they found important non-uniformities in brainstem rs-fMRI signals, as rs-fMRI signals from the MNI-trace ROI were significantly more similar to the participant-trace ROI than to the MNI-sphere ROI. They then found that choice of ROI also impacts whole-brain functional connectivity, as measures of PAG functional connectivity throughout the brain were more similar between MNI-trace and participant-trace compared to MNI-sphere and participant-trace. Finally, they found that ROI choice impacts detection of disease-related differences, as functional connectivity differences between pelvic pain patients and healthy controls were much more apparent using the MNI-trace ROI compared to the MNI-sphere ROI. These results indicate that the ROI used to localize the PAG is critical, especially when examining brain functional connectivity changes in chronic visceral pain patients.

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

TOWARDS A NEW PARADIGM IN BLADDER PAIN SYNDROME AND INTERSTITIAL CYSTITIS

Philip Hanno, Magnus Fall, Jane Meijlink, Jørgen Nordling. *BJU Int.* 2020 Sep 1. doi: 10.1111/bju.15223. Online ahead of print. PMID: 32870562 DOI: 10.1111/bju.15223

Hunner lesion disease, termed 'interstitial cystitis' since the description of Guy Hunner's "elusive ulcer" a century ago, referred to a specific disease with specific findings on endoscopy associated with a typical symptom complex. Unfortunately, there were many patients with a similar symptom presentation who did not meet this restricted definition. Some would have infection, some would have overactive bladder, some would suffer from effects of pelvic radiation, and many would have no known etiology or findings on evaluation other than the symptoms alone.

CLINICAL MANAGEMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A REVIEW ON CURRENT RECOMMENDATIONS AND EMERGING TREATMENT OPTIONS

Josie Colemeadow, Arun Sahai, Sachin Malde. *Review Res Rep Urol.* 2020 Aug 18;12:331-343. doi: 10.2147/RRU.S238746. eCollection 2020. PMID: 32904438

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

Bladder pain syndrome (BPS) is a chronic condition characterized by pelvic pain or pressure which is perceived to be originating from the bladder, accompanied by one or more urinary symptoms, including frequency, urgency and nocturia. The precise etiology of BPS is not fully understood. Chronic bacterial infection, defective glycosaminoglycan (GAG) layer of the bladder urothelium, inappropriate activation of mast cells in the suburothelial layer of the bladder, autoimmune-mediated mechanisms and autonomic nervous system dysfunction have all been implicated. Treatments targeted at each of these mechanisms have been developed with mixed outcomes. High-quality research into the treatment options is lacking and it is difficult to draw definite conclusions. The treatment approach is multimodal and should be patient specific, targeting the symptoms which they find most bothersome. Conservative treatment, including patient education, behavioural modification, dietary advice, stress relief and physical therapy is an essential initial management strategy for all patients. If no response is observed, oral treatments such as amitriptyline are likely to offer the greatest response. Cystoscopy is essential to phenotype patients, and Hunner lesion directed therapy with fulguration or resection can be performed at the same time. Intravesical instillation of DMSO or lidocaine, detrusor injections of botulinum toxin A and neuromodulation can be used if initial management fails to improve symptoms. Oral cyclosporin can be trialled in those experienced with its use; however, it is associated with significant adverse events and requires intense monitoring. Lastly, radical surgery should be reserved for those with severe, unremitting BPS, in which quality of life is severely affected and not improved by previously mentioned interventions. Future work investigating exact aetiological factors will help target the development of efficacious treatment options, and several promising oral and intravesical treatments are emerging.

UPDATE ON THE PATHOPHYSIOLOGY OF INTERSTITIAL CYSTITIS /BLADDER PAIN SYNDROME

Yoshiyuki Akiyama. *Curr Bladder Dysfunct Rep* 15, 1–8 (2020). <https://doi.org/10.1007/s11884-019-00569-w>
IC/BPS is a chronic, potentially debilitating condition characterized by lower urinary tract symptoms and pain perceived to be related to the bladder. The etiology of IC/BPS has been rigorously studied for more than a century but remains unknown. IC/BPS comprises a wide variety of clinical phenotypes with different potential etiologies. Recently, the importance of IC/BPS subtyping has become recognized. In this review, Akiyama revisits current hypotheses on IC/BPS pathophysiology and discusses the most likely causes of IC/BPS according to current research. Recent histological and genomic analyses revealed that IC/BPS with Hunner lesions is a distinct inflammatory disorder characterized by epithelial denudation and frequent clonal expansion of infiltrating B cells, in association with biological processes involved in immune responses and infectious disease. Meanwhile, IC/BPS without Hunner lesions is an unrelated, non-inflammatory disorder with few histological changes, and which is potentially associated with systemic neurophysiological/endocrine abnormalities. Recent evidence has also cast doubt on the importance of features that have been conventionally considered significant in IC/BPS pathophysiology, such as mast cell infiltration or glomerulation. The author concludes that IC/BPS with Hunner lesions should be considered IC, and IC/BPS without Hunner lesions should be considered BPS. Clear and proper phenotyping of IC/BPS is necessary for the successful diagnosis and treatment of IC/BPS and to facilitate future research on IC/BPS pathophysiology.

BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IN CONTEMPORARY UK PRACTICE: OUTCOMES OF PHENOTYPE-DIRECTED MANAGEMENT

Anoushka Neale, Nabiah Malik, Claire Taylor, Arun Sahai, Sachin Malde. *Low Urin Tract Symptoms*. 2020 Aug 31. doi: 10.1111/luts.12343. Online ahead of print. PMID: 32869495.

BPS/IC is a heterogeneous disorder with variation in management worldwide. Phenotyping aims to personalize therapy and optimize outcomes. The most well-described phenotype is Hunner lesion disease (HLD). The prevalence of HLD and outcome of phenotype-directed management in the UK is not well-studied. Neale and colleagues describe the management of a contemporary cohort of patients with BPS/IC in the UK. Retrospective analysis of all patients with BPS/IC from January 2015–November 2018. Outcomes of patients who underwent laser ablation to Hunner lesions were collected using the Global Response Assessment tool. One hundred and sixty-three patients were included. 78% were female and patients had experienced symptoms for an average 6 years (1–30) prior to specialist assessment. It was concluded that the presence of HLD in patients with BPS/IC is not uncommon. Pelvic imaging rarely identifies any cause for pain and so cystoscopy under anesthesia is essential for accurate phenotyping. Phenotype-directed management with holmium laser ablation to Hunner lesions has good short-term efficacy in improving pain, but re-intervention is often required.

PHENOTYPES OF BPS/IC

Sachin Malde, Arun Sahai. *Current Bladder Dysfunction Reports volume 15, pages203–213(2020)*. <https://doi.org/10.1007/s11884-020-00599-9>

The aim of this review was to summarise the latest research related to different phenotypes of BPS/IC, addressing the evidence for current well-defined phenotypes as well as identifying novel potential phenotypes and highlighting areas for future study. Two distinct phenotypes of BPS/IC are well-recognised: Hunner's lesion disease and non-Hunner's lesion BPS/IC. Recent studies have shown these phenotypes exhibit distinct clinical, pathological and cystoscopic features, and targeted treatment to Hunner's lesions can prove effective. Recent studies have also identified new potential phenotypes based on biochemical, molecular and histological markers, pathophysiological mechanisms of disease, clinical features, cystoscopic findings, radiological features and urodynamic factors. This evidence has improved our understanding of the underlying mechanism of disease and may enable more personalised and targeted therapy in the future. Novel phenotypes of BPS/IC relate to the presence of certain biomarkers, alterations in the urinary microbiome, the characteristics of pain and presence of co-existing somatic and psychosocial conditions, altered patterns of brain white matter changes and urodynamic features. Further study is required to evaluate whether these potential phenotypes are clinically useful based on their ability to guide treatment selection and predict outcome from therapy, and therefore optimise therapeutic outcomes.

A COMPARISON OF TWO INTRAVESICAL BLADDER INSTILLATIONS FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

J Keane, N Young, J Goh, M Atherton, J Yin, K Moore, P Hall, P Higgs, A Leitch, J Lee, A Rosamilia. *Eur J Obstet Gynecol Reprod Biol*. 2020 Nov 1;256:230-234. doi: 10.1016/j.ejogrb.2020.10.060. Online ahead of print. PMID: 33248378 DOI: 10.1016/j.ejogrb.2020.10.060

Bladder pain syndrome (BPS) is a chronic pain condition associated with injury to the glycosaminoglycan (GAG) layer. Ke4ane et al aimed to prospectively evaluate iAluRil[®] with multi-centre tertiary urogynaecology collaboration. They hypothesised that iAluRil[®] (a GAG therapy) would demonstrate equivalent symptom, pain and QOL scores compared to DMSO controls. iAluRil[®] was administered for 7 instillations over 3 months in 34 women over 6 sites. 18 historical DMSO controls were matched 2:1. At baseline and 3 months post treatment validated questionnaires were collected. Both iAluRil[®] and DMSO were associated with statistically significant improvements in IC/BPS specific questionnaire scores. iAluRil[®] showed statistically significant improvements in pain, symptoms, and QOL. 45 % of iAluRil[®] recipients had a greater than 50 % reduction in pain score as represented by the VAS. DMSO was also effective in improving measures of IC/BPS with statistically significant decreases in ICSI and ICPI. There was no statistically significant difference in the size of the effect between DMSO and iAluRil[®]. It was concluded that iAluRil[®] is well tolerated and associated with significant improvements in pain and symptom scores. Almost half of refractory BPS will have a 50 % decrease in pain score at three months post treatment. This effect size is similar to DMSO.

COMPARATIVE EFFECTIVENESS AND SAFETY OF INTRAVESICAL INSTILLATION TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Shengzhuo Liu, Chi Zhang, Liao Peng, Yiping Lu, Deyi Luo. Review Int Urogynecol J. 2020 Sep 4. doi: 10.1007/s00192-020-04490-3. Online ahead of print. PMID: 32886173.

A large variety of agents are available for intravesical instillation treatment of IC/BPS. The purpose of the study was to compare the efficacy and safety of those agents. PubMed, the Cochrane Library, and Embase were searched from database inception to February 2020 for randomized controlled trials. The language of publication was limited in English. Population, intervention, comparison, outcome, and study design was used to assess the eligible studies for inclusion and the Cochrane Collaboration's risk of bias tool was used to assess the methodological quality of the studies included. The primary outcome was O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) and O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) improvement. Eleven randomized controlled trials covering 8 agents with 902 patients were enrolled. According to the results of the ICPI and ICSI, 0.1 µM resiniferatoxin was more effective than other therapies. Combination therapy of hyaluronic acid and chondroitin sulphate ranked second in ICSI, third in ICPI, and first in the visual analog scale (VAS). Among regimens included for complication comparison, chondroitin sulphate was safer than other agents, with a probability of 78.5%. It was concluded that resiniferatoxin (0.1 µM) is more effective at ICPI and ICSI improvement than other agents. The authors concluded that more well-designed randomized controlled trials with a large sample size directly comparing the efficacy and safety of those agents are in need in the future to confirm their findings.

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. 2020 Nov 16. doi: 10.1097/SPV.0000000000000985. Online ahead of print. PMID: 33208655 DOI: 10.1097/SPV.0000000000000985

IC/BPS is a chronic pain condition that significantly affects patient quality of life. Volpe et al 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 pain syndrome 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.

METABOLIC SYNDROME IN WOMEN WITH AND WITHOUT INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Liao Peng, Xing-Peng Di, Shi-Xin He, Xiao Zeng, Hong Shen, Hui-Li Zhu, De-Yi Luo. Int Urogynecol J. 2020 Nov 19. doi: 10.1007/s00192-020-04605-w. Online ahead of print. PMID: 33215272 DOI: 10.1007/s00192-020-04605-w

The aim of this study was to compare the frequency of metabolic syndrome (MetS) in patients with and without IC/BPS. This case-control study evaluated the indicators of MetS in 287 females with IC/BPS and in 287 females without IC/BPS in West China Hospital between January 2010 and January 2020. Then, the number of voids per day, frequency of night urination, O'Leary-Sant Interstitial Cystitis Symptom/Problem Index, and visual analog scale were examined in the two groups. Based on both the National Cholesterol Education Program Adult Treatment Panel III recommendations and the International Diabetes Federation criteria, the distribution of MetS was statistically higher in patients with IC/BPS than in the control group, with 34.8% vs 17.8% and 34.2% vs 20.9%, respectively. Regarding symptom scores, the IC/BPS group demonstrated significantly higher scores than the control group in all aspects. More patients with anxiety, insomnia, hypertension, and diabetes mellitus were observed in the IC/BPS group. Moreover, the findings indicated that patients with IC/BPS had a higher BMI and larger waist circumference. Blood tests presented a significantly higher level of fasting glycemia, serum cystatin-C, and triglycerides in patients with IC/BPS. Furthermore, higher ORs for the occurrence of MetS among cases were observed, although this was not statistically significant. It was concluded that MetS frequency was relatively high in patients with IC/BPS. Further research is needed to understand the common pathophysiologic mechanism of IC/BPS and MetS.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AS REFERRED PAIN FROM INJURED T12/L1 NERVES: SYMPTOMATIC IMPROVEMENT WITH RESECTION OF ILIOINGUINAL AND ILIOHYPOGASTRIC NERVES

Megan E Gornet, Akash Chandawarkar, Amin Herati, A Lee Dellon. Urology. 2020 Dec 3;S0090-4295(20)31424-2. doi: 10.1016/j.urology.2020.11.034. Online ahead of print. PMID: 33279610 DOI: 10.1016/j.urology.2020.11.034

The purpose of this study from the USA was to evaluate the specific contribution of ilioinguinal (II) and iliohypogastric (IH) nerve injury and referred pain to interstitial cystitis/bladder pain syndrome (IC/BPS) and patient-reported chronic pelvic pain (CPP), and to enumerate the effects of II and IH nerve resection on the pain and voiding symptoms in patients with IC/BPS. This was a prospective cohort study of eight patients with ICS/BPS who had prior abdominal surgery. All patients received diagnostic image guided T12/L1 nerve blocks, followed by II and IH nerve resections. Validated O'Leary-Sant ICS symptom indices (OSPI) and pelvic pain and urgency/frequency patient symptoms scale (PUF) scores were collected at specified intervals pre- and post-operatively. Median scores at pre-operative (OSPI 13.9, PUF 20.4) and one week time points (OSPI 5.9, PUF 11), as well as differences between pre-operative and ten month time points (OSPI 3.7, PUF 6) were all statistically significant. The mean difference in score from pre-operative to longest follow-up as measured by the OSPI was -14.4 and by PUF -10.3. All time points registered demonstrated improvement in pain scores. There were no surgical complications or adverse events. It was concluded that II and IH nerve resection may be an effective and durable treatment option for those with prior abdominal surgery who have referred ICS/BPS pain from these injured nerves.

THE EFFECT OF INTRAVESICAL HYALURONIC ACID THERAPY ON URODYNAMIC AND CLINICAL OUTCOMES AMONG WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yu-Chen Peng, Sherry Yueh-Hsia Chiu, Min Feng, Ching-Chung Liang. Taiwan J Obstet Gynecol. 2020 Nov;59(6):922-926. doi: 10.1016/j.tjog.2020.09.021. PMID: 33218413 DOI: 10.1016/j.tjog.2020.09.021

Treatment of IC/BPS is often delayed because of a lack of objective data during diagnosis. This study was conducted to determine the clinical validity of using urodynamic studies to investigate the effect of intravesical hyaluronic acid (HA) treatment among women with IC/BPS. 30 patients with IC/BPS undergoing 6-month intravesical instillation of HA were recruited. Pretreatment evaluation involved a urinalysis and urinary culture, urinary cytology, a 3-day voiding diary, and cystoscopy with hydrodistention of the bladder. Urodynamic study was performed before and after HA treatment. Symptomatic changes were assessed using a questionnaire covering lower urinary tract symptoms, the O'Leary-Sant symptom index and problem indexes (ICSI and ICPI), and the visual analog scale for pain and urgency. Patient demographics, urinary symptoms, ICSI/ICPI scores, pain and urgency scores, and urodynamic results before and after HA treatment were compared. Urinary frequency, nocturia, urgency, pelvic pain, bladder capacity, ICSI, and ICPI were significantly improved after HA treatment. Comparing urodynamic parameters, the volumes at first desire to void (FDV) and maximum cystometric capacity were significantly increased after HA treatment. Before HA treatment, a negative correlation existed between

the ICSI and ICPI and urodynamic parameters, including maximum flow rate and bladder capacity, but there were no significant correlations after treatment. Before HA treatment, a negative correlation was discovered between nocturia and FDV. However, after HA treatment, there were no significant correlations between urinary symptoms and urodynamic parameters. The authors concluded that their results indicate that the improvement of urinary symptoms of IC/BPS after HA treatment is associated with increased FDV and maximum cystometric capacity. The value of FDV and the frequency of nocturia after treatment may become useful objective indicators for prognosis of IC/BPS.

A HIGH MOLECULAR WEIGHT HYALURONIC ACID BIPHASIC DISPERSION AS POTENTIAL THERAPEUTICS FOR INTERSTITIAL CYSTITIS

Peadar R Rooney, Vijaya Krishna Kannala, Niranjana G Kotla, Ana Benito, Damien Dupin, Iraida Loinaz, Leo R Quinlan, Yury Rochev, Abhay Pandit. J Biomed Mater Res B Appl Biomater. 2020 Oct 26. doi: 10.1002/jbm.b.34751. Online ahead of print. PMID: 33103826 DOI: 10.1002/jbm.b.34751

Interstitial cystitis (IC) is a progressive bladder disease characterized by increased urothelial permeability, inflammation of the bladder with abdominal pain. While there is no consensus on the etiology of the disease, it was believed that restoring the barrier between urinary solutes and (GAG) urothelium would interrupt the progression of this disease. Currently, several treatment options include intravesical delivery of hyaluronic acid (HA) and/or chondroitin sulfate solutions, through a catheter to restore the urothelial barrier, but have shown limited success in preclinical, clinical trials. Herein the authors report for the first time successful engineering and characterization of biphasic system developed by combining cross-linked hyaluronic acid and naïve HA solution to decrease inflammation and permeability in an in vitro model of interstitial cystitis. The cross-linking of HA was performed by 4-arm-polyethylenimine chemistry. The HA formulations were tested for their viscoelastic properties and the effects on cell metabolism, inflammatory markers, and permeability. This study demonstrates the therapeutic effects of different ratios of the biphasic system and reports their ability to increase the barrier effect by decreasing the permeability and alteration of cell metabolism with respect to relative controls. Restoring the barrier by using biphasic system of HA therapy may be a promising approach to IC.

NEW FRONTIERS FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME - FOCUSED ON STEM CELLS, PLATELET-RICH PLASMA, AND LOW-ENERGY SHOCK WAVE

Chih-Chieh Lin, Yun-Ching Huang, Wei-Chia Lee, Yao-Chi Chuang. Int Neurourol J. 2020 Sep;24(3):211-221. doi: 10.5213/inj.2040104.052. Epub 2020 Sep 30. PMID: 33017892 DOI: 10.5213/inj.2040104.052

IC/BPS, characterized by bladder pain and irritative voiding symptoms, is a frustrating disease without effective treatment. The cause is still largely not understood, although urothelium ischemia/hypoxia, apoptosis, denudation, and infiltration of inflammatory cells are common histopathological findings. The current uncertainty regarding the etiology and pathology of IC/BPS has a negative impact on its timely and successful treatment; therefore, the development of new treatment modalities is urgently needed. The authors from Taiwan present advances in our knowledge on this topic and review the potential application of regenerative medicine for the treatment of IC/BPS. This article provides information on the basic characteristics and clinical evidence of stem cells, platelet-rich plasma (PRP), and low-energy shock waves (LESWs) based on a literature review with a search strategy for articles related to IC/BPS, stem cells, PRP, and LESW published in MEDLINE and PubMed. Stem cells, PRP, and LESW, which modulate inflammatory processes and promote tissue repair, have been proven to improve bladder regeneration, relieve bladder pain, inhibit bladder inflammation, and increase bladder capacity in some preclinical studies. However, clinical studies are still in their infancy. Based on the mechanisms of action of stem cells, PRP, and LESW documented in many preclinical studies, the potential applications of regenerative medicine for the treatment of IC/BPS is an emerging frontier of interest. However, solid evidence from clinical studies remains to be obtained.

INCREASED TRANSIENT RECEPTOR POTENTIAL MELASTATIN 8 EXPRESSION IN THE DEVELOPMENT OF BLADDER PAIN IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Liyang Wu, Jianzhong Zhang, Fei Zhou, Peng Zhang. Urology. 2020 Oct 10;S0090-4295(20)31241-3. doi: 10.1016/j.urology.2020.09.037. Online ahead of print. PMID: 33045289 DOI: 10.1016/j.urology.2020.09.037

The purpose of this study from Beijing was to explore the role of TRPM8 in the occurrence and development of bladder pain in IC /BPS patients. The differences in the content and location distribution of TRPM8 in bladder were compared between IC/BPS and control group. All enrolled patients answered questionnaires such as O'Leary-Sant symptom index, VAS, QOL and PUF score, then bladder specimens were collected. Analyses such as qRT-PCR, western blot, and immunofluorescence were performed to determine the changes in TRPM8

content and expression in neurons and sensory nerves between the IC/BPS and control group, and the relationships between TRPM8 and various clinical scores were also analyzed. There were significant differences in the O'Leary-Sant score, PUF score, VAS and QOL score between IC/BPS and the control group ($P < 0.05$). Compared with the control group, the expression levels of TRPM8 mRNA and protein were significantly increased in the IC/BPS bladder tissues. Immunofluorescence examination also revealed that 1) the number of neurons and sensory nerves displayed a significant upward trend in the bladder tissue of IC/BPS patients 2) the expression levels of TRPM8 on neurons and sensory nerves also increased significantly in IC/BPS group. It was concluded that in IC/BPS patients, TRPM8 content increased significantly and mainly expressed on increased neurons and sensory nerves in bladder tissue. These results may indicate a mechanism by which bladder pain is more easily spread in IC/BPS patients and may also indicate an important mechanism for pain sensitization in such patients.

THE FIVE PRIMARY PROSTAGLANDINS STIMULATE CONTRACTIONS AND PHASIC ACTIVITY OF THE URINARY BLADDER UROTHELIUM, LAMINA PROPRIA AND DETRUSOR

Zane Stromberga, Russ Chess-Williams, Christian Moro. *BMC Urol.* 2020 Apr 29;20(1):48. doi: 10.1186/s12894-020-00619-0. PMID: 32349725 PMCID: PMC7191740 DOI: 10.1186/s12894-020-00619-0.

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Inflammation is often associated with several bladder dysfunctions, including OAB and IC/PBS. As such, inflammation of the bladder and the actions of inflammatory mediators may contribute to the development of urinary symptoms. This study assessed the actions of PGE₂, PGF₂, PGD₂, TXA₂, and PGI₂ on urinary bladder urothelium with lamina propria (U&LP), and detrusor smooth muscle. It was concluded that the urinary bladder U&LP and detrusor respond to a variety of prostaglandin agonists, with their activation resulting in direct contractions, as well as increases to spontaneous contractile activity. This study presents the prostaglandin receptor system as a potential therapeutic target for lower urinary tract dysfunction.

RELEVANCE OF THE ENDOSCOPIC EVALUATION IN THE DIAGNOSIS OF BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS

Alessandro Morlacco, Mariangela Mancini, Matteo Soligo, Fabio Zattoni, Arturo Calpista, Giuseppe Vizzielli, Rosario Patti, Francesco Gerardo Mandato, Andrea Celeste Barneschi, Filiberto Zattoni, Massimo Iafrate, Fabrizio Dal Moro, *European Reference Network for rare UROGENital disease and complex conditions (ERN eUROGEN)*. *Urology.* 2020 Jun 30;S0090-4295(20)30787-1. doi: 10.1016/j.urology.2020.06.032. PMID: 32619597 DOI: 10.1016/j.urology.2020.06.032

The purpose of this study from Italy was to assess the relevance of the endoscopic evaluation in clinically suspected cases of BPS/IC, using ESSIC criteria, established in 2008 by the European Society for the Study of Interstitial Cystitis (ESSIC). The authors included all patients who underwent endoscopic evaluation between January 01, 2015 and October 31, 2019 for clinical suspicion of BPS/IC. Collected data included demographic and baseline clinical features, endoscopic appearance (prior and after hydrodistension), and bladder wall biopsy results, both defined according to ESSIC criteria. Data were cross tabulated to define ESSIC phenotypes, while subgroups and multivariate analyses were carried out to assess the influence of clinical variables on ESSIC phenotypes. Fifty-two subjects were included, mainly women (92%). Median age at evaluation was 45 (32.9-58.2) years. At hydrodistension, 21 patients (42%) had positive and 29 (58%) had negative findings. Grade 2-3 glomerulations were found in 18 patients, while Hunner lesions were reported only in 1 patient. Positive results at biopsy were found in 24 pts (51.1%), while negative in 23 (48.9%). Overall, the positive and negative concordance between hydrodistension and biopsy results was 78%. No significant differences in ESSIC subtypes were found after stratification based on clinical features and at multivariate analysis. Retrospective design is the main limitation. It was concluded that cystoscopy with hydrodistension and biopsy do have a role in the diagnostic pathway of BPS/IC. However, results should be considered in the clinical context of the individual patient.

CHARACTERIZATION AND VALIDATION OF A CHRONIC MODEL OF CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN RATS

Céline Augé, Xavier Gamé, Nathalie Vergnolle, Philippe Lluel, Sophie Chabot. *Front Pharmacol.* 2020 Aug 28;11:1305. doi: 10.3389/fphar.2020.01305. eCollection 2020. PMID: 32982733 PMCID: PMC7485435 DOI: 10.3389/fphar.2020.01305

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IC/BPS is a chronic inflammatory disease characterized by visceral pain and voiding symptoms. IC/BPS is still an unsolved enigma with ineffective diagnosis criteria and treatment. A main limitation in IC/BPS understanding is

the lack of appropriate preclinical model. Cyclophosphamide (CYP) is commonly used as an experimental model for IC/BPS in rodent. However, the proposed models are very aggressive, contrasting with what occurs in clinic, and often associated with severe toxicity and high mortality rate. In addition, visceral pain, the hallmark symptom of IC/BPS, has been validated in only few of them. In this study, Augé and colleagues from France developed a chronic model of CYP-induced IC/BPS in female rats. In their protocol, no severe weight loss occurred and the survival rate was 100%. In accordance with human pathology, chronic CYP-injected rats developed severe painful behavior whereas only sparse inflammation was observed. Inflammatory response was characterized by bladder edema and focal urothelial damage but absence of massive infiltrate. This chronic model showed persistent symptoms indicative for a central sensitization mechanism. They further demonstrate that CYP-induced chronic visceral pain was significantly reduced by curative treatment with clinically relevant compounds (gabapentin, ibuprofen, and laluril®). They therefore developed and validated a rat model of chronic cystitis that shares strong similarity with human non-ulcerative IC/BPS features without overtly affecting the animal health. This model will thus provide mechanistic insights of the disease and help to evaluate therapeutic agents for IC/BPS.

CLINICAL RELEVANCE OF BLADDER HISTOPATHOLOGICAL FINDINGS AND THEIR IMPACT ON TREATMENT OUTCOMES AMONG PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: AN INVESTIGATION OF THE EUROPEAN SOCIETY FOR THE STUDY OF INTERSTITIAL CYSTITIS HISTOPATHOLOGICAL CLASSIFICATION

Jia-Fong Jhang, Yung-Hsiang Hsu, Yuan-Hong Jiang, Han-Chen Ho, Hann-Chorng Kuo. J Urol. 2020 Aug 28;101097JU0000000000001334. doi: 10.1097/JU.0000000000001334. Online ahead of print. PMID: 32856961

The current study aimed to investigate the clinical significance of European Society for the Study of Interstitial Cystitis (ESSIC) bladder histopathological classification and its impact on treatment outcomes among patients with IC/BPS. Bladder biopsy specimens obtained from severe, treatment refractory IC/BPS patients were analyzed by a single pathologist blinded to clinical data. Inflammatory cell infiltration and urothelium denudation, eosinophil infiltration, plasma cell infiltration, lamina propria haemorrhage, and granulation in specimens were evaluated separately. Patients with at least one histopathological finding were classified as ESSIC type C, with the rest being classified as ESSIC type A. Current overall treatment outcomes were determined via telephone interview. Bladder specimens were obtained from 352 patients with IC/BPS. Bladder inflammation, urothelium denudation, eosinophil and plasma cell infiltration, lamina propria haemorrhage, and granulation were present in 69.6%, 44.6%, 9.1%, 15.3%, 4.8%, and 5.1% of the bladder specimens, respectively. Approximately 78.7% of the patients included herein were ESSIC type C and had a smaller cystometric bladder capacity and higher bladder pain compared to ESSIC type A. Although individual histopathological findings were not associated with treatment outcome, a higher proportion of ESSIC type A patients had worse, unchanged or < 25% improvement outcomes compared to ESSIC type C patients. Bladder histopathological findings were associated with clinical parameters and differences in patients-reported treatment outcomes. Accordingly, patients with IC/BPS who had no remarkable bladder histopathological findings had less favourable treatment outcomes compared to those who did.

SYSTEMIC THERAPY FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (BPS/IC): SYSTEMATIC REVIEW OF PUBLISHED TRIALS IN THE LAST 5 YEARS

Pedro Abreu-Mendes, Rui Pinto, Paulo Dinis Oliveira. Curr Bladder Dysfunct Rep 15, 192–202 (2020). <https://doi.org/10.1007/s11884-020-00592-2>

Systemic drug therapy licensed and present in worldwide guidelines for bladder pain syndrome/interstitial cystitis (BPS/IC) has been relatively stable for the last years. This systematic review aims to assess trials enrolling BPS/IC patients, published in the last 5 years. The authors abided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement to define retrieved trials. The keywords used in the search were “interstitial cystitis”, “bladder pain syndrome” and “trial”. Five additional papers were added: three published before 2015, due to the added value to the present work, and two published in abstract form only, retrieved from previous systematic reviews. The pursuit of better and novel treatment modalities for BPS/IC patients is constant. Different classes of drugs were tried as potential systemic therapy in BPS/IC patients. Among retrieved trials, positive results were reported with sildenafil, certolizumab, amitriptyline, gefapixant, and cyclosporine A. Other drugs failed to prove their efficacy. When using other licensed drugs for BPS/IC, several trials showed inconclusive results or failed to meet the criteria at interim analyses. The interpretation of BPS/IC trial results is not straightforward especially when compared to other pathologies, due to difficulty in characterizing and phenotyping patients. Overall, both positive and inconclusive trials should motivate peers to continue the search

for novel therapies in this condition. Trials with better designs and with a larger number of individuals are needed.

RE: SYSTEMIC THERAPY FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (BPS/IC): SYSTEMATIC REVIEW OF PUBLISHED TRIALS IN THE LAST 5 YEARS

Karl-Erik Andersson. Eur Urol. 2020 Nov 27;S0302-2838(20)30938-6. doi: 10.1016/j.eururo.2020.11.037. Online ahead of print. PMID: 33257030 DOI: 10.1016/j.eururo.2020.11.037

The study by Abreu-Mendes et al confirms that old and new systemic pharmacological treatments for BPS/IC have shown only limited success and that only a few of the treatments reported during the last 5 yr meet reasonable efficacy and safety criteria. It would be useful to apply the same approach to an evaluation of drugs introduced into guidelines before this time period. Further well-designed studies are required to identify drugs that deserve to remain on "treatment lists" or can be included as new entities for optimal treatment of BPS/IC.

SACRAL NEUROMODULATION IN THE MANAGEMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

David Hernández-Hernández, Bárbara Padilla-Fernández, Miguel Ángel Navarro-Galmés, Stephany Hess-Medler, María Milagros Castro-Romera, David Manuel Castro-Díaz. Curr Bladder Dysfunct Rep 15, 83–92 (2020). <https://doi.org/10.1007/s11884-020-00579-z>

This review addresses current literature available on sacral neuromodulation (SNM) in the management of BPS/IC. SNM has emerged in recent years as a minimally invasive option of management for refractory BPS/IC patients that otherwise should undergo reconstructive procedures. Although not approved by the FDA for this specific group of patients, the available data show a favourable response in both objective and subjective variables with a long-lasting effect. The implantation rate after the test phase is greater with the insertion of the quadripolar tined lead than with the monopolar percutaneous nerve evaluation. Most complications can be managed with reprogramming. The reintervention rate is still high, although it decreases when excluding surgeries for battery exchange. Sacral neuromodulation should be considered in the treatment algorithm of patients with BPS/IC, as suggested in international guidelines. It provides symptomatic relief in a significant proportion of patients, being a fully reversible procedure with a very favourable complications' profile. Reintervention or explantation risk factors have not been consistently established.

BLADDER DIARY CHARACTERISTICS AND PROGRESS IN PATIENTS WITH PAINFUL BLADDER SYNDROME

[Article in En, Spanish]

Luis López-Fando, Miguel Ángel Jiménez-Cidre, José Miguel Gómez de Vicente, Salvador Arlandis-Guzmán, Agustín Franco-de-Castro, Eva M^a Valero Fernández. Arch Esp Urol. 2020 Sep;73(7):624-633. PMID: 32886077

The utility and importance of the 3-day Bladder Diary (3dBd) for the diagnosis and management of patients with Bladder Pain Syndrome (BPS) were analyzed. This epidemiological, observational, longitudinal and multicentric study was carried out under usual conditions of clinical practice. 37 Functional Urology and Urodynamics units included 329 women with BPS according to the criteria of the International Society for the Study of Bladder Pain Syndrome (ESSIC). Of all patients included, 319 were evaluable (79 with new diagnosis and 240 in follow-up). Sociodemographic and clinical variables were collected together with variables related to cystoscopy, biopsy and physical examination and BPS diagnostic tests. Patients completed the "Bladder Pain/Interstitial Cystitis - Symptom Score"(BPIC-SS), "Patient Global Impression of Severity" (PGI-S) and "EuroQoL-5D-5L" (EQ-5D-5L) questionnaires besides of the 3dBd. Results of the 3dBd were described according to urinary symptoms and the symptoms reported through questionnaires, in addition their association was studied. In anamnesis, 74.9% of patients reported increased Urinary Frequency (UF), 59.6% urgency and 72.7% nocturia compared to 88.7%, 55.9% and 73.6% as reflected in the 3dBd. The highest correlation indexes (CI) were obtained between BPIC-SS and UF/24h (0.45) and between UF/24 h and PGI-S (-0.36) and EQ-5D-5L (-0.33). Mean voiding volume was higher in patients with better BPIC-SS score (163.72 (SD 68.02ml) y 154.1 (SD 70.63 ml)), at 6 and 12 months. The authors concluded that 3dBd has proven to be a useful and complementary tool to the anamnesis in the evaluation of the repercussion of pain in the micturition pattern and for the differential diagnosis of the symptoms of BPS patients. It also allows to obtain complete and objective information about the symptoms. Although it is necessary to incorporate other tools that complete the clinical characterization of these patients.

CLINICAL MANIFESTATIONS AND RESULTS OF CYSTOSCOPY IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Rashad Sholan. North Clin Istanbul. 2020 Aug 18;7(5):417-424. doi: 10.14744/nci.2020.23245. eCollection 2020. PMID: 33163875 PMCID: PMC7603858 DOI: 10.14744/nci.2020.23245

IC/BPS refers to diseases that are challenging to identify, diagnose and treat. Thus, there is a need to study the clinical and cystoscopic picture of IC/BPS. The present research from Baku, Azerbaijan aims to study the clinical manifestations and results of cystoscopy with hydrodistension in women with IC/BPS. One hundred twenty-six women with clinically diagnosed IC/BPS were examined - their mean age was 46.7±14.0 years. Patients were surveyed on pelvic pain and urgency/frequency patient symptom score (PUF), visual analogue scale (VAS) and urgency severity scale (USS). All patients underwent a potassium test (PST) and cystoscopy with hydrodistension. Statistical analysis was performed using SPSS software version 15.0 (SPSS Inc., Chicago, Illinois, USA). The author found a relationship established between the clinical manifestations of IC/BPS among examined women and changes in the wall of the bladder. The data obtained from their investigation can help increase IC/BPS diagnostics and improve IC/BPS treatment results.

PROTEOMIC ANALYSIS OF BLADDER BIOPSIES FROM INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS WITH AND WITHOUT HUNNER'S LESIONS REVEALS DIFFERENCES IN EXPRESSION OF INFLAMMATORY AND STRUCTURAL PROTEINS

Elijah P Ward, Sarah N Bartolone, Michael B Chancellor, Kenneth M Peters, Laura E Lamb. BMC Urol. 2020 Nov 7;20(1):180. doi: 10.1186/s12894-020-00751-x. PMID: 33160333 DOI: 10.1186/s12894-020-00751-x

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IC/BPS is a bladder disease usually characterized by pain, urgency, and frequency. Interstitial cystitis is currently classified into two subtypes, with and without Hunner's lesions. However, the underlying etiology of interstitial cystitis and its subtypes are largely unknown. To better understand the biological changes in the bladder of IC/BPS patients, Ward and colleagues directly analyzed bladder tissue of IC patients, both those with Hunner's lesions and those without. Proteins in the bladder biopsies were analyzed using nanoscale high-performance liquid chromatography-tandem mass spectrometry. Disease subgroups were compared and significantly expressed proteins were mapped using STRING to determine protein associations and functions. They found that patients with Hunner's lesions had significant increases in inflammatory and endoplasmic reticulum stress proteins, with a decrease in cellular adhesive proteins, compared to patients without Hunner's lesions. These patients also exhibited a decrease in proteins associated with the Rap1 signaling pathway, which regulates cell proliferation and wound healing. When comparing diseased and non-disease-apparent tissue in patients with Hunner's lesions, diseased tissue exhibited a decrease in ubiquitination proteins. In summary, there are significant differences in protein expression found in the bladders of IC patients with and without Hunner's lesions, indicating a disturbance in proteins associated with cellular adhesion, proliferation, protein processing, and wound healing.

SMALL FIBER POLYNEUROPATHY IS ASSOCIATED WITH NON-BLADDER-CENTRIC INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS

Tyler L Overholt, Catherine A Matthews, Robert J Evans, Gopal Badlani, Christine Ahn, Trang Simon, Stephen J Walker. Female Pelvic Med Reconstr Surg. 2020 Oct 26. doi: 10.1097/SPV.0000000000000972. Online ahead of print. PMID: 33109931 DOI: 10.1097/SPV.0000000000000972

IC/BPS comprises at least 2 phenotypes. Bladder centric patients typically demonstrate low bladder capacity (BC), often with Hunner lesion (HL), whereas non-bladder-centric patients typically have normal cystoscopic findings and more co-occurring nonurologic symptoms/syndromes (NUS), contributing to widespread pain beyond the bladder. Small fiber polyneuropathy (SFPN) is significantly associated with fibromyalgia, a frequent IC/BPS codiagnosis and may play an etiologic role in IC/BPS. The authors assessed SFPN status in bladder-centric versus non-bladder-centric IC/BPS patients. Distal leg biopsies were obtained from 11 IC/BPS patients after therapeutic hydrodistention. Specimens were embedded/sectioned per standard protocol and stained for protein gene product 9.5, an intraepidermal nerve fiber marker. To determine SFPN status, intraepidermal nerve fiber density was calculated and compared with normative reference values stratified by age/sex. The SFPN prevalence and reported comorbidities were compared between low BC and/or HL-positive (bladder-centric) versus non-low BC, HL (non-bladder-centric) patients. In this pilot study, SFPN was significantly more common in non-bladder-centric IC/BPS, that is, those patients who also reported greater prevalence of NUS, including fibromyalgia, migraines, anxiety/panic disorders, allergies, and asthma. These findings suggest that SFPN may have an etiologic role in a larger, systemic pain syndrome and should be explored further.

MANAGING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN OLDER ADULTS

Alyssa Gracely, Anne P Cameron. Drugs Aging. 2020 Oct 23. doi: 10.1007/s40266-020-00810-w. Online ahead of print. PMID: 33094445 DOI: 10.1007/s40266-020-00810-w

In this review from Michigan/USA, the current literature regarding pharmacotherapy treatment strategies available for the management of IC/BPS in older adults is addressed. The focus is on those treatments described by the American Urologic Association guidelines, organized according to clinical phenotype. Symptoms at presentation can vary with age, with older adults being more likely to experience nocturia, urinary incontinence, and Hunner's lesions than their younger counterparts. As such, treatment of IC/BPS should follow an individualized multimodal plan based on the patient's unique phenotype(s), starting with the most conservative options and escalating as needed. The side-effect profile and medication interactions should be reviewed, especially when treating older adults, requesting the aid of pharmacists or the primary care physician as needed to safely provide treatment.

BIOMATERIAL-ASSISTED DRUG DELIVERY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME TREATMENT

Zhijun Lin, Hanze Hu, Bolong Liu, Yanyan Chen, Yu Tao, Xiangfu Zhou, Mingqiang Li. Review J Mater Chem B. 2020 Nov 12. doi: 10.1039/d0tb02094j. Online ahead of print. PMID: 33179709 DOI: 10.1039/d0tb02094j

IC/BPS is a chronic and painful bladder condition afflicting patients with increased urinary urgency and frequency as well as incontinence. Owing to the elusive pathogenesis of IC/BPS, obtaining effective therapeutic outcomes remains challenging. Current administrative routes such as intravesical-bladder injection improve the treatment efficacy and reduce systemic side effects. However, the bladder permeability barrier hinders drug penetration into the bladder wall to meet the desired therapeutic expectation. These issues can be addressed by encapsulating drugs into biomaterials. When appropriately exploited, they would increase the drug dwelling time in the bladder, enhance the penetration of mucosa and improve the therapeutic response of IC/BPS. In this review, the authors first elucidate the pathogenesis and animal models of IC/BPS. They then highlight recent representative biomaterial-assisted drug delivery systems for IC/BPS treatment. Finally, they discuss the challenges and outlook for further developing biomaterial-based delivery systems for IC/BPS management.

SUPPRESSION OF ADENOSINE A_{2A} RECEPTORS ALLEVIATES BLADDER OVERACTIVITY AND HYPERALGESIA IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS BY INHIBITING TRPV1

Yang Yang, Hengshuai Zhang, Qudong Lu, Xin Liu, Yi Fan, Jingzhen Zhu, Bishao Sun, Jiang Zhao, Xingyou Dong, Longkun Li. Biochem Pharmacol. 2020 Nov 12;114340. doi: 10.1016/j.bcp.2020.114340. Online ahead of print. PMID: 33189675 DOI: 10.1016/j.bcp.2020.114340

IC/BPS is a type of chronic bladder inflammation characterized by increased voiding frequency, urgency and pelvic pain. The sensitization of bladder afferents is widely regarded as one of the pathophysiological changes in the development of IC/BPS. There is evidence that adenosine A_{2a} receptors are involved in regulating the sensitization of sensory afferents. However, the effect of adenosine A_{2a} receptors on cystitis remains unknown. In this study from China, a rat model of chronic cystitis was established by intraperitoneal injection with cyclophosphamide (CYP). Cystometry and behavioral tests were performed to investigate bladder micturition function and nociceptive pain. The rats with chronic cystitis showed symptoms of bladder overactivity, characterized by an increase in bladder voiding frequency and voiding pressure. CYP treatment significantly increased the expression of the A_{2a} receptor in bladder afferent fibers and dorsal root ganglion (DRG) neurons. The A_{2a} receptor antagonist ZM241385 prevented bladder overactivity and hyperalgesia elicited by CYP-induced cystitis. In addition, the A_{2a} receptor and TRPV1 were coexpressed on DRG neurons. The TRPV1 antagonist capsaizepine blocked bladder overactivity induced by the A_{2a} receptor agonist CGS21680. In contrast, ZM241385 significantly inhibited the capsaicin-induced increase in intracellular calcium concentration in DRG neurons. These results suggest that suppression of adenosine A_{2a} receptors in bladder afferents alleviates bladder overactivity and hyperalgesia elicited by CYP-induced cystitis in rats by inhibiting TRPV1, indicating that the adenosine A_{2a} receptor in bladder afferents is a potential therapeutic target for the treatment of IC/BPS.

EXPERIMENTALLY INDUCED BLADDER PERMEABILITY EVOKES BLADDER AFFERENT HYPERSENSITIVITY IN THE ABSENCE OF INFLAMMATION

Luke Grundy, Ashlee Caldwell, Amanda Lumsden, Ehsan Mohammadi, Gerhard Hannig, Beverley Greenwood Van-Meervald, Stuart M Brierley. Front Neurosci. 2020 Oct 23;14:590871. doi: 10.3389/fnins.2020.590871. eCollection 2020. PMID: 33192275 PMCID: PMC7645115 DOI: 10.3389/fnins.2020.590871

IC/BPS is a chronic urological condition characterised by urinary urgency, frequency and pelvic pain, that significantly impacts the quality of life for ~5% of women. Bladder sensation is coordinated by primary afferent sensory neurons that innervate the bladder wall, translating bladder stretch into signals that travel to the brain via the spinal cord. Whilst the pathophysiology of IC/BPS remains unknown, an increase in the permeability of the bladder urothelium has been proposed as an initiating cause. The authors from Australia and the US

experimentally increased bladder permeability and tracked bladder afferent sensitivity for up to 28 days. They found that one day after increasing bladder epithelial permeability with in vivo bladder infusion of protamine sulfate, mechanosensitive bladder afferents exhibited significant hypersensitivity to bladder filling. This mechanical hypersensitivity was characterised by significantly increased peak afferent firing rates and a decrease in the activation threshold of individual afferents. Bladder afferent hypersensitivity occurred in the absence of inflammation and changes in bladder muscle compliance, indicating a direct sensitisation of peripheral afferent endings. Bladder afferent mechanosensitive responses to distension returned to control levels by day 7 post-protamine sulfate treatment and remained at control levels at 28-days post-treatment. They demonstrate here, contrary to the prevailing hypothesis, that increased bladder permeability alone does not induce chronic bladder afferent sensitisation. Whilst experimentally induced changes in bladder permeability are able to induce transient bladder afferent hypersensitivity in the absence of inflammation, highly regulated homeostatic mechanisms exist to rapidly repair the urothelial barrier and normalise bladder afferent mechanosensitivity. Together, these data suggest that additional pathophysiology is required to induce chronic bladder dysfunction.

BLOCKADE OF ACID-SENSING ION CHANNELS INCREASES URINARY BLADDER CAPACITY WITH OR WITHOUT INTRAVESICAL IRRITATION IN MICE

Mitsuharu Yoshiyama, Hideki Kobayashi, Masayuki Takeda, Isao Araki. *Front Physiol.* 2020 Oct 26;11:592867. doi: 10.3389/fphys.2020.592867. eCollection 2020. PMID: 33192609 PMCID: PMC7649782 DOI: 10.3389/fphys.2020.592867

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Yoshiyama et al conducted this study to examine whether acid-sensing ion channels (ASICs) are involved in the modulation of urinary bladder activity with or without intravesical irritation induced by acetic acid. All in vivo evaluations were conducted during continuous infusion cystometry in decerebrated unanesthetized female mice. During cystometry with a pH 6.3 saline infusion, an i.p. injection of 30 µmol/kg A-317567 (a potent, non-amiloride ASIC blocker) increased the intercontraction interval (ICI) by 30%, whereas vehicle injection had no effect. An intravesical acetic acid (pH 3.0) infusion induced bladder hyperactivity, with reductions in ICI and maximal voiding pressure (MVP) by 79% and 29%, respectively. A-317567 (30 µmol/kg i.p.) alleviated hyperreflexia by increasing the acid-shortened ICI by 76%. This dose produced no effect on MVP under either intravesical pH condition. Further analysis in comparison with vehicle showed that the increase in ICI (or bladder capacity) by the drug was not dependent on bladder compliance. Meanwhile, intravesical perfusion of A-317567 (100 µM) had no effect on bladder activity during pH 6.0 saline infusion cystometry, and drug perfusion at neither 100 µM nor 1 mM produced any effects on bladder hyperreflexia during pH 3.0 acetic acid infusion cystometry. A-317567 has been suggested to display extremely poor penetrability into the central nervous system and thus to be a peripherally active blocker. The authors concluded that their results suggest that blockade of ASIC signal transduction increases bladder capacity under normal intravesical pH conditions and alleviates bladder hyperreflexia induced by intravesical acidification and that the site responsible for this action is likely to be the dorsal root ganglia.

THE ROLE OF YOGA IN THE MANAGEMENT OF BLADDER PAIN SYNDROME: A SINGLE-ARM PILOT STUDY

Salil Khandwala, Jason Cruff. *Adv Mind Body Med.* 2020 Fall;34(4):4-9. PMID: 33186125

BPS is a devastating urologic condition characterized by irritative bladder symptoms, pelvic pain, and dyspareunia. First-line treatment includes dietary, self-care and behavioral modifications. The ancient practice of yoga is well suited to treat BPS, but evidence is lacking on its use. This study investigated the feasibility and efficacy of an integrated yoga module on BPS outcomes as measured by self-reported questionnaires from baseline to 3 months after therapy. Patients rated their experiences with yoga therapy positively. It was concluded that yoga therapy for BPS showed evidence of benefit for improving bothersome bladder symptoms, pain and voiding. A randomized controlled trial will follow to investigate the efficacy of this yoga module against a control group.

[A NEW APPROACH TO UNDERSTANDING THE PATHOGENESIS AND TREATMENT OF INFECTIOUS AND INFLAMMATORY DISEASES OF THE UROGENITAL TRACT] [Article in Russian]

E V Kulchavenya. *Urologiia.* 2020 Nov;(5):99-105. PMID: 33185356

Current trends in understanding the pathogenesis of infectious and inflammatory urogenital disorders are highlighted in this review by Kulchavenya. The etiological and pathogenetic significance of increased intestinal permeability for pathogens in the development of various diseases has been convincingly proved. There is no doubt about the pathogenetic role of increased permeability of the bladder mucosa, which can result in interstitial cystitis (IC). The association of intestinal diseases with IC has been established. In rats, the induction

of intestinal inflammation may cause increased permeability of the bladder mucosa. In the postoperative period, bacteria are translocated from the gastrointestinal tract to the urinary tract, which is associated with stress. Particular attention is paid to the therapy based on new knowledge about the pathogenesis of infectious and inflammatory diseases of the urogenital tract. Possibilities of decreasing intestinal and bladder permeability using rebamipide are described. Various therapeutic mechanisms of action made it possible to use this drug in endoscopy, ophthalmology, chemotherapy and rheumatology. The antioxidant and anti-inflammatory properties of rebamipide has been shown in-vitro. Intravesical instillation of rebamipide accelerates the recovery of damaged urothelium and its barrier function, and also influences on bladder hyperactivity. Thus, the first results of using rebamipide in urology are encouraging; however, further research is required.

IN VIVO AND EX VIVO ASSESSMENT OF BLADDER HYPER-PERMEABILITY AND USING MOLECULAR TARGETED MAGNETIC RESONANCE IMAGING TO DETECT CLAUDIN-2 IN A MOUSE MODEL FOR INTERSTITIAL CYSTITIS

Nataliya Smith, Debra Saunders, Megan Lerner, Michelle Zalles, Nadezda Mamedova, Daniel Cheong, Ehsan Mohammadi, Tian Yuan, Yi Luo, Robert E Hurst, Beverley Greenwood-Van Meerveld, Rheal A Towner. PLoS One. 2020 Oct 23;15(10):e0239282. doi: 10.1371/journal.pone.0239282. eCollection 2020. PMID: 33095778 DOI: 10.1371/journal.pone.0239282

The purpose of this study was to determine if the URO-MCP-1 mouse model for bladder IC/BPS is associated with in vivo bladder hyper-permeability, as measured by contrast-enhanced MRI (CE-MRI), and assess whether molecular-targeted MRI (mt-MRI) can visualize in vivo claudin-2 expression as a result of bladder hyper-permeability. It is known that permeability plays a substantial role in IC/BPS. Claudins are tight junction membrane proteins that are expressed in epithelia and endothelia and form paracellular barriers and pores that determine tight junction permeability. Claudin-2 is a molecular marker that is associated with increased hyperpermeability in the urothelium. The URO-MCP-1 mouse model for IC/BPS was found to have a significant increase in bladder permeability, following liposaccharide (LPS) exposure, compared to saline-treated controls. mt-MRI- and histologically-detectable levels of the claudin-2 probe were found to increase with LPS -induced bladder urothelial hyper-permeability in the URO-MCP-1 IC mouse model. Levels of protein expression for claudin-2 were confirmed with immunohistochemistry and immunofluorescence imaging. Claudin-2 was also found to highly co-localize with zonula occludens-1 (ZO-1), a tight junction protein. It was concluded that the combination of CE-MRI and TEER approaches were able to demonstrate hyper-permeability, a known feature associated with some IC/BPS patients, in the LPS-exposed URO-MCP-1 mouse model. This MRI approach could be clinically translated to establish which IC/BPS patients have bladder hyper-permeability and help determine therapeutic options. In addition, the in vivo molecular-targeted imaging approach can provide invaluable information to enhance understanding associated with bladder urothelium hyper-permeability in IC/BPS patients, and perhaps be used to assist in developing further therapeutic strategies.

INFLUENCE OF PATIENT SEX ON THE EFFECTIVENESS OF SACRAL NEUROMODULATION: A COHORT STUDY FROM CHINA

Meng Lingfeng, Tian Zijian Zhang Wei, Zhang Yaoguang, Wang Jianye, Liao Limin, Ling Qing, Zhang Peng, Wei Zhongqing, Zhong Tie, Xu Zhihui, Wen Wei, Li Jiayi, Luo Deyi. Int J Surg. 2020 Oct 17;S1743-9191(20)30743-3. doi: 10.1016/j.ijisu.2020.10.007. Online ahead of print. PMID: 33080412 DOI: 10.1016/j.ijisu.2020.10.007

Sacral neuromodulation (SNM) has been widely used to treat lower urinary tract dysfunction. Studies have shown a higher conversion rate among female patients than among male patients. However, the influence of gender on the clinical effectiveness of SNM remains unclear. The authors from China aimed to confirm whether patients of both genders show similar benefits after SNM treatment. Clinical data of patients with lower urinary tract symptoms associated with pelvic floor dysfunction (overactive bladder, neurogenic bladder, interstitial cystitis/painful bladder syndrome, idiopathic urinary retention) treated with SNM in 10 medical centres in China between January 2012 and December 2016 were retrospectively collected. The patients were classified by gender. Variations in objective (voiding diary) and subjective scores in the baseline, testing, and last follow-up periods were compared. Data were analysed using statistical measures. The study included 203 patients (93 males, 110 females). There were no statistical differences in baseline information between the two groups, both groups showed improvement over time. Unsatisfactory improvement was observed in the quality of life and sexual life scores of both groups over the entire treatment period. Although there was a difference in the maximum voiding volume between the groups at baseline, no difference was observed at the last follow-up, unlike in the average volume where a difference was noted at the last follow-up. While there were no differences in quality of life, sexual life, or pelvic pain and urinary urgency frequency scores at baseline, a significant difference was observed at the last follow-up, and the degree of improvement was less among female patients. It was concluded that SNM treatment elicited a similar effect on patients of both gender; however, a significant

difference was observed regarding patient satisfaction with the treatment. Further preoperative patient education, especially, for female patients with IC/BPS may improve patient satisfaction.

REPEATED INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA IMPROVE SYMPTOMS AND ALTER URINARY FUNCTIONAL PROTEINS IN PATIENTS WITH REFRACTORY INTERSTITIAL CYSTITIS

Yuan-Hong Jiang, Yuh-Chen Kuo, Jia-Fong Jhang, Cheng-Ling Lee, Yung-Hsiang Hsu, Han-Chen Ho, Hann-Chorng Kuo. Sci Rep. 2020 Sep 16;10(1):15218. doi: 10.1038/s41598-020-72292-0. PMID: 32939046

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Repeated intravesical injections of autologous platelet-rich plasma (PRP) have been shown to improve symptoms in patients with interstitial cystitis/bladder pain syndrome (IC/BPS); however, there is a paucity of objective evidence of the effectiveness of this therapy. In this study, the authors investigated the changes in urinary markers after PRP treatment. Forty patients with IC/BPS who were refractory to conventional therapy received four injections of PRP at monthly intervals; 10 mL PRP solution with 2.5 times the peripheral blood platelet concentration was used. Urine levels of thirteen functional proteins, growth factors, and cytokines were assessed at baseline and at the 4th PRP injection. The clinical parameters included visual analog scale (VAS) pain score, daily urinary frequency, nocturia episodes, functional bladder capacity, and global response assessment (GRA). The GRA and symptom score significantly decreased post-treatment. In patients with $GRA \geq 2$, the success rates at 1 month and at 3 months after the 4th PRP injection were 70.6% and 76.7%, respectively. The VAS pain score, frequency, and nocturia showed a significant decrease. Urinary levels of nerve growth factor, matrix metalloproteinase-13, and vascular endothelial growth factor significantly decreased post-treatment; platelet-derived growth factor-AB showed a significant increase at the 4th PRP treatment compared with baseline. In this study, repeated intravesical PRP injections provided significant symptom improvement in IC/BPS patients with concomitant changes in the related biomarker levels.

DOES CYSTOSCOPY METHOD AFFECT THE INVESTIGATION OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS?

Visha K Taylor, Ellen Morris, Alka A Bhide, Ruwan Fernando, Guiseppe A Digesu, Vik Khullar. Int Urogynecol J. 2020 Sep 21. doi: 10.1007/s00192-020-04512-0. Online ahead of print. PMID: 32955597

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Cystoscopic investigation to identify associated histological findings of increased mast cells in the detrusor muscle has been recommended by the International Society for the Study of Bladder Pain Syndrome (ESSIC) in the investigation of bladder pain syndrome/interstitial cystitis (BPS/IC). The aim of this study was to identify if the cystoscopy approach impacts the biopsy results when investigating women presenting with symptoms of BPS/IC. Taylor and colleagues performed a single-centre retrospective analysis of 300 bladder biopsy reports from 2015 to 2018 from women undergoing cystoscopy for BPS/IC. Biopsies obtained using closed cup forceps through a flexible (FC) or rigid cystoscope (RC) were compared. Fifty-eight FC biopsies were compared with 242 RC biopsies. FC biopsies had a smaller mean diameter and volume compared with RC biopsies. There was no significant difference in the histological depth of sampling to the muscularis propria. A total of 292 samples had CD117 immunohistochemical staining for mast cell count (MCC) analysis. The MCC/mm² was significantly lower in FC biopsies. Sixteen percent of FC samples compared with 60% of RC samples had a high MCC >28/mm². There was no significant difference in positive microbiology culture between FC (21%) and RC (28%) sampling. It was concluded that rigid and flexible cystoscopy can be used to investigate BPS/IC as recommended by international societies. However, the biopsy method impacts the mast cell count analysis, which can influence diagnosis and management. Therefore, RC would be the optimal investigation.

SEXUAL DYSFUNCTION IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A CASE-CONTROL STUDY

Amit Agrawal, Susanta Tripathy, Deepak Kumar. Indian J Urol. Jul-Sep 2020;36(3):212-215. doi: 10.4103/iju.IJU_145_20. Epub 2020 Jul 1. PMID: 33082637 PMCID: PMC7531377 DOI: 10.4103/iju.IJU_145_20
IC/BPS is a chronic debilitating illness characterized by urinary frequency, urgency, and pelvic pain. IC/BPS adversely affects the sexual well-being of the patients. Agrawal and colleagues from India used the Female Sexual Function Index (FSFI) to compare sexual dysfunction (FSD) in women with IC/BPS versus controls in an Indian cohort where such data is lacking. Patients with IC/BPS had a significantly higher PUF score as compared to the control group (7.843 vs. 3.656). These patients also scored worse on the total adjusted FSFI score and individually in all domains of sexual function. Twenty-nine (90.62%) patients of the IC/BPS group had FSD as compared to 12 (37.5%) of patients in the control group. Pain was the most common presenting complaint and was seen in 65.25% of patients in the IC/BPS group as compared to only 31.25% of patients in the control group.

The authors concluded that the results of their study show that women with IC/BPS have more pain and sexual dysfunction than controls.

[\[ELECTRON MICROSCOPIC CHARACTERIZATION OF THE MUCOUS MEMBRANE OF THE BLADDER WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME IN THE EXPERIMENT\]](#)

[Article in Russian]

R F Sholan, E K Gasimov. Urologiia. 2020 Sep;(4):14-17. PMID: 32897008

This study from Azerbaijan looked at the nature and severity of the reorganization of the structural elements of the bladder wall on experimental models of IC / BPS at optical and ultrastructural levels. The experimental model of IC/BPS was created on 22 white New Zealand female rabbits weighing 1500-2000 g. The animals were divided into 2 groups: group 1 - 15 rabbits, which were introduced into the bladder wall urine taken from the animals bladder; Group 2 (control) - 7 animals that were injected into the bladder wall with a 0.9% NaCl solution. The biomaterial was examined by electron microscopy. The structural elements of the lamina propria of the bladder mucosa were evaluated. In the bladder mucosa of the experimental model, perivascular infiltration by inflammatory cells, pronounced edema of the lamina propria of the bladder mucosa, and the presence of numerous plasma cells having close contacts with macrophages, fibroblasts, and lymphocytes were revealed. In the nucleus of lymphocytes of a peripherally located supercondensed heterochromatin showed their apoptotic state. Edematous fluid was determined, penetrating mainly through the fenestra, located in the peripheral parts of the endothelial cells of capillaries and postcapillary venules. The study of the structural elements of the lamina propria of the bladder mucosa in the experiment by the method of electron microscopy made it possible to identify changes caused by the inflammatory process, both of an acute and productive nature. The results obtained showed that toxic damage to the lamina propria of the bladder mucosa causes apoptosis of fibroblasts of the lamina propria, leads to loosening of collagen fibers and, ultimately, to a decrease in the protective factors of the mucous membrane.

[DOES WEATHER TRIGGER UROLOGIC CHRONIC PELVIC PAIN SYNDROME FLARES? A CASE-CROSSOVER ANALYSIS IN THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF THE CHRONIC PELVIC PAIN RESEARCH NETWORK](#)

Jieni Li, Tiange Yu, Irum Javed, Chaitanya Siddagunta, Ratna Pakpahan, Marvin E Langston, Leslie K Dennis, Darrel M Kingfield, David J Moore, Gerald L Andriole, H Henry Lai 9, Graham A Colditz, Siobhan Sutcliffe, MAPP Research Network. Neurourol Urodyn. 2020 Jun;39(5):1494-1504. doi: 10.1002/nau.24381. Epub 2020 May 4. PMID: 32893408

The purpose of this MAPP Network study was to investigate whether meteorological factors (temperature, barometric pressure, relative humidity, ultraviolet index [UVI], and seasons) trigger flares in male and female urologic chronic pelvic pain patients. The authors assessed flare status every 2 weeks in their case-crossover study of flare triggers in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain 1-year longitudinal study. Flare symptoms, flare start date, and exposures in the 3 days preceding a flare or the date of questionnaire completion were assessed for the first three flares and at three randomly selected nonflare times. They linked these data to daily temperature, barometric pressure, relative humidity, and UVI values by participants' first 3 zip code digits. Values in the 3 days before and the day of a flare, as well as changes in these values, were compared to nonflare values by conditional logistic regression. Differences in flare rates by astronomical and growing seasons were investigated by Poisson regression in the full study population. A total of 574 flare and 792 nonflare assessments (290 participants) were included in the case-crossover analysis, and 966 flare and 5389 nonflare (409 participants) were included in the full study analysis. Overall, no statistically significant associations were observed for daily weather, no patterns of associations were observed for weather changes, and no differences in flare rates were observed by season. The authors note that they found minimal evidence to suggest that weather triggers flares, although they cannot rule out the possibility that a small subset of patients is susceptible.

[SHIONONE ALLEVIATES NLRP3 INFLAMMASOME MEDIATED PYROPTOSIS IN INTERSTITIAL CYSTITIS INJURY](#)

Xin Wang , Hao Yin, Ling Fan, Yiqun Zhou, Xiaolong Tang, Xiaojun Fei, Hailin Tang, Juan Peng, Junjun Zhang, Yi Xue, Jianping Luo, Qinglei Jin, Qingjiang Jin. Int Immunopharmacol. 2020 Nov 19;107132. doi: 10.1016/j.intimp.2020.107132. Online ahead of print. PMID: 33223465 DOI: 10.1016/j.intimp.2020.107132

Shionone is a triterpenoid component derived from the herbal medicine *Aster tataricus*, and it has been reported to possess marked anti-inflammatory properties. The activation of NLRP3 inflammasome plays an important role in cystitis, and the effect of Shionone on NLRP3 inflammasome-dependent pyroptosis remains unclear. In this study, the authors established an interstitial cystitis (IC) rat model and SV-HUC-1 cell model with CYP or LPS +

ATP treatment to mimic inflammation response and induce NLRP3 inflammasome activation. Shionone treatment significantly attenuated the bladder wet weight, score of edema and hemorrhage, enhanced the viability of SV-HUC-1 cell, decreased the rate of pyroptosis. Moreover, Shionone reduced the expression of NF- κ B, NLRP3, ASC, Pro-caspase-1, Caspase-1, GSDMD, GSDMD-N at the mRNA and protein levels both in rat and SV-HUC-1 cell model, demonstrating NLRP3 inflammasome pathway was blocked and pyroptosis degree was reduced. These results indicated that Shionone could alleviate interstitial cystitis in Rat model and enhancing the viability of SV-HUC-1 cells via NF- κ B/NLRP3/GSDMD-N pathway, which illustrated that Shionone could be used as a drug candidate for the treatment of interstitial cystitis.

[EVALUATION OF THERAPEUTIC EFFECT OF INTRATRIGONAL INJECTION OF ABOBOTULINUMTOXINA\(DYSPORT\) AND HYDRODISTENTION IN REFRACTORY INTERSTITIAL CYSTITIS /BLADDER PAIN SYNDROME](#)

Mahtab Zargham, Mahdiah Mahmoodi, Hamid Mazdak, Farhad Tadayon, Mansooreh Mansori, Maryam Kazemi, Mohamad Hatef Khorami, Narjes Saberi. Urol J. 2020 Nov 23. doi: 10.22037/uj.v16i7.5879. Online ahead of print. PMID: 33236337 DOI: 10.22037/uj.v16i7.5879

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There are two brands of BotulinumtoxinA(BTXA) that commonly used in treatment of Lower Urinary Tract Disease: OnabotulinumtoxinA(Ona-BTXA) and AbobotulinumtoxinA (Abo-BTXA). The present study was conducted to assess the potential therapeutic and adverse effect of Abo-BTXA or Dysport for IC/BPS. Twenty-two out of 52 women diagnosed with IC/BPS who were refractory or had a low response to oral treatments of IC/BPS after 6 months, were included in the study. The end-point was O'Leary-Sant Score (OSS) including "symptoms" and "problem" indexes (ICSI and ICPI respectively) assessment after 1,3and 6 months after Abo-BTXA injection. Each patient underwent cystoscopy and immediately after hydrodistention received intratrigoal injections of 300 IU of Abo-BTXA (Dysport®) in 30 sites. The effect and side effects of this treatment over time have been investigated. Complications including high post void residual urine (PVR), bladder rupture, and urinary tract infections (UTI) were also assessed. The mean age of patients was 46.2±13.7 years and median OSS was 27.8±5.8.: After single injection ICSI, ICPI and total OSS significantly reduced in 1, 3, and 6 months follow up; rate of decrease total OSS was 39.5%, 36%, 18%, respectively. Its effect lasted up to six months and started to decrease after 1 months (p-value<0.05). Complications included urinary retention (PVR>200ml), bladder rupture, and UTI in 13.5%, 4.3%, and 18% of the patients, respectively. It was concluded that intravesical injection of 300IU Abo-BTX(Dysport) could be a useful approach for the treatment of patients with refractory IC/BPS in a period of six months.

HUNNER LESION

[PRESENTING AN ATLAS OF HUNNER LESIONS IN INTERSTITIAL CYSTITIS WHICH CAN BE IDENTIFIED WITH OFFICE CYSTOSCOPY](#)

Carrie Ronstrom, H Henry Lai. Neurourol Urodyn. 2020 Sep 9. doi: 10.1002/nau.24500. Online ahead of print. PMID: 32902893 DOI: 10.1002/nau.24500

This article provides an atlas of representative images of the variability in Hunner lesion appearance aimed at assisting clinicians in proper visual office diagnosis of Hunner lesions. Available cystoscopic images of Hunner lesions were reviewed from patients with interstitial cystitis or bladder pain syndrome (IC/BPS) treated by a single clinician between 2011 and 2020. For most patients, initial cystoscopy was performed in the office under local anesthesia. Images were categorized by variations in appearance. Data including Hunner lesion descriptions and patient demographics were retrospectively collected from the medical record. Only patients who had images available, received triamcinolone injection and/or fulguration of Hunner lesions, and reported improvement of their symptoms following treatment were included in the atlas. Thirty-one IC/BPS patients with Hunner lesions had cystoscopic images available for review. The authors created an atlas of representative images. Variations in appearance include classic lesions with or without a central coagulum, inflamed lesions, non-inflamed lesions, groupings of lesions, and lesions with a red waterfall bleeding appearance. They concluded that there is variation in cystoscopic appearance of Hunner lesions. Most Hunner lesions can be identified during office visits using flexible cystoscopy and local anesthesia without hydrodistention or general anesthesia. Proper visual diagnosis of Hunner lesions is of utmost importance as these patients with IC/BPS respond greatly to endoscopic intervention. This atlas will serve as a reference for clinicians and researchers, so they are able to better identify and manage these patients.

[COMMENT ON "PRESENTING AN ATLAS OF HUNNER LESIONS IN INTERSTITIAL CYSTITIS WHICH CAN BE IDENTIFIED WITH OFFICE CYSTOSCOPY" BY RONSTROM AND LAI](#)

Magnus Fall. *Neurourol Urodyn*. 2020 Nov 4. doi: 10.1002/nau.24569. Online ahead of print. PMID: 33150601
DOI: 10.1002/nau.24569.

HUNNER LESION PHENOTYPE IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

H Henry Lai, Nicholas A Pickersgill, Joel M Vetter. *J Urol*. 2020 Sep;204(3):518-523. doi: 10.1097/JU.0000000000001031. Epub 2020 Mar 30. PMID: 32223699 DOI: 10.1097/JU.0000000000001031

Lai and colleagues compared demographics, clinical presentation, comorbidities, urinary profiles, and treatment responses between patients with IC/BPS with and without Hunner lesions. They performed a systematic review of the literature in PubMed® in February 2019. Publications were included if they compared data between patients with interstitial cystitis/bladder pain syndrome with and without Hunner lesions, yielding 59 articles. Meta-analysis was performed on a subset of clinical characteristics. Meta-analysis showed that patients with interstitial cystitis/bladder pain syndrome with Hunner lesions were significantly older, reported higher urinary frequency, nocturia and Interstitial Cystitis Symptom Index, but lower cystometric bladder capacity compared to those with interstitial cystitis/bladder pain syndrome without Hunner lesions. There were no differences in pain scores, symptom duration or sex between the 2 groups. While some studies reported higher rates of comorbid pain syndromes (eg fibromyalgia) among patients without Hunner lesions, overall results were conflicting. Patients with Hunner lesions had higher urinary levels of pro-inflammatory cytokines/chemokines (CXCL10, NGF, IL-6, IL-8, MIF), luminal nitric oxide and responded well to endoscopic treatment of the Hunner lesions (eg fulguration or triamcinolone injection). In comparative studies patients with interstitial cystitis/bladder pain syndrome with Hunner lesions responded better to oral cyclosporine A than those without Hunner lesions. The authors concluded that systematic review and meta-analysis demonstrated significant differences in demographics, clinical presentation, urinary marker profiles, and treatment responses between patients with and without Hunner lesions, suggesting that they may represent 2 distinct clinical phenotypes. Studies are needed to investigate their mechanistic differences.

LONG-TERM OUTCOMES OF ULCERATIVE INTERSTITIAL CYSTITIS AFTER COMPLETE TRANSURETHRAL RESECTION WITH THERAPEUTIC HYDRODISTENTION

Sang Wook Lee, Woong Bin Kim, Kwang Woo Lee, Jun Mo Kim, Jae Heon Kim, Ji Eun Moon, Si Hyun Kim, Young Ho Kim. *Int Urol Nephrol*. 2020 Sep 14. doi: 10.1007/s11255-020-02637-1. Online ahead of print. PMID: 32926313 DOI: 10.1007/s11255-020-02637-1

The authors analyzed the long-term efficacy of simultaneous transurethral resection (TUR) and therapeutic hydrodistention in patients with ulcerative interstitial cystitis (IC) who did not experience recurrence on long-term follow-up. They studied 132 female patients who underwent TUR followed by hydrodistention to treat ulcerative IC between January 2010 and January 2017, and who were available for follow-up, for more than 36 months. Of the 132 patients, those who did not suffer recurrence within 36 months after surgery were allocated to group I and those who had a recurrence within the same period were assigned to group II. They found that upon simultaneous performance of TUR and therapeutic hydrodistention in patients with ulcerative IC, 49.2% showed favorable outcomes for 3 years.

IMMUNOMODULATORY THERAPIES FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yoshiyuki Akiyama, Yukio Homma. *Curr Bladder Dysfunct Rep* 15, 186–191 (2020). <https://doi.org/10.1007/s11884-020-00593-1>

IC/BPS is a chronic, debilitating condition of unknown etiology characterized by persistent pain perceived to be related to the urinary bladder and lower urinary tract symptoms. Evidence shows that immunological inflammatory responses underlie the pathophysiology of IC/BPS with Hunner lesions but not that of IC/BPS without Hunner lesions. Here, the authors review the current understanding of the immunological inflammatory nature of IC/BPS with Hunner lesions and the clinical outcomes of immunomodulatory therapies. Open trials show that steroids improve validated symptom scores and pain scale score markedly in patients with IC/BPS with Hunner lesions. Open trials and a randomized study show that cyclosporine A improves urinary frequency, pain intensity, and bladder capacity significantly in IC/BPS patients, showing therapeutic superiority in the Hunner lesion subtype. A randomized double-blind study showed that certolizumab pegol significantly improves patient-reported global response assessments of pain, urgency, and overall symptoms, and reduces the Interstitial Cystitis Symptom/Problem Index scores and pain scale score at 18 weeks. These results suggest that immunomodulatory therapy is more effective for IC/BPS patients with Hunner lesions than for IC/BPS without Hunner lesions. It was concluded that IC/BPS with Hunner lesions is associated specifically with immunological overreactions in the bladder; thus, immunomodulatory therapy could be a promising treatment option. Further

studies focusing on the therapeutic responsiveness of IC/BPS subtypes are warranted to promote a tailored approach to clinical management of IC/BPS. To achieve this therapeutic strategy, clear and proper subtyping of IC/BPS is mandatory.

EFFECTS OF NON-ABLATIVE VAGINAL ERBIUM:YAG LASER TREATMENT FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A CASE SERIES (UNICORN-2 STUDY)

N Okui, M Okui, Z Vizintin. Climacteric. 2020;23(sup1):S14-S17. doi: 10.1080/13697137.2019.1703940.

PMID: 33124452 DOI: 10.1080/13697137.2019.1703940

The authors conducted a study to verify the effectiveness of non-ablative vaginal erbium:YAG laser (VEL) treatment for patients with IC/BPS who were resistant to conventional treatments. A total of 12 patients without improvement after several treatments before 2016 underwent VEL treatment once a month for 12 months as per their convenience. The numeric rating scale-11 (NRS-11), O'Leary-Sant interstitial cystitis symptom and problem indexes (ICSI and ICPI), functional bladder capacity, and daily urinary frequency were obtained. In total, nine patients responded to the treatment and three did not. The NRS-11 scores and ICSI and ICPI improved in all responders. The bladder capacity and urinary frequency also normalized. The residual effect lasted for 18 months from the first treatment without long-term side-effects. VEL treatment is a safe and effective treatment in patients with IC/BPS.

COMPLEMENTARY, ALTERNATIVE AND TRADITIONAL THERAPY

COMPLEMENTARY AND ALTERNATIVE MEDICINE FOR THE MANAGEMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A RECENT UPDATE

Xibei Jia, Tess Couss, Neha Rana, Kristene E. Whitmore. Curr Bladder Dysfunct Rep 15, 214–218 (2020). <https://doi.org/10.1007/s11884-020-00594-0>

IC/BPS affects many women in the USA and its management can be challenging for the providers. In addition to conventional treatment options outlined by the American Urologic Association (AUA) guidelines, many complementary and alternative medicines (CAM) have been gaining popularity. Our study aims to review recent publications on CAM and management of IC/BPS. This literature search included all studies that addressed complementary or alternative methods of treating IC/BPS patients from the last 5 years. The authors identified studies that involve the following categories: diet therapy, acupuncture therapy, mind-body intervention, pelvic floor physical therapy, and massage. They found that intensive dietary manipulation can improve symptoms of IC/BPS, and the effect can last up to a year. Acupuncture therapy can be effective in managing IC/BPS symptoms in the first 3 months after intervention, but the effect decreased over time. Mind-body interventions can be used as an adjunct to the usual care in the treatment of IC/BPS, and it helped improve the Global Response Assessment scores. Lastly, Thiele massage demonstrated negative impact in the perception of pain in patients with IC/BPS and should not be used as a monotherapy. Current studies are limited by small number of patients and mixed quality of evidence. Larger, high-quality studies are needed to evaluate the effect of CAM on IC/BPS symptoms. Other forms of CAM as well as combined therapies should also be studied in the future. The authors concluded that providers should consider CAM as an adjunct in the treatment of IC/BPS.

HOUTTUYNIA CORDATA EXTRACT AMELIORATES BLADDER DAMAGE AND IMPROVES BLADDER SYMPTOMS VIA ANTI-INFLAMMATORY EFFECT IN RATS WITH INTERSTITIAL CYSTITIS

Wenbiao Li, Fei Yang, Hailun Zhan, Bolong Liu, Jiarong Cai, Yun Luo, Xiangfu Zhou. Evid Based Complement Alternat Med. 2020 Oct 9;2020:9026901. doi: 10.1155/2020/9026901. eCollection 2020. PMID: 33133219

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The mechanism of IC/BPS remains unclear to date, but reports showed that bladder inflammation and increasing number of activating mast cells in bladder tissues were common in patients with IC/BPS. Houttuynia cordata is widely used in Chinese traditional medicine, and its function of anti-inflammation has been proved. The purpose of this study was to investigate the efficacy and possible mechanisms of the Houttuynia cordata (HC) extract in the treatment of IC/BPS. According to the authors, this study demonstrated that the Houttuynia cordata extract can effectively inhibit mast cell proliferation and activation and downregulate proinflammatory cytokine in a rat model of IC/BPS induced with cyclophosphamide and might be potentially valuable for the treatment of IC/BPS.

PROTECTIVE EFFECT OF ASTER TATARICUS EXTRACT ON NLRP3-MEDIATED PYROPTOSIS OF BLADDER UROTHELIAL CELLS

Xin Wang, Ling Fan, Hao Yin, Yiqun Zhou, Xiaolong Tang, Xiaojun Fei, Hailin Tang, Juan Peng, Xiaoqin Ren, Yi Xue, Chunli Zhu, Jianping Luo, Qinglei Jin, Qingjiang Jin. *J Cell Mol Med.* 2020 Oct 8. doi: 10.1111/jcmm.15952. Online ahead of print. PMID: 33030301 DOI: 10.1111/jcmm.15952

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Aster tataricus L.f. is a traditional Eastern Asian herbal medicine used for the relief of uroschisis-related illnesses and has been demonstrated clinically to exert satisfied effects. However, the mechanism of its therapeutic action remains unclear. The present study from Suzhou, China aimed to evaluate the protective mechanism of *Aster tataricus* extract (ATE) on CYP or LPS + ATP-induced interstitial cystitis (IC). The authors successfully constructed the induced IC Sprague-Dawley (SD) rat model and IC human urothelium cell (SV-HUC-1) model. The main compounds of ATE were determined by LC-MS. After intervention, the changes on the bladder wall morphology and inflammation were observed in each group. SV-HUC1 cell viability was measured by MTT and double stained with Hoechst 33342 and propidium iodide (PI). The expression levels of NLRP3, Pro-caspase-1, Caspase-1 p20, GSDMD, GSDMD-N and Cleave-IL-1 β in vivo and in vitro in different groups were detected by Western blotting. ATE significantly alleviated oedema and haemorrhage and reduced the inflammation index and histopathological score in SD rat bladder. The results of cell revealed that ATE could improve cell viability and decrease pyroptosis ratio. The expression of NLRP3 and other pyroptosis-related protein was remarkably decreased by ATE both in vivo and in vitro. ATE may be used as an inhibitor of NLRP3 in treating IC. The discovery of NLRP3/Caspase-1/GSDMD-N as a new protective pathway provides a new direction for protecting cell against IC.

COVID-19 ASSOCIATED CYSTITIS

[COVID-19 INFLAMMATION RESULTS IN URINE CYTOKINE ELEVATION AND CAUSES COVID-19 ASSOCIATED CYSTITIS \(CAC\)](#)

Laura E Lamb, Nivedita Dhar, Ryan Timar, Melissa Wills, Sorabh Dhar, Michael B Chancellor. *Med Hypotheses.* 2020 Nov 5;110375. doi: 10.1016/j.mehy.2020.110375. Online ahead of print. PMID: 33213997 PMCID: PMC7644255 DOI: 10.1016/j.mehy.2020.110375

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Coronavirus disease 2019 (COVID-19) causes a wide range of symptoms, including several unexpected symptoms such as loss of taste, skin changes, and eye problems. Lamb and colleagues recently observed patients with documented COVID-19 develop de novo severe genitourinary symptoms, most notably urinary frequency of ≥ 13 episodes/24 h and nocturia ≥ 4 episodes/night. They call these associated urinary symptoms COVID-19 associate cystitis (CAC). COVID-19 severity is associated with inflammation. They collected urine samples from COVID-19 patients, including patients with CAC, and found elevation of proinflammatory cytokines also in the urine. It has been previously shown that patients with urinary incontinence and ulcerative interstitial cystitis/bladder pain syndrome have elevated urinary inflammatory cytokines compared to normal controls. The authors therefore hypothesize that CAC, with presentation of de novo severe urinary symptoms, can occur in COVID-19 and is caused by increased inflammatory cytokines that are released into the urine and/or expressed in the bladder. The authors believe that the most important implications of their hypothesis are: 1) Physician caring for COVID-19 patients should be aware of COVID-19 associate cystitis (CAC); 2) De novo urinary symptoms should be included in the symptom complex associated with COVID-19; and 3) COVID-19 inflammation may result in bladder dysfunction.

PAIN THERAPY

[CHARACTERISTICS OF ANALGESIC PATCH FORMULATIONS](#)

Srinivas Nalamachu, Jeffrey Gudin. *Review J Pain Res.* 2020 Sep 22;13:2343-2354. doi: 10.2147/JPR.S270169. eCollection 2020. PMID: 33061549 PMCID: PMC7520099 DOI: 10.2147/JPR.S270169

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Topical and transdermal formulations are a common means of pharmaceutical drug delivery. If a drug is able to penetrate transcutaneously, the skin is an ideal site for the delivery of medications for both local (topical) and systemic (transdermal) effects. The administration of analgesics through the skin poses several potential advantages to those administered orally including compliance, the ability to deliver a drug to a peripheral target site and more stable and sustained plasma levels. One method of drug delivery is with the use of patch formulations - also known as patch systems. Typically, transdermal patches deliver medications intended to reach the systemic circulation, whereas topical patches are designed to keep medication localized for targeted

delivery in proximity to the application site. There are a variety of technologies and materials utilized in patches, as well as penetration and formulation enhancers that ultimately affect the performance, efficacy and safety of the patch system. The degree of adherence to the skin is also of critical importance in drug delivery. Patches that lift up or fall off before the prescribed time period may represent a therapeutic failure and must be replaced, increasing patch utilization and cost to the healthcare system or to the patient. The added risk from accidental exposure makes poor patch adhesion a safety issue as well. A variety of analgesics are currently available as patch formulations including local anesthetics, capsaicin, nonsteroidal anti-inflammatory drugs and opioids. This review will highlight each of those patch delivery systems and introduce newer patch technologies that lend towards improved adhesion and compliance. Understanding the designs, limitations and benefits of patch systems will allow clinicians to select between these therapies when appropriate for their patients.

MICROBIOME

[URINARY MICROBIOME IN UNCOMPLICATED AND INTERSTITIAL CYSTITIS: IS THERE ANY SIMILARITY?](#)

Süleyman Yıldırım, Daniel Shoskes, Sanjay Kulkarni, Pilar Laguna. *World J Urol.* 2020 Nov;38(11):2721-2731. doi: 10.1007/s00345-020-03099-x. Epub 2020 Jan 31. PMID: 32006175

Acute/uncomplicated cystitis is the most common bacterial infection causing inflammation in the bladder tissues and predominantly diagnosed in women. Interstitial cystitis may too cause inflammation in the bladder but its etiology has been elusive. Even though the site and symptoms of both diseases are largely shared, state of the urinary microbiome in these disorders have not been comparatively evaluated before. The purpose of this review was to assess and qualitatively compare structure and composition of the urinary microbiome in acute/uncomplicated cystitis and interstitial cystitis. The authors report that the evidence gleaned from the literature on the urinary microbiome associated with the acute and interstitial cystitis does not point to convergence of microbiome similarities between the two diseases. More studies with direct sampling of the bladder tissues besides sampling bladder surfaces are warranted for accurate comparison of microbiome similarity between the two conditions. The future research on interstitial cystitis microbiome should include stratified cohorts with prospective design.

[\[THE ROLE OF THE MICROBIOME IN UROLOGY\]](#)

[Article in German]

G Magistro, J Marcon, L Eismann, Y Volz, C G Stief. *Review Urologe A.* 2020 Oct 12. doi: 10.1007/s00120-020-01368-6. Online ahead of print. PMID: 33044634 DOI: 10.1007/s00120-020-01368-6

With the advent of novel high throughput-sequencing technologies, the authors gained greater insights into the complex and diverse interactions of the microbiome for health and disease in the human body. The concept of urinary sterility has long been dismissed and now there is an endeavour to decipher various microbial signatures associated with a disease. A dysbalance of the microbiome appears to have a substantial impact on the pathogenesis of both malignant and benign conditions. Novel preventive and therapeutic approaches and biomarker systems have been proposed for prostate cancer, renal cell carcinoma and bladder cancer based on microbiome analyses. The exclusion of a microbial origin was always part of the diagnosis of benign disorders such as interstitial cystitis, urinary urge incontinence or chronic prostatitis/chronic pelvic pain syndrome. The authors are of the opinion that an imbalanced microbial profile plays an essential role for the pathogenesis and disease management of these challenging conditions.

MULTIPLE DRUG INTOLERANCE

[TACKLING THE PATIENT WITH MULTIPLE DRUG "ALLERGIES": MULTIPLE DRUG INTOLERANCE SYNDROME](#)

Autumn Guyer, Melissa Iammatteo, Merhunisa Karagic, Eric Macy, Elina Jerschow. *J Allergy Clin Immunol Pract.* 2020 Oct;8(9):2870-2876. doi: 10.1016/j.jaip.2020.08.033. PMID: 33039011 DOI: 10.1016/j.jaip.2020.08.033

As populations age, the prevalence of reported drug "allergy" increases, often leading to suboptimal care and increased morbidity because of unnecessary avoidance of safe and effective medications. Evaluation by a drug allergy specialist is often warranted when a patient has more than 2 unrelated drug "allergies" listed in the medical record. In this commentary, the authors clarify and propose standard terminology to use when evaluating patients with multiple drug allergy labels including and more specifically when diagnosing multiple drug intolerance syndrome and the much rarer multiple drug hypersensitivity syndrome. They review epidemiology and key features of multiple drug intolerance syndrome and multiple drug hypersensitivity

syndrome. They summarize the methodologic and practical diagnostic workup and management of individuals with MDIS to assist with the accurate de-labelling of drug "allergies" in the electronic health record.

LOWER URINARY TRACT

OAB AND IC/BPS: TWO CONDITIONS OR A CONTINUUM OF ONE?

Kai B. Dallas, Carrie S. Stewart, Lenore A. Ackerman, Jennifer T. Anger. Curr Bladder Dysfunct Rep 15, 15–20 (2020). <https://doi.org/10.1007/s11884-019-00567-y>

OAB and IC/BPS are defined as syndromes consisting of “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence” and “an unpleasant sensation perceived to be related to the urinary bladder, associated with lower urinary tract symptoms,” respectively. Distinguishing between the two diagnoses can be challenging and although OAB and IC/BPS are traditionally considered separate conditions, more evidence is emerging to suggest a continuum between the symptoms. This review considers the two conditions existing on a continuum by reviewing relevant definitions, phenotypes, and treatment considerations. Recent studies have suggested that up to 25% of patients with IC/BPS reported urge incontinence and 35% of patients with OAB described bladder pain. Analysis assessing validated questionnaires revealed that scores could distinguish controls from patients with storage LUTS but were not able to distinguish between those with OAB and IC/BPS. A novel scoring system spanning domain of urgency incontinence and bladder pain was validated and provided 91% diagnostic accuracy. OAB and IC/BPS symptoms overlap significantly and it remains unclear if patients with IC/BPS and OAB are unique populations or specific phenotypes of the same condition. The authors propose that “OAB-dry” patients without fear of leakage may represent a variant of IC/BPS. Unbiased phenotyping based on more accurate symptomatic descriptions may help reveal the correlations of variants of lower urinary tract symptoms with both prognosis and treatment responses.

RELATIONSHIP OF BLADDER PAIN WITH CLINICAL AND URINARY MARKERS OF NEUROINFLAMMATION IN WOMEN WITH URINARY URGENCY WITHOUT URINARY INCONTINENCE

Alex Soriano, Uduak Andy, Daisy Hassani, Kristene Whitmore, Heidi Harvie, Anna P Malykhina., Lily Arya. Female Pelvic Med Reconstr Surg. 2020 Oct 1. doi: 10.1097/SPV.0000000000000951. Online ahead of print. PMID: 33009262

The hypothesis of the authors is that in women with urinary urgency without incontinence, bladder pain is associated with the presence of neurogenic inflammation in the bladder wall and neuroinflammatory biomarkers in the urine. They conducted a prospective cross-sectional study of women with urinary urgency without incontinence. Urinary symptoms were measured using Female Genitourinary Pain Index. Neuropathic pain, a clinical biomarker of neuroinflammation, was measured using the PainDETECT questionnaire. Inflammatory neuropeptides measured in the urine included nerve growth factor (NGF), brain-derived neurotrophic factor, vascular endothelial growth factor, and osteopontin. Neuropathic pain scores and urinary neuropeptide levels were compared between patients with and without bladder pain using univariable and multivariable analyses. In 101 women with urinary urgency without incontinence, 62 (61%) were in the bladder pain group (visual analog scale score, ≤ 3), whereas 39 (39%) were in the no bladder pain group. Urinary symptom scores and neuropathic pain scores were significantly higher for the bladder pain group than for the no bladder pain group. On multivariable analysis after controlling for age, body mass index, and severity of urinary urgency, bladder pain score was significantly associated with elevated urinary levels of vascular endothelial growth factor and osteopontin, whereas the neuropathic pain score was significantly associated with an increased NGF level. The authors concluded that in women with urinary urgency without incontinence, bladder pain is associated with the presence of clinical and urinary biomarkers of neuroinflammation.

TIME FOR A BOTULINUM TOXIN PASSPORT?

Luke Stroman, Dudley Robinson, Sachin Malde, Arun Sahai. NeuroUrol Urodyn. 2020 Nov;39(8):2546-2549. doi: 10.1002/nau.24514. Epub 2020 Sep 28. PMID: 32985718 DOI: 10.1002/nau.24514

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The increasing usage of BTXA across different medical specialties and for multiple indications within a given timeframe, may lead to safe dosing recommendations being exceeded, with a theoretical increased risk of systemic adverse events, such as distal muscle weakness which have been reported following BTXA injection. Multidisciplinary prescribing could occur without clear discussion across specialties and therefore methods to prevent potential serious adverse events should be considered. Therefore, the authors propose the use of a

botulinum toxin passport that could be carried by patients to all appointments to reduce and mitigate these risks.

[LASER TECHNOLOGY APPLICATIONS IN FUNCTIONAL UROLOGY AND UROGYNECOLOGY]

[Article in Spanish. Abstract in English, Spanish]

José Miguel Gómez de Vicente, Carlos Trelles Guzmán. Arch Esp Urol. 2020 Oct;73(8):709-723. PMID: 33025916
LASER (Light Amplification by Stimulated Emission of Radiation) technology consists of the emission of a high-energy light beam. In medicine, it is used to cut, coagulate, fragment and evaporate biological or synthetic tissues. In the field of Functional Urology and Urogynecology its use has been widely explored. This article tries to give an overview of its applications in this subspecialty. There are different types of lasers and different application modalities to treat a wide variety of functional pathologies, including interstitial cystitis, trigonitis, mesh complications, urinary incontinence or pelvic organ prolapse. In some of them its use has been abandoned, despite the fact that, theoretically, they offer advantages over other therapies, such as in the case of interstitial cystitis. In others there is still not enough evidence in terms of safety and efficacy to be an alternative to other conventional treatments. Although laser therapy offers certain advantages over other treatments, its use has not been generalized in the subspecialty of Functional Urology and Urogynecology. More evidence is needed to demonstrate its efficacy and safety.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

PENTOSAN POLYSULFATE MACULOPATHY: WHAT UROLOGISTS SHOULD KNOW IN 2020

Jan Alberto Paredes Mogica, Elise J B De. Urology. 2020 Oct 9;S0090-4295(20)31240-1. doi: 10.1016/j.urology.2020.08.072. Online ahead of print. PMID: 33045286 DOI: 10.1016/j.urology.2020.08.072

The purpose of this review of current literature was to assess whether an association exists between Pentosan Polysulfate Sodium (PPS) and the development of macular disease, as it is the only oral medication approved by the Food and Drug Administration for the management of interstitial cystitis. A systematic review was conducted by the authors separately, with review methods established prior to the conduct of the review. Databases searched included PubMed, Ovid, Medline, EBSCO, and Google Scholar. A search was conducted for the terms "Pentosan Polysulfate Maculopathy", "Pentosan Polysulfate Retinopathy" and "Interstitial Cystitis Maculopathy". All papers reporting on primary data were included. A total of 14 papers reporting on primary data were identified. Most papers reported on the development of macular disease in the setting of chronic Pentosan Polysulfate Sodium exposure. No randomized controlled trials have been performed to date and data was insufficient to perform a meta-analysis. Nevertheless, patients with interstitial cystitis were more likely to receive a diagnosis of maculopathy after several years of the medication use. The authors concluded that although the nature of the published studies renders them prone to confounders, currently available data suggest an increased risk for developing maculopathy after years of Pentosan Polysulfate Sodium use. In light of this, and the marginal effectiveness of the medication for the average individual, they suggest that education be provided as to the possible association and that regular ophthalmic evaluation be recommended for patients who continue chronic use of Pentosan Polysulfate Sodium.

CURRENT STATUS OF ORAL PENTOSAN POLYSULPHATE IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Rajesh Taneja. Review Int Urogynecol J. 2020 Sep 7. doi: 10.1007/s00192-020-04517-9. Online ahead of print. PMID: 32894327.

Oral pentosan polysulphate (PPS) has been used in the treatment of bladder pain syndrome/interstitial cystitis (BPS/IC) for almost 35 years. However, in some recent studies, questions have been raised about its efficacy in treating this condition. Taneja from India has evaluated the published medical literature and discusses the clinical utility of oral PPS in the treatment of BPS/IC. PUBMED was searched for BPS/IC, treatment and PPS. Of the initial 398 articles screened, 7 randomized controlled trials, 3 systematic reviews and 3 meta-analyses were finally included in this study (Fig. 1). Other relevant literature such as observational studies and various clinical guidelines was also reviewed. The inclusion criteria, intervention methodology and end points of the studies were examined. Of the seven RCTs, five found a clear beneficial role of oral PPS in IC/BPS. The only study which did not have cystoscopy as a diagnostic and inclusion criterion failed to show any benefit of oral PPS compared to placebo. Two out of three meta-analyses clearly concluded that oral PPS had a positive role to play in the treatment of BPS/IC. Various open-label studies did conclude in favour of oral PPS as a treatment modality for these patients. The author concluded that oral PPS remains a useful pharmacological agent for treatment of BPS/IC, even though it may be effective only in a subgroup of patients.

CANNABINOIDS

[CANNABINOIDS IN UROLOGY. WHICH BENIGN CONDITIONS MIGHT THEY BE APPROPRIATE TO TREAT: A SYSTEMATIC REVIEW](#)

C Taylor, B Birch. Review Urology. 2020 Oct 28;S0090-4295(20)31289-9. doi: 10.1016/j.urology.2020.10.024. Online ahead of print. PMID: 33129871 DOI: 10.1016/j.urology.2020.10.024

There is growing evidence suggesting cannabinoids may provide suitable alternatives to conventional treatments in an increasing number of clinical settings. This review evaluates how cannabinoids are used to treat certain benign urological pathologies and to clarify the clinical value of this data. This review includes 62 papers and was undertaken per PRISMA's guidelines, it evidences the therapeutic potential of cannabinoids in the management of specific benign urological diseases, most notably neurogenic bladder dysfunction (clinical studies), renal disease (animal studies) and interstitial cystitis (animal studies). However, whilst cannabinoids are increasingly used, they cannot be considered reliable alternatives to more recognised treatments.

IC/BPS AND AUTOIMMUNE DISORDERS

[PREVALENCE OF AUTOIMMUNE DISORDERS AMONG BLADDER PAIN SYNDROME PATIENTS' RELATIVES](#)

Minna M Kujala, Teuvo L Tammela, Antti Pöyhönen, Tapio Forsell, Susanna Pasanen, Ilkka Paananen, Antero Horte, Mikael Leppilähti, Jukka Sairanen. Scand J Urol. 2020 Sep 23;1-6. doi: 10.1080/21681805.2020.1821766. Online ahead of print. PMID: 32964777

Possible genetic background and autoimmune etiology of Bladder Pain Syndrome (BPS, formerly Interstitial Cystitis, IC) has been suggested. The authors studied whether familial clustering of BPS, other autoimmune diseases or fibromyalgia exist among BPS patients' genetically close relatives, possibly reflecting some common predisposing genetic background of these diseases. A total of 420 first- or second-degree relatives of 94 BPS patients fulfilling the NIDDK criteria were asked to fill in a survey on the self-reported diagnosis of urinary tract diseases, fibromyalgia and 23 autoimmune diseases, together with filling the O'Leary-Sant symptom score. The ones with high symptom scores were interviewed and, if necessary, referred to a further clinical consultation. The prevalence of other diseases was compared to previously published prevalence percentages. 334 (80%) of 420 family members returned the questionnaire. Only one of the relatives fulfilled the NIDDK criteria, and one sibling pair among the original BPS patients was found. Asthma, ulcerative colitis, fibromyalgia, iritis and rheumatoid arthritis were more common in the study population than in the reference populations. The reported prevalence of atopic dermatitis and rhinoconjunctivitis causing allergies were lower. In addition, the results show that the O'Leary-Sant symptom score is not reliable in screening for new BPS cases. The authors are of the opinion that their study suggests that in BPS patients' families, fibromyalgia and autoimmune diseases including asthma, and especially the non-allergic form of asthma, may be over-represented.

CHRONIC PELVIC PAIN

[CHRONIC PELVIC PAIN: IMPORTANCE OF COMPATIBLE CLINICAL TRIAL OUTCOMES](#)

Amy L Shafir. BJOG. 2020 Sep 12. doi: 10.1111/1471-0528.16492. Online ahead of print. PMID: 32920978

Chronic pelvic pain (CPP), often defined as non-cyclical pelvic pain lasting for 6 months or longer, affects approximately 2-24% of women, depending on the CPP definition used (Daniels et al. BMJ 2010;341:c4834). While CPP can be a symptom associated with a variety of health conditions (including endometriosis, irritable bowel syndrome, and interstitial cystitis), at least 30% of women undergoing laparoscopic surgery have no associated disease diagnosis or clear pathologic cause for their pain.

[PUDENDAL NEUROMODULATION FOR PELVIC PAIN](#)

Alyssa Gracely, Priyanka Gupta. Curr Bladder Dysfunct Rep 15, 113–120 (2020). <https://doi.org/10.1007/s11884-020-00588-y>.

This article addressed current literature regarding the role of neuromodulation for the treatment of pelvic pain with a focus on pudendal neuromodulation. The mechanism of action for pudendal nerve stimulation and technique for pudendal neuromodulation was reviewed and literature regarding the efficacy of neuromodulation for the treatment of pelvic pain summarized. Multiple studies have demonstrated efficacy of various modalities of neuromodulation in the treatment of chronic pelvic pain. Neuromodulation may be an effective treatment option for the treatment of chronic pelvic pain, with studies showing a reduction of pain and an improvement in quality of life with various neuromodulation modalities. However, the quality of these studies is generally poor and further large-scale, randomized controlled trials are required.

LAPAROSCOPIC TRANSPERITONEAL PUDENDAL NERVE AND ARTERY RELEASE FOR PUDENDAL ENTRAPMENT SYNDROME

Renaud Bollens, Georges Mjaess, Julien Sarkis, Anthony Kallas Chemaly, Elie Nemr, Karim Daher, Albert Semaan, Josselin Abi Chebel, Fabienne Absil, Fouad Aoun. Surg Endosc. 2020 Oct 13. doi: 10.1007/s00464-020-08092-4. PMID: 33048235 DOI: 10.1007/s00464-020-08092-4

Pudendal nerve and artery entrapment is an underdiagnosed pathology responsible for several urinary, sexual and anorectal complaints. The aim of this study was to evaluate safety and feasibility of laparoscopic transperitoneal pudendal nerve and artery release in a large retrospective cohort of patients with pudendal nerve entrapment syndrome with both a short and long-term follow-up. It was concluded that a complete laparoscopic pudendal nerve and artery release, from the sciatic spine through the Alcock's canal, is a fast and safe surgery with promising functional results. A large prospective trial is needed to validate such an approach.

FIBROMYALGIA

THE 4 U'S RULE OF FIBROMYALGIA: A PROPOSED MODEL FOR FATIGUE IN A SAMPLE OF WOMEN WITH FIBROMYALGIA: A QUALITATIVE STUDY

Lilian Velasco-Furlong, Lorena Gutiérrez-Hermoso, Beatriz Mateos-Pintado, Daniel Garvi-de Castro, Sheila Blanco-Rico, Lucía Sanromán-Canelada, Sofía López-Roig, María Ángeles Pastor-Mira, Cecilia Peñacoba-Puente. Int J Environ Res Public Health. 2020 Aug 27;17(17):E6224. doi: 10.3390/ijerph17176224. PMID: 32867186.

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

Although fatigue usually goes unnoticed, it is a symptom that poses great challenges to patients with fibromyalgia and is a strong limitation. The aim of this study was to identify and describe the variables involved in fatigue in nine different situations of the Goal Pursuit Questionnaire (GPQ) that may occur in the daily lives of women with fibromyalgia, according to an ABC (Antecedents-Behaviors-Consequences) model. This study followed a qualitative descriptive research method and a deductive-inductive hybrid approach based on a phenomenological paradigm. Twenty-six women with fibromyalgia participated in focus group discussions between February and March of 2018. Thematic content analysis was carried out from transcribed verbatim interviews. The authors identified nine major themes that emerged from the participants' conversations: self-imposed duties, muscle fatigue, overwhelming feeling of tiredness, difficulty thinking, difficulty concentrating, negative emotions, lifestyle changes, affected everyday activities, and lack of motivation for daily activities and social interactions. They concluded that the ABC model allowed certain elements to emerge regarding the fatigue experience, highlighting its importance as a symptom in fibromyalgia. This additional analysis of the ABC model showed that fatigue can be described through the 4 U's Rule, which is integrated by these four adjectives: (1) Unpredictable, (2) Uncontrollable, (3) Unseen, and (4) Unintelligible. Identifying these characteristics can contribute to a better understanding of fibromyalgia in addition to better treatment for these patients.

USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN FIBROMYALGIA: RESULTS OF AN ONLINE SURVEY

Andrea R Pfalzgraf, Carroline P Lobo, Vincent Giannetti, Kimberly Dupree Jones. Pain Manag Nurs. 2020 Sep 3;S1524-9042(20)30164-8. doi: 10.1016/j.pmn.2020.07.003. Online ahead of print. PMID: 32893131.

Fibromyalgia is a chronic condition which may negatively impact various aspects of patients' lives. Many people with fibromyalgia look to complementary and alternative medicine treatments for symptom relief. The three main objectives of this study were to examine self-reported complementary and alternative medicine use in patients with fibromyalgia, to determine associations between the use of complementary and alternative medicine treatments and patients' self-reported quality of life and self-reported pain levels.

SJÖGREN'S SYNDROME

PREMATURE ONSET OF SJÖGREN'S SYNDROME IS PRONE TO BE COMPLICATED WITH RENAL TUBULAR ACIDOSIS

Qian Wang, Sheng-Ming Dai. Int J Rheum Dis. 2020 Aug 19. doi: 10.1111/1756-185X.13947. Online ahead of print. PMID: 32815322.

Sjögren's syndrome (SS) is a common systemic autoimmune disease. SS usually occurs among middle-aged women with a peak incidence age of approximately 50 years old. Kidney involvement is relatively uncommon in SS, which is mostly characterized as interstitial nephritis and may result in renal tubular acidosis (RTA). But premature onset of SS seems to be prone to RTA. The authors from China reported four cases of premature onset SS who developed into RTA at a relatively young age and three of whom suffered from severe

osteomalacia. All of them shared a disease onset under age eighteen. Two of them presented hypokalemic periodic paralysis initially, one presented purpura and one endured xerophthalmia at first place. Three of them complicated with osteomalacia under age thirty. All 4 cases did not receive proper medical care in time due to a prolonged delay of diagnosis. The authors aim to raise the alarm over misdiagnosis/underdiagnosis of the disorder among young people.

PRIMARY SJÖGREN'S SYNDROME OF EARLY AND LATE ONSET: DISTINCT CLINICAL PHENOTYPES AND LYMPHOMA DEVELOPMENT

Andreas V Goules, Ourania D Argyropoulou, Vasileios C Pezoulas, Loukas Chatzis, Elena Critselis, Saviana Gandolfo, Francesco Ferro, Marco Binutti, Valentina Donati, Sara Zandonella Callegger, Alike Venetsanopoulou, Evangelia Zampeli, Maria Mavrommati, Paraskevi V Voulgari, Themis Exarchos, Clio P Mavragani, Chiara Baldini, Fotini N Skopouli, Dimitrios I Fotiadis, Salvatore De Vita, Haralampos M Moutsopoulos, Athanasios G Tzioufas. Front Immunol. 2020 Oct 19;11:594096. doi: 10.3389/fimmu.2020.594096. eCollection 2020. PMID: 33193443 PMCID: PMC7604905 DOI: 10.3389/fimmu.2020.594096

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The purpose of this study was to investigate the clinical, serological and histologic features of primary Sjögren's syndrome (pSS) patients with early (young ≤ 35 years) or late (old ≥ 65 years) onset and to explore the differential effect on lymphoma development. From a multicentre study population of 1997 consecutive pSS patients, those with early or late disease onset, were matched and compared with pSS control patients of middle age onset. Data driven analysis was applied to identify the independent variables associated with lymphoma in both age groups. Young pSS patients had higher frequency of salivary gland enlargement (SGE, lymphadenopathy, Raynaud's phenomenon, autoantibodies, C4 hypocomplementemia, hypergammaglobulinemia, leukopenia, and lymphoma, while old pSS patients had more frequently dry mouth, interstitial lung disease, and lymphoma compared to their middle-aged pSS controls, respectively. In young pSS patients, cryoglobulinemia, C4 hypocomplementemia, lymphadenopathy, and SGE were identified as independent lymphoma associated factors, as opposed to old pSS patients in whom SGE, C4 hypocomplementemia and male gender were the independent lymphoma associated factors. Early onset pSS patients displayed two incidence peaks of lymphoma within 3 years of onset and after 10 years, while in late onset pSS patients, lymphoma occurred within the first 6 years. It was concluded that patients with early and late disease onset constitute a significant proportion of pSS population with distinct clinical phenotypes. They possess a higher prevalence of lymphoma, with different predisposing factors and lymphoma distribution across time.

MEETING REPORTS

BLADDER PAIN SYNDROME AND INTERSTITIAL CYSTITIS BEYOND HORIZON: REPORTS FROM THE GLOBAL INTERSTITIAL CYSTITIS/BLADDER PAIN SOCIETY (GIBS) MEETING 2019 MUMBAI - INDIA

Mohammad Sajjad Rahnama'i, Aida Javan, Navita Vyas, Sandor Lovasz, Neelanjana Singh, Mauro Cervigni, Sanjay Pandey, Jean-Jacques Wyndaele, Rajesh Taneja. Anesth Pain Med. 2020 May 12;10(3):e101848. doi: 10.5812/aapm.101848. eCollection 2020 Jun. PMID: 32944561

At the Global Interstitial Cystitis/Bladder Pain Syndrome Society (GIBS) meeting, the organization and participants were committed to delivering world-class expertise and collaboration in research and patient care. Under the umbrella of GIBS, leading research scholars from different backgrounds and specialties, as well as clinicians, from across the globe interested in the science and art of practice IC/BPS were invited to deliberate on various dimensions of this disease. The meeting aimed to have global guidelines to establish firm directions to practicing clinicians and patients alike on the diagnosis and treatment of this disease entity.

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