

International Painful Bladder Foundation

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

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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:

- Upcoming ESSIC Annual Meeting – 29 November-1 December 2018, Florence, Italy
- Review of the Joint Meeting of the 4th International Consultation on Interstitial Cystitis Japan (ICICJ) and the Annual Meeting of the Society of Interstitial Cystitis of Japan (SICJ)
- Brief Review of the Annual Congress of the European Association of Urology 2018
- IMI-PainCare Research Project launched
- Publications
- Calendar of Upcoming Events
- Research Update
- Donations & Sponsoring

UPCOMING ESSIC MEETING - 29 NOVEMBER-1 DECEMBER 2018, FLORENCE, ITALY

The ESSIC 2018 Annual Meeting will be held at the Auditorium al Duomo Conference Centre located in the historic Via de' Cerretani, a few steps from the central railway station and the Duomo cathedral in Florence, Italy. Address: Via de' Cerretani, 54/R, 50123 Florence. Meeting Chair is Professor Giulio del Popolo, ESSIC Coordinator Professor Mauro Cervigni. Save the date in your diary as this is an important meeting on the IC/BPS calendar and there is much to be discussed. For registration and further information, go to www.essicmeeting.eu

REVIEW OF THE JOINT MEETING OF THE 4TH INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS JAPAN (ICICJ) AND THE ANNUAL MEETING OF THE SOCIETY OF INTERSTITIAL CYSTITIS OF JAPAN (SICJ) HELD IN KYOTO 17-18 APRIL 2018 WITH AN INTERNATIONAL DISCUSSION MEETING ON 16TH APRIL

This 4th ICICJ conference marked 15 years of the International Consultation on Interstitial Cystitis Japan (ICICJ) and 17 years of the Society of Interstitial Cystitis of Japan (SICJ). The conference was attended by experts from some 14 countries, as well as many eminent urologists from the host country Japan. Participants also included patient representatives (including 3 from Europe who were among the speakers).

Although the theme this year was "Hunner Lesion", the conference took a critical look at the current situation in the whole field of IC/BPS/HSB and the problems we face today in the widest sense, not least of all the financial situation.

It was realized by all that clinical studies have to be improved with the aim of achieving reliable and comparable data. Attention was drawn by the patient advocates to the lack of reimbursement and consequent lack of access to treatment by patients. This was strongly picked up by many other speakers and it was agreed that something has to be done to sort out this problem with the regulatory authorities. The best treatment in the world is of little use if it is unavailable and/or unaffordable. Good clinical studies with evidence are essential. Without them there is neither approval nor reimbursement. Phenotyping and subtyping are essential elements here to try to ensure homogeneous study groups.

There is likewise an urgent need for standard nomenclature and standard definitions of that nomenclature. This is vital in an electronic world. While valuable research is being done at many centres, the lack of internationally accepted criteria makes it difficult or impossible to compare data or to organize the large trans-border, multi-centre studies and clinical trials which are now required.

It was abundantly clear that a great deal of time and effort is now needed to cover some of the many issues, controversies and confusion worldwide. In order to be able to achieve any solutions and the urgently needed

international consensus which should form the basis of clinical studies, it is evident that not only is structured global collaboration needed but also – most importantly – a willingness to do this.

To read the complete IPBF review of the ICICJ conference, [click here](#) or go to IPBF home page www.painful-bladder.org

Please note: The proceedings of this ICICJ meeting will be published in a special open access supplement of the International Journal of Urology (IJU) either at the end of this year or the beginning of next.

BRIEF REVIEW OF THE EUROPEAN ASSOCIATION OF UROLOGY (EAU) ANNUAL CONGRESS 16-20 MARCH 2018, COPENHAGEN, DENMARK

The 33rd annual congress of the European Association of Urology was held this year in Copenhagen, Denmark. While there has been a noticeable decline in interest in recent years at the EAU annual congress in chronic urogenital pain such as IC/BPS and hypersensitive bladder, Sunday 18th March did include several sessions of some interest to our field, while the Lovasz syringe adaptor for intravesical instillation attracted much attention. Particularly interesting was the specialty session for the European Reference Network (ERN) for Rare and Complex Urogenital Diseases and Conditions and eUROGEN. Information about ERNs in general can be found at https://ec.europa.eu/health/ern/overview_en.

The EAU patient information session highlighted the fact that the EAU now has its own patient information section at <http://patients.uroweb.org/>, albeit still limited and no sign of patient information on IC/BPS yet. The main purpose of this website is to provide patients with reliable, unbiased, comprehensive, clear information in urology. It should be good quality but easily read and understood. One of the speakers in this session emphasized that patients must be involved in developing the information. A particularly interesting presentation by Dr M.R. van Balken concerned health illiteracy and the taboo that rests on this. Many patients will not admit that they cannot read. Furthermore, Europe, with its waves of migrants, has many people who have little or no knowledge of the host language, while at the same time huge variations in levels of literacy and education mean that information produced for one group may be incomprehensible to another. This emphasizes that however much information (or symptom scores) we all produce, it is of no use if patients can neither read nor understand it.

In Plenary Session 4: Contemporary Storage Lower Urinary Tract Symptoms Management, Dr Benoit Peyronnet of Rennes University Hospital, France discussed Pathophysiology of non-neurogenic OAB: rather multifactorial than idiopathic syndrome. Bearing in mind that the IC/BPS and hypersensitive bladder world is currently focusing much attention on how to get realistic phenotyping off the ground, it was particularly interesting to hear Dr Peyronnet putting forward a suggestion in this session as to how overactive bladder (OAB) could potentially be phenotyped. [Click here](#) to read more.

IMI-PainCare RESEARCH PROJECT LAUNCHED PUBLIC-PRIVATE PARTNERSHIP TACKLES MAJOR CHALLENGES IN THE CARE OF PAIN PATIENTS

To improve the care of patients with acute or chronic pain, a consortium from academia, small and medium-sized enterprises (SMEs), pain societies, patient organizations and the pharmaceutical industry launched the research project “IMI-PainCare – Improving the care of patients suffering from acute or chronic pain” on April 01, 2018. The consortium strives to develop a toolbox that can streamline the research and development process for novel analgesic drugs and improve treatment quality in clinical practice. The project comprises three sub-projects across all phases of the pharmaceutical value chain – from early research to clinical practice – addressing major challenges in the care of patients suffering from acute or chronic pain in a complementary manner. It is anticipated that tools will be validated that will allow patient stratification and enrichment as recommended by the recent EMA/CHMP/970057/2011 guideline on pain treatment.

Pain management is essential for all medical conditions, as it is one of the major dimensions of Quality-of-life scores that patients report. Additionally, chronic pain may outlast the normal healing process (e.g. after surgery). It can be a symptom of a chronic disease (e.g. endometriosis, bladder pain syndrome, diabetic neuropathy) or may occur without any signs of an underlying disease. The treatment of both acute and chronic pain is often inadequate, which underlines the high need for innovative solutions to improve pain management. This is partly due to a poor translation of results from preclinical models into clinical trials, and partly due to a lack of sophistication in outcome reporting and accurate division of patients into subgroups in clinical trials.

“Acute and persistent pain of different origins represent a common medical, social, and economic burden, and improvement of its management is still a major challenge for all health care systems. I look forward to working towards innovative solutions to these unmet medical needs together with my partners of IMI-PainCare which

represents an unprecedented close cooperation between academia, SMEs, patient organizations, pain societies and pharmaceutical companies,” Rolf-Detlef Treede, University of Heidelberg, explained. “I am delighted that we were able to bring together the expertise of 40 partners to drive innovative solutions in pain management. The joint work of these best-in-class experts may enable us to provide pain patients with the appropriate prevention or treatment for their condition at the right time”, Petra Bloms-Funke, Grünenthal, stated.

The three sub-projects are:

- **“Providing standardized consented patient-reported outcome measures” (PROMPT)**, led by Winfried Meissner, University of Jena, and Hiltrud Liedgens, Grünenthal.

- **“Functional pain biomarkers” (BioPain)**, led by Rolf-Detlef Treede, University of Heidelberg, and Keith Phillips, Eli Lilly and Company.

- **“Translational research in pelvic pain” (TRiPP)**, led by Katy Vincent, University of Oxford, and Jens Nagel, Bayer. This sub-project is of special interest to our field of IC/BPS/HSB. It has a special focus on pain related to endometriosis and interstitial cystitis / bladder pain syndrome and is located in clinical practice as well as the early stage of disease understanding to provide a robust pre-clinical environment for drug development. “We aim to determine subgroups within these diseases and identify biomarkers of these clinical phenotypes. Ultimately, we hope this strategy will move towards more personalised treatments for these distressing conditions”, Katy Vincent stated. “It is of key importance to understand better the molecular pathways leading to inflammation and chronic pelvic pain both in endometriosis and bladder pain syndrome and to assure that these are reflected in pre-clinical models to improve their translational value for clinical research”, Jens Nagel added.

Three patient representatives are taking part in this TRiPP sub-project: Jane Meijlink (International Painful Bladder Foundation) for IC/BPS, Judy Birch (Pelvic Pain Support Network UK) for endometriosis and Lone Hummelshoj (endometriosis.org, World Endometriosis Society) also for endometriosis. This kind of patient participation is strongly supported by the IMI.

About the Innovative Medicines Initiative

This important Innovative Medicines Initiative (IMI) is a partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). It is working to improve health by speeding up the development of, and patient access to, the next generation of medicines, particularly in areas where there is an unmet medical or social need. It does this by facilitating collaboration between the key players involved in healthcare research, including universities, pharmaceutical companies, and other companies active in healthcare research, small and medium-sized enterprises (SMEs), patient organizations, and medicines regulators. This approach has proven highly successful, and IMI projects are delivering exciting results that are helping to advance the development of urgently-needed new treatments in diverse areas.

Kick-Off Meeting

A highly successful kick-off meeting was held in Aachen, Germany on 5/6 June 2018 and was also attended by the patient representatives who all played an active role.

More info on IMI: www.imi.europa.eu

More info on the IMI-PainCare project: www.imi-paincare.eu

We will be bringing you further news about this this research project in future IPBF e-Newsletters.

PUBLICATIONS

BLADDER PAIN SYNDROME – AN EVOLUTION

Editors: Hanno, P.M., Nordling, J., Staskin, D.R., Wein, A.J., Wyndaele, J.J.

Published by: Springer; 2018. 175 pages. eBook ISBN 978-3-319-61449-6. Hardcover ISBN 978-3-319-61448-9

Further information: <http://www.springer.com/gp/book/9783319614489>

AUA UROLOGY CARE FOUNDATION EDUCATIONAL MATERIALS

<http://urologyhealth.org/educational-materials>

The American Urological Association (AUA) has a Urology Care Foundation with educational materials for patients on a wide variety of urological disorders which can be downloaded free on this website.

These include a guide on interstitial cystitis/bladder pain syndrome at <http://urologyhealth.org/educational-materials/interstitial-cystitis/bladder-pain-syndrome-patient-guide>

FDA AND EMA HAVE VERY INFORMATIVE WEBSITES FOR PATIENTS AND PROFESSIONALS

The European Medicines Agency (EMA)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=

US Food & Drug Administration (FDA)

<https://www.fda.gov/>

SJÖGREN'S SYNDROME: INFORMATION FOR PATIENTS AND PROFESSIONALS

Stay updated with Sjögren's syndrome and associated disorders, including its relationship with disorders of the lower urinary tract such as IC/BPS, with Dr Joop P. van de Merwe's continually evolving online book:

http://www.painful-bladder.org/pbs_ic_ass_dis.html. Available in two versions: English and Dutch.

CALENDAR OF UPCOMING EVENTS

INTERNATION UROGYNECOLOGICAL ASSOCIATION (IUGA)

26-30 June 2018, Vienna, Austria

<https://iugameeting.org/>

INTERNATIONAL CONTINENCE SOCIETY ANNUAL SCIENTIFIC MEETING 2018

28-31 August 2018, Philadelphia, USA

www.ics.org/2018

IASP 17th WORLD CONGRESS ON PAIN

12-16 September 2018, Boston, USA

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

ELUTS 2018 (European Lower Urinary Tract Symptoms Meeting)

20-22 September 2018, Milan Italy

For IC/BPS training, see:

<https://eluts.uroweb.org/wp-content/uploads/ESU-ESFFU-Masterclass-on-Functional-urology.pdf>

<https://eluts.uroweb.org/wp-content/uploads/Programme-ELUTS18-V3.pdf>

Further information: www.eluts18.org

CONVERGENCES PP: Convergences in Pelvipерineal Pain

25 - 27 October, Royal Library of Belgium, Brussels, Belgium

Simultaneous translation in English

www.convergencespp.com

ESSIC ANNUAL MEETING 2018

29 November – 1 December

Auditorium al Duomo, Florence, Italy.

<https://www.essicmeeting.eu/>

RESEARCH UPDATE

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS, BLADDER PAIN SYNDROME, 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.

TERMINOLOGY REPORTS/GUIDELINES

[GUIDELINE OF GUIDELINES: BLADDER PAIN SYNDROME.](#)

Malde S, Palmisani S, Al-Kaisy A, Sahai A. *BJU Int.* 2018 May 19. doi: 10.1111/bju.14399. [Epub ahead of print] PMID: 29777618

Bladder pain syndrome (BPS) is a severely debilitating, chronic disorder of unknown aetiology that has a significant negative impact on quality of life. A community-based study of American women has reported a high prevalence of 2.7% - 6.5% [1]. Despite this, there is still a lack of consensus worldwide on how to define the condition, the nomenclature to use, and how to optimally treat patients. This is reflected in the considerable variation in management worldwide, and the divergent recommendations in national and international guidelines. The aim of this review from the UK is to summarise the key findings from the numerous major guidelines for BPS, highlighting areas of disagreement and uncertainty.

[RECONSIDERING THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN DEFINITION OF PAIN.](#)

Cohen M, Quintner J, van Rysewyk S. *Pain Rep.* 2018 Mar 5;3(2):e634. doi: 10.1097/PR9.0000000000000634. eCollection 2018 Mar. PMID: 29756084

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

The definition of pain promulgated by the International Association for the Study of Pain (IASP) is widely accepted as a pragmatic characterisation of that human experience. Although the Notes that accompany it characterise pain as "always subjective," the IASP definition itself fails to sufficiently integrate phenomenological aspects of pain. This essay reviews the historical development of the IASP definition, and the commentaries and suggested modifications to it over almost 40 years. Common factors of pain experience identified in phenomenological studies are described, together with theoretical insights from philosophy and biology. A fuller understanding of the pain experience and of the clinical care of those experiencing pain is achievable through greater attention to the phenomenology of pain, the social "intersubjective space" in which pain occurs, and the limitations of language. Based on these results, a revised definition of pain is offered: Pain is a mutually recognizable somatic experience that reflects a person's apprehension of threat to their bodily or existential integrity.

[THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN DEFINITION OF PAIN: AS VALID IN 2018 AS IN 1979, BUT IN NEED OF REGULARLY UPDATED FOOTNOTES.](#)

Treede RD. *Pain Rep.* 2018 Mar 5;3(2):e643. doi: 10.1097/PR9.0000000000000643. eCollection 2018 Mar. PMID: 29756089

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

Milton Cohen, John Quintner, and Simon van Rysewyk proposed a revision of the IASP definition of pain of 1979. This commentary by R-D Treede summarizes why this proposal is useful for guiding assessment of pain, but not its definition. According to Treede, they misinterpret some central elements of the International Association for the Study of Pain (IASP) definition.

[AN INTERNATIONAL UROGYNECOLOGICAL ASSOCIATION \(IUGA\)/INTERNATIONAL CONTINENCE SOCIETY \(ICS\) JOINT REPORT ON THE TERMINOLOGY FOR THE ASSESSMENT OF SEXUAL HEALTH OF WOMEN WITH PELVIC FLOORDYSFUNCTION.](#)

Rogers RG, Pauls RN, Thakar R, Morin M, Kuhn A, Petri E, Fatton B, Whitmore K, Kinsberg S, Lee J. *Neurourol Urodyn.* 2018 Apr;37(4):1220-1240. doi: 10.1002/nau.23508. Epub 2018 Feb 14. PMID: 29441607

The terminology in current use for sexual function and dysfunction in women with pelvic floor disorders lacks uniformity, which leads to uncertainty, confusion, and unintended ambiguity. The terminology for the sexual health of women with pelvic floor dysfunction needs to be collated in a clinically-based consensus report. This report combines the input of members of the Standardization and Terminology Committees of two International Organizations, the International Urogynecological Association (IUGA), and the International Continence Society (ICS), assisted at intervals by many external referees. Internal and external review was developed to exhaustively examine each definition, with decision-making by collective opinion (consensus). Importantly, this report is not meant to replace, but rather complement current terminology used in other fields for female sexual health and to clarify terms specific to women with pelvic floor dysfunction. A clinically based terminology report for sexual health in women with pelvic floor dysfunction encompassing over

100 separate definitions, has been developed. Key aims have been to make the terminology interpretable by practitioners, trainees, and researchers in female pelvic floor dysfunction. Interval review (5-10 years) is anticipated to keep the document updated and as widely acceptable as possible. A consensus-based terminology report for female sexual health in women with pelvic floor dysfunction has been produced aimed at being a significant aid to clinical practice and a stimulus for research.

CURRENT BEST PRACTICE IN THE MANAGEMENT OF CYSTITIS AND PELVIC PAIN.

Douglas-Moore JL, Goddard J. Ther Adv Urol. 2017 Oct 25;10(1):17-22. doi: 10.1177/1756287217734167. eCollection 2018 Jan. PMID: 29344093

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

Bladder pain syndrome (BPS) is a difficult disorder to diagnose and subsequently manage despite having been recognized for more than 200 years according to references in medical literature. There are currently three widely accepted guidelines on BPS: the American Urological Association Guidelines; the Royal College of Obstetricians and Gynaecologists in conjunction with the British Society of Urogynaecologists Guidelines; and the European Association of Urology Guidelines. These guidelines have similarities to each other but also significant differences. This leaves clinicians still confused about this condition and how to appropriately manage the 'real' patient. The authors review the current guidelines and appropriate literature and put forward a clinically usable management strategy.

FDA BRUDAC 2018 CRITERIA FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME CLINICAL TRIALS: FUTURE DIRECTION FOR RESEARCH.

Nickel JC, Moldwin R. J Urol. 2018 Feb 13. pii: S0022-5347(18)30208-8. doi: 10.1016/j.juro.2018.02.011. [Epub ahead of print] PMID: 29452126

Nickel & Moldwin write that for 3 decades the 1988 NIDDK (National Institutes of Diabetes and Digestive and Kidney Diseases) criteria for the research definition of interstitial cystitis (IC) has not only driven the design and outcomes for clinical trials, but also shaped the definition of the clinical condition.¹ In the last 4 decades only 2 interventions, intravesical dimethyl sulfoxide (RIMSO-50) and pentosan polysulfate sodium (Elmiron), have been approved (1978 and 1996, respectively) for the treatment of IC. On December 7, 2017 the FDA (U.S. Food and Drug Administration) convened the BRUDAC (Bone, Reproductive, and Urologic Drugs Advisory Committee) to examine and update the definition and criteria necessary for enrollment and outcomes required for clinical trials evaluating interventions for IC and bladder pain syndrome (BPS).

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

If you would like to know more about the MAPP Research Network and its work, [click here](#) to go to the home page.

SUB-NOXIOUS INTRAVESICAL LIPOPOLYSACCHARIDE TRIGGERS BLADDER INFLAMMATION AND SYMPTOM ONSET IN A TRANSGENIC AUTOIMMUNE CYSTITIS MODEL: A MAPP NETWORK ANIMAL STUDY.

Kogan P, Xu S, Wang Y, O'Donnell MA, Lutgendorf SK, Bradley CS, Schrepf A, Kreder KJ, Luo Y. Sci Rep. 2018 Apr 26;8(1):6573. doi: 10.1038/s41598-018-24833-x. PMID: 29700406

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

Patients with interstitial cystitis/bladder pain syndrome (IC/BPS) can potentially develop symptom flares after exposure to minor bladder irritants such as subclinical bacterial infection. To reproduce this symptom onset, Kogan and colleagues intravesically instilled a sub-noxious dose of uropathogenic *E. coli* component lipopolysaccharide (LPS) in young URO-OVA/OT-I mice, a transgenic autoimmune cystitis model that spontaneously develops bladder inflammation at ≥ 10 weeks of age. Female URO-OVA/OT-I mice (6-weeks old) were treated intravesically with phosphate-buffered saline (PBS) or PBS containing a sub-noxious dose (1 μ g) of LPS. Mice were evaluated for bladder inflammation, pelvic pain, and voiding dysfunction at days 1, 7, and 14 post-treatment. Their results indicate that a single sub-noxious dose of intravesical LPS triggers early bladder inflammation and symptom onset in URO-OVA/OT-I mice, providing a useful model for IC/BPS symptom flare study.

CORRELATES OF HEALTH CARE SEEKING ACTIVITIES IN PATIENTS WITH UROLOGICAL CHRONIC PELVIC PAIN SYNDROMES: FINDINGS FROM THE MAPP COHORT.

Clemens JQ, Stephens-Shields A, Naliboff BD, Lai HH, Rodriguez L, Krieger JN, Williams DA, Kusek JW, Landis JR; [MAPP Research Network](#). *J Urol*. 2018 Jan 4. pii: S0022-5347(18)30004-1. doi: 10.1016/j.juro.2017.12.055. [Epub ahead of print] PMID: 29307682

Clemens and colleagues examined health care seeking activities during a 12-month period in a cohort of men and women with urological chronic pelvic pain syndrome. A total of 191 men and 233 women with urological chronic pelvic pain syndrome were followed with biweekly, internet-based questionnaires about symptoms and health care seeking activities, including 1) health care provider contacts, 2) office visits, 3) emergency room/urgent care visits, 4) medication changes and 5) medical procedures. Multivariable modelling was used to determine the association of demographic and clinical variables with health care seeking. Super users were defined as individuals who reported health care seeking activity at least 11 times during the 23 biweekly assessments. Worse baseline pain severity and female gender were associated with a higher rate of all health care seeking activities except emergency room/urgent care visits. A nonurological chronic pain condition was associated with more provider contacts, office visits and medical procedures. Greater baseline depression symptoms were associated with more provider contacts, office visits and medication changes. Other examined variables, including patient age, symptom duration, catastrophizing, anxiety, urinary symptom severity and symptom variability, had a minimal association with health care seeking. Health care seeking activities were strongly influenced by the severity of pain in patients with urological chronic pelvic pain syndrome but not by urinary symptom severity. Women and patients with nonurological overlapping pain conditions were more likely to be seen and treated for symptoms.

[**A MAPP NETWORK STUDY: OVEREXPRESSION OF TUMOR NECROSIS FACTOR-A IN MOUSE UROTHELIUM MIMICS INTERSTITIAL CYSTITIS.**](#)

Yang W, Searl TJ, Yaggie RE, Schaeffer AJ, Klumpp DJ. *Am J Physiol Renal Physiol*. 2018 Feb 21. doi: 10.1152/ajprenal.00075.2017. [Epub ahead of print] PMID: 29465304

IC/BPS is a chronic bladder condition associated with pain and voiding dysfunction that is often regarded as a neurogenic cystitis. Patient symptoms are correlated with the presence of urothelial lesions. Yang and colleagues previously characterized a murine neurogenic cystitis model that recapitulates mast cell accumulation and urothelial lesions, and these events were dependent upon TNF. To further explore the role of TNF in bladder inflammation and function, they generated a transgenic mouse model with chronic TNF overexpression in urothelium under the control of the uroplakin II (UPII) promoter. Transgenic mouse lines were maintained by backcross onto wild-type C57BL/6J mice and evaluated for pelvic tactile allodynia as a measure of visceral pain, urinary function and urothelial lesions. TNF mRNA and protein were expressed at greater levels in bladders of UPII-TNF mice than wild type. UPII-TNF mice showed significantly increased urinary frequency and decreased void volume. UPII-TNF mice had increased urothelial apoptosis and loss of urothelial integrity consistent with urothelial lesions. Overexpression of TNF was also associated with pelvic tactile allodynia. Consistent with these findings UPII-TNF mice exhibited increased bladder afferents activity in response to stretch ex vivo. In summary, UPII-TNF mice display significant pelvic pain, voiding dysfunction, urothelial lesions and sensory input. Thus UPII-TNF mice are a novel model for characterizing mechanisms of IC symptoms and evaluating therapies.

[**PHYSICAL EXAMINATION FOR MEN AND WOMEN WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROME: A MAPP \(MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN\) NETWORK STUDY.**](#)

Yang CC, Miller JL, Omidpanah A, Krieger JN. *Urology*. 2018 Mar 28. pii: S0090-4295(18)30276-0. doi: 10.1016/j.urology.2018.03.021. [Epub ahead of print] PMID: 29604315

The purpose of this study was to examine the feasibility of implementing a standardized, clinically relevant genitourinary examination for both men and women, and to identify physical examination findings characteristic of urologic chronic pelvic pain syndrome (UCPPS). This study analyzed 2 samples: men and women with UCPPS who participated in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Epidemiology and Phenotyping (EP) Study, and age-matched controls who were either positive for chronic fatigue syndrome or healthy (pain-free). Yang and colleagues compared physical examination findings in both positive and healthy controls with UCPPS cases: findings from both the EP examinations and from an extended genitourinary examination. EP and extended examinations were performed on 143 participants: 62 UCPPS cases (30 women, 32 men), 42 positive controls (15 women, 27 men), and 39 healthy controls (22 women, 17 men). EP examinations showed that pelvic floor tenderness was more prevalent in cases (55.0%) than in positive (14.6%) or healthy controls (10.5%). Extended examinations revealed specific areas of tenderness in the pelvic floor musculature. Cases were also more likely than healthy controls to report tenderness in multiple areas, including suprapubic, symphysis pubis, and posterior superior iliac spine, and on bimanual examination. No

comparative findings were specific to biological sex, and no evidence of pudendal neuropathy was observed on extended examination of cases or controls. The extended genitourinary examination is an easily administered addition to the assessment of men and women during evaluation for UCPPS. Physical findings may help to better categorize patients with UCPPS into clinically relevant subgroups for optimal treatment.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

ADVANCES IN INTRAVESICAL THERAPY FOR BLADDER PAIN SYNDROME (BPS)/INTERSTITIAL CYSTITIS (IC).

Meng E, Hsu YC, Chuang YC. *Low Urin Tract Symptoms*. 2018 Jan;10(1):3-11. doi: 10.1111/luts.12214. PMID: 29341502

BPS/IC is a chronic symptom complex that may cause bothersome storage symptoms and pain or discomfort of the bladder, adversely affecting a patient's quality of life. The etiology of BPS/IC remains unclear, and its cause may be multifactorial. Diagnosis of BPS/IC is based on clinical features, and the possibility of other conditions must be ruled out first. Although no definitive treatment is currently available for BPS/IC, various intravesical therapies are used for BPS/IC, including heparin, hyaluronic acid, chondroitin sulfate, pentosan polysulfate, dimethylsulfoxide, liposomes, and botulinum onabotulinum toxinA (BoNT-A). This review from Taiwan summarizes the intravesical therapy for BPS/IC and discusses recent advances in the instillation of liposomal-mediated BoNT-A and other newly developed intravesical therapies.

PRODROME AND NON-PRODROME PHENOTYPES OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Warren JW, Jian N, Gallicchio L, Wu D, Clauw DJ. *Urology*. 2018 May 15. pii: S0090-4295(18)30458-8. doi: 10.1016/j.urology.2018.05.004. [Epub ahead of print] PMID: 29775697

This aim of this study was to test the hypothesis that risk factors for BPS/IC in women differ between those with and without the BPS/IC prodrome. Incident cases of BPS/IC and healthy controls were recruited nationally. More than half the BPS/IC cases reported subsyndromal urinary symptoms for decades before onset of BPS/IC and were identified as having the prodrome. Risk factors for BPS/IC were examined separately for cases with and without the prodrome using a set of matched controls. Two risk factors distinguished 178 prodrome from 134 non-prodrome cases. One was "UTIs" in the year before BPS/IC onset, possibly a manifestation of the prodrome itself. The other was the presence of the maximal number of non-bladder syndromes (NBSs): prodrome cases were 12 times more likely than non-prodrome cases to have ≥ 4 NBSs. Additional risk factors for prodrome and/or non-prodrome cases were the direct association of exogenous female hormones, as well as three inverse associations: type 2 diabetes mellitus, multiple pregnancies, and current daily smoking. Prodrome cases developed urinary symptoms in their early twenties (i.e., the prodrome) and were at very high risk of numerous NBSs. Non-prodrome cases developed urinary symptoms in their early forties (i.e., full-blown BPS/IC) and were no more likely than controls to have the maximal number of NBSs. These findings are consistent with recent suggestions of two BPS/IC phenotypes, one with systemic and psychosocial manifestations and the other more specific to the bladder. Additionally, several risk factors identified here might be hints of related or causal nervous system pathophysiologies.

(Ed.: Definition of **prodrome** - an early symptom indicating the onset of a disease or illness).

DISTRIBUTION OF MAST CELL SUBTYPES IN INTERSTITIAL CYSTITIS: IMPLICATIONS FOR NOVEL DIAGNOSTIC AND THERAPEUTIC STRATEGIES?

Malik ST, Birch BR, Voegeli D, Fader M, Foria V, Cooper AJ, Walls AF, Lwaleed BA. *J Clin Pathol*. 2018 May 15. pii: jclinpath-2017-204881. doi: 10.1136/jclinpath-2017-204881. [Epub ahead of print] PMID: 29764932

The aim of this study was to identify the presence and geographical distribution of mast cell (MC) subtypes: MC_T (tryptase positive-chymase negative) and MC_{TC} (tryptase positive-chymase positive) in bladder tissue. Bladder tissue was obtained from 14 patients with PBS/IC and normal histology from University Hospital Southampton tissue bank. Sequential tissue slices were immunohistochemically stained for MC subtypes using anti-MC tryptase (for MC_T and MC_{TC}) and anti-MC chymase (for MC_{TC}). Stained sections were photographed, and positively stained MCs were quantified using ImageJ. Data were analysed using descriptive statistics and individual paired t-tests. There was a significant difference in the density of MCs between each layer of the disease bladder, with the greatest accumulation within the detrusor. There was a significant increase in MC_{TC} subtype in the lamina in PBS/IC. The authors are of the opinion that their results suggest that mastocytosis is present within all layers of disease bladder, especially the muscle layer. The varying increase in MC subtypes in the lamina and mucosa may explain the variability in PBS/IC symptoms. A high influx of MC_{TC} in the mucosa of individuals who also had ulceration noted within their diagnostic notes may be of the Hunner's ulcer

subclassification. These findings suggest a relationship between the pathogenesis of MC subtypes and the clinical presentation of PBS/IC. A cohort study would further elucidate the diagnostic and/or therapeutic potential of MCs in patients with PBS/IC.

ADELMIDROL + SODIUM HYALURONATE IN IC/BPS OR CONDITIONS ASSOCIATED TO CHRONIC UROTHELIAL INFLAMMATION. A TRANSLATIONAL STUDY.

Ostardo E, Impellizzeri D, Cervigni M, Porru D, Sommariva M, Cordaro M, Siracusa R, Fusco R, Gugliandolo E, Crupi R, Schievano C, Inferrera A, Di Paola R, Cuzzocrea S; *Urology Study Group*. *Pharmacol Res*. 2018 May 22. pii: S1043-6618(18)30497-3. doi: 10.1016/j.phrs.2018.05.013. [Epub ahead of print] PMID: 29800607

IC/BPS, characterized by frequent urination, bladder inflammation and pain, is a particularly challenging disease and a clear unmet medical need in terms of identifying new therapeutic strategies. The aim of this study from Italy was to evaluate the anti-inflammatory effects of intravesical Vessilen® (a new formulation of 2% adelmidrol (the diethanolamide derivative of azelaic acid) + 0.1% sodium hyaluronate) administration in rodent models of IC/BPS and in IC/BPS patients or other bladder disorders. Acute and chronic animal models of cystitis were induced by a single or repetitive intraperitoneal injections of cyclophosphamide (CYP); patients with IC/BPS or with bladder pain syndrome associated with symptoms of the lower urinary tract treated once weekly by bladder instillation of Vessilen® for 8 weeks. CYP instillation caused macroscopic and histological bladder alterations, inflammatory infiltrates, increased mast cell numbers, bladder pain, increased expression of nitrotyrosine, decreased expression of endothelial tight junction zonula occludens-1. Intravesical Vessilen® treatment was able to ameliorate CYP induced bladder inflammation and pain by inhibiting nuclear factor- κ B pathway and inflammatory mediator levels as well as reduced mechanical allodynia and nerve growth factor levels. A significant improvement in quality of life and symptom intensity was evident in patients with IC/BPS or other bladder disorders treated with Vessilen®. The authors therefore believe that Vessilen® could be a new therapeutic approach for human cystitis.

FEMALE VETERANS WITH DIAGNOSES OF BOTH CHRONIC PELVIC PAIN AND OVERACTIVE BLADDER; HOW DO THEY COMPARE TO WOMEN DIAGNOSED WITH INTERSTITIAL CYSTITIS?

Volpe KA, Cichowski SB, Komesu YK, Rogers RG, Murata A, Murata G. *Female Pelvic Med Reconstr Surg*. 2018 May 10. doi: 10.1097/SPV.0000000000000597. [Epub ahead of print] PMID: 29746393

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The objective of this study was to compare women with a known diagnosis of IC to a population that might be at risk for the diagnosis of IC, women with diagnoses of both chronic pelvic pain (CPP) and overactive bladder (OAB). There were more patients diagnosed with CPP and OAB compared with patients diagnosed with IC in this population of female veterans. Given the high rate of comorbid anxiety and depression in both groups, further study is warranted to determine whether these women are misdiagnosed.

DIFFERENTIAL REGULATION OF BLADDER PAIN AND VOIDING FUNCTION BY SENSORY AFFERENT POPULATIONS REVEALED BY SELECTIVE OPTOGENETIC ACTIVATION.

DeBerry JJ, Samineni VK, Copits BA, Sullivan CJ, Vogt SK, Albers KM, Davis BM, Gereau IV RW. *Front Integr Neurosci*. 2018 Feb 12;12:5. doi: 10.3389/fnint.2018.00005. eCollection 2018. PMID: 29483864

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Bladder-innervating primary sensory neurons mediate reflex-driven bladder function under normal conditions and contribute to debilitating bladder pain and/or overactivity in pathological states. The goal of this study was to examine the respective roles of defined subtypes of afferent neurons in bladder sensation and function *in vivo* via direct optogenetic activation.

COMPARISON OF INFLAMMATORY URINE MARKERS IN PATIENTS WITH INTERSTITIAL CYSTITIS AND OVERACTIVE BLADDER.

Furuta A, Yamamoto T, Suzuki Y, Gotoh M, Egawa S, Yoshimura N. *Int Urogynecol J*. 2018 Jan 25. doi: 10.1007/s00192-017-3547-5. [Epub ahead of print] PMID: 29372285

Chronic inflammatory conditions seem to be a shared characteristic in patients with interstitial cystitis (IC) and overactive bladder (OAB). Furuta and colleagues from Japan and USA therefore measured 40 inflammatory urine markers in IC patients with or without Hunner's lesions (HIC and NHIC respectively) and OAB patients. Urine was collected from consecutive HIC patients, NHIC patients, and age and gender-matched OAB patients with no history of IC, recurrent urinary tract infection or bladder cancer. The diagnosis of IC was based on the Asian IC guideline criteria. A representative 40 inflammatory growth factors, cytokines, and chemokines in urine were measured using a MILLIPLEX immunoassay kit. Statistical differences in these markers among the groups were

determined by nonparametric ANOVA followed by multiple comparison test. The diagnostic efficiency of these markers was measured using receiver operating characteristic analysis. Vascular endothelial growth factor (VEGF), interleukin-1 α (IL-1 α), IL-6, and chemokines including CCL2, CCL5, CXCL1, CXCL8, and CXCL10 were significantly increased in HIC and NHIC patients compared with OAB patients. The significant increases in CXCL8 and CXCL10 were also found in HIC patients compared with NHIC patients. However, there were no significant differences in the other urine markers among the groups. It was therefore concluded that the increases in angiogenesis-associated proteins such as VEGF and CXCL10 may be pathophysiologically important for the development of IC.

EFFICACY AND SAFETY OF SACRAL AND PERCUTANEOUS TIBIAL NEUROMODULATION IN NON-NEUROGENIC LOWER URINARY TRACT DYSFUNCTION AND CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE.

Tutolo M, Ammirati E, Heesakkers J, Kessler TM, Peters KM, Rashid T, Sievert KD, Spinelli M⁸, Novara G, Van der Aa F, De Ridder D. Eur Urol. 2018 Jan 11. pii: S0302-2838(17)30978-8. doi: 10.1016/j.eururo.2017.11.002. [Epub ahead of print] PMID: 29336927

Neuromodulation is considered in patients with non-neurogenic lower urinary tract dysfunction (LUTD) not responsive to conservative treatment. The purpose of this study was to systematically review the available studies on efficacy and safety of sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS) in non-neurogenic LUTDs not responsive to conservative treatments. A literature research was conducted in PubMed/Medline and Scopus, restricted to articles in English, published between January 1998 and June 2017, with at least 20 patients and 6 months of follow-up. Twenty-one reports were identified. Concerning SNM, the improvement of $\geq 50\%$ in leakage episodes ranged widely between 29% and 76%. Overall dry rate ranged between 43% and 56%. Overall success/improvement rate in PTNS varied between 54% and 59%. Symptom improvement or efficacy in interstitial cystitis/bladder pain syndrome patients appeared to be lower compared with other indications in both techniques. Safety data showed fewer side effects in patients submitted to PTNS. It was concluded that neuromodulation gives good results and is a safe therapy for patients with overactive bladder or chronic nonobstructive urinary retention with long-lasting efficacy. Moreover, PTNS has been shown to have good success rates and fewer side effects compared with SNM. These data have to be confirmed with long-term follow-up.

ADVANCES IN INTRAVESICAL THERAPY FOR BLADDER PAIN SYNDROME (BPS)/INTERSTITIAL CYSTITIS (IC).

Meng E, Hsu YC, Chuang YC. Low Urin Tract Symptoms. 2018 Jan;10(1):3-11. doi: 10.1111/luts.12214. PMID: 29341502

Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a chronic symptom complex that may cause bothersome storage symptoms and pain or discomfort of the bladder, adversely affecting a patient's quality of life. The etiology of IC/BPS remains unclear, and its cause may be multifactorial. Diagnosis of IC/BPS is based on clinical features, and the possibility of other conditions must be ruled out first. Although no definitive treatment is currently available for IC/BPS, various intravesical therapies are used for IC/BPS, including heparin, hyaluronic acid, chondroitin sulfate, pentosan polysulfate, dimethylsulfoxide, liposomes, and botulinum onabotulinumtoxinA (BoNT-A). This review from Taiwan summarizes the intravesical therapy for IC/BPS and discusses recent advances in the instillation of liposomal-mediated BoNT-A and other newly developed intravesical therapies.

[BLADDER HYDRODISTENSION IN TREATING PATIENTS WITH INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME]. [Article in Russian]

Al'-Shukri SK, Kuz'min IV, Slesarevskaya MN, Ignashov YA. Urologiia. 2018 Mar;(1):26-29. PMID: 29634130

This study from Russia aimed to evaluate the effectiveness of bladder hydrodistension in the treatment of IC/BPS, depending on the duration of the procedure. The study comprised 71 women aged 51.6+/-8.3 years with a 5.2+/-2.3 year history of IC/BPS. All patients underwent bladder hydrodistension (BH). Depending on the duration of BH, patients were divided into 4 groups. The distension time in group 1, group 2, group 3 and group 4 was 1 min, 2 min, 4 min and 6 min, respectively. The treatment effectiveness was assessed 1 month after BH by subjective assessment of patients, Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale questionnaire, a visual analog pain scale (VAS), and voiding diaries. At one month after BH, a positive effect was observed in 32 (45.1%) patients. In groups 1, 2, 3 and 4 the treatment was effective in 20%, 55%, 45% and 47.6% of patients, respectively. Clinical effectiveness of BH with distension time of 1 min was significantly lower than that of 2, 4, and 6 min. At the same time, the authors did not find significant differences in the effectiveness of this procedure with distension time of 2, 4 and 6 min. The results of this

study suggest that BH is an effective treatment in patients suffering from IC/BPS. At the same time, they show that the distension time of 2 min. is optimal from the point of view of clinical effectiveness, since the longer duration of the procedure is excessive, and the shorter time is insufficient.

DELETION OR PHARMACOLOGICAL BLOCKADE OF TOLL-LIKE RECEPTOR 4 (TLR4) CONFERS PROTECTION AGAINST CYCLOPHOSPHAMIDE-INDUCED MOUSE CYSTITIS.

de Oliveira MG, Mónica FZ, Calmasini FB, Alexandre EC, Tavares EBG, Soares AG, Costa SKP, Antunes E. Am J Physiol Renal Physiol. 2018 May 2. doi: 10.1152/ajprenal.00100.2018. [Epub ahead of print] PMID: 29717937
IC/BPS is a chronic inflammatory disease without consistently effective treatment. De Oliveira and colleagues from Brazil investigate the role of toll-like receptor (TLR4) on voiding dysfunction and inflammation in the cyclophosphamide (CYP)-induced mouse cystitis. Their findings reveal a central role for TLR4 signalling pathway in initiating CYP-induced bladder dysfunction and inflammation, and thus emphasize that TLR4 receptor blockade may have clinical value for IC/BPS treatment.

INFLAMMATION AND TISSUE REMODELING IN THE BLADDER AND URETHRA IN FELINE INTERSTITIAL CYSTITIS.

Kullmann FA, McDonnell BM, Wolf-Johnston AS, Lynn AM, Getchell SE, Ruiz WG, Zabbarova IV, Ikeda Y, Kanai AJ, Roppolo JR, Bastacky SI, Apodaca G, Buffington CAT, Birder LA. Front Syst Neurosci. 2018 Apr 13;12:13. doi: 10.3389/fnsys.2018.00013. eCollection 2018. PMID: 29706873

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IC/BPS is a debilitating chronic disease of unknown etiology. A naturally occurring disease termed feline interstitial cystitis (FIC) reproduces many features of IC/BPS patients. To gain insights into mechanisms underlying IC/BPS, Kullmann and colleagues investigated pathological changes in the lamina propria (LP) of the bladder and proximal urethra in cats with FIC, using histological and molecular methods. Their data suggest a more prominent role for chronic inflammation and tissue remodelling than previously thought, which may result in alterations in mucosal signalling within the urinary bladder and proximal urethra that may contribute to altered sensations and pain in cats and humans with this syndrome.

MOLECULAR PATHOGENESIS OF INTERSTITIAL CYSTITIS BASED ON MICRORNA EXPRESSION SIGNATURE: MIR-320 FAMILY-REGULATED MOLECULAR PATHWAYS AND TARGETS.

Arai T, Fuse M, Goto Y, Kaga K, Kurozumi A, Yamada Y, Sugawara S, Okato A, Ichikawa T, Yamanishi T, Seki N. J Hum Genet. 2018 May;63(5):543-554. doi: 10.1038/s10038-018-0419-x. Epub 2018 Mar 12. PMID: 29531336
Interstitial cystitis (IC), also known as bladder pain syndrome, is a chronic inflammatory disease that affects the bladder. The symptoms of IC vary, including feeling an urgent need for immediate urination and of needing to urinate often, as well as bladder or pelvic pain. Despite its high incidence, no molecular diagnostic methods are available for IC, and the molecular pathogenesis is unknown. microRNAs (miRNA) can regulate expression of RNA transcripts in cells and aberrant expression of miRNAs is associated with several human diseases. Arai and colleagues from Japan investigated the molecular pathogenesis of IC based on miRNA expression signatures. RNA sequencing of miRNA levels in IC tissues and comparison with levels in normal bladder tissue and bladder cancer revealed dysregulated expression of 366 miRNAs (203 and 163 down- and upregulated miRNAs, respectively). In particular, miR-320 family miRNAs(miR-320a, miR-320b, miR-320c, miR-320d and miR-320e) had downregulated expression in IC tissues. Genome-wide gene expression analyses and in silico database analyses showed that three transcription factors, E2F-1, E2F-2 and TUB, are regulated by miR-320 family miRNAs. Immunostaining of IC tissues confirmed that these transcription factors are overexpressed in IC tissues. Novel approaches that identify aberrantly expressed miRNA regulatory networks in IC could provide new prognostic markers and therapeutic targets for this disease.

URINE NERVE GROWTH FACTOR (NGF) LEVEL, BLADDER NERVE STAINING AND SYMPTOM/PROBLEM SCORES IN PATIENTS WITH INTERSTITIAL CYSTITIS.

Tonyali S, Ates D, Akbiyik F, Kankaya D, Baydar D, Ergen A. Adv Clin Exp Med. 2018 Feb;27(2):159-163. doi: 10.17219/acem/69231. PMID: 29521057

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Although there have been numerous theories regarding IC/BPS etiology, the physiopathology of the disease still remains unclear and there is a lack of certain treatment. The aim of this study from Turkey was to assess the role of nerve fibers and nerve growth factor (NGF) in the etiopathogenesis of IC/BPS symptoms by demonstrating if there is a correlation between urine NGF levels, amount of peripheral nerves in bladder mucosa and symptom severity. A prospective clinical study was conducted with 15 IC/BPS patients and 18 controls. Urine

NGF levels were measured by enzyme-linked immunosorbent assay (ELISA). Bladder punch biopsies were obtained from 15 IC/BPS patients and 9 controls. Immunohistochemistry was performed for S-100 to highlight peripheral nerve twigs in bladder mucosa. The O'Leary-Sant Interstitial Cystitis Symptom and Problem Index (OSICSPI) was used to assess symptom severity and effects of the disease on the patients' life. The authors concluded that NGF seems to be a promising biomarker in IC/BPS. It may help clinicians in diagnoses and patient follow-up. Thus, unnecessary, expensive and invasive tests, interventions and treatments might be avoided.

[A GENOME-SCALE DNA METHYLATION STUDY IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Bradley MS, Burke EE, Grenier C, Amundsen CL, Murphy SK, Siddiqui NY. Neurourol Urodyn. 2018 Jan 24. doi: 10.1002/nau.23489. [Epub ahead of print] PMID: 29363787

The purpose of this study from the USA was to assess the feasibility of using voided urine samples to perform a DNA methylation study in females with interstitial cystitis/bladder pain syndrome (IC/BPS) as compared to age- and race-matched controls. A unique methylation profile could lead to a non-invasive, reproducible, and objective biomarker that would aid clinicians in the diagnosis of IC/BPS. Nineteen IC/BPS patients and 17 controls were included. IC/BPS patients had an Interstitial Cystitis Symptom Index score of >8; controls had no bladder symptoms. DNA was extracted from pelleted urine sediment. Samples with >500 ng of genomic DNA underwent quantitative DNA methylation assessment using the Illumina Infinium MethylationEPIC BeadChip. Age- and race-matching was applied prior to analysis. Linear regression models were used to compare average methylation between IC/BPS cases and controls at each cytosine guanine dinucleotide site (loci where methylation can occur). Sixteen participants (eight IC/BPS age- and race-matched to eight controls) had adequate DNA for methylation analysis. A total of 688 417 CpG sites were analyzed. In exploratory pathway analysis utilizing the top 1000 differentially methylated CpG sites, the mitogen-activated protein kinase (MAPK) pathway was overrepresented by member genes. The results demonstrate the feasibility of using voided urine specimens from women with IC/BPS to perform DNA methylation assessments. Additionally, the data suggest genes within or downstream of the MAPK pathway exhibit altered methylation in IC/BPS.

[IMPROVING THE UTILITY OF CLINICAL PHENOTYPING IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: FROM UPOINT TO INPUT.](#)

Crane A, Lloyd J, Shoskes DA. Can J Urol. 2018 Apr;25(2):9250-9254. PMID: 29680002

The phenotyping system UPOINT has proven effective in men with chronic pelvic pain syndrome (CPPS), but is more limited in patients with IC/PBS since by definition all patients have the urinary and organ specific phenotype. Furthermore, AUA guidelines recommend a sequential tiered approach to therapy rather than the multimodal UPOINT scheme. Crane and colleagues sought to modify UPOINT to be more practical and efficacious for IC/PBS. They developed a new phenotype by removing the urinary and organ specific domains from UPOINT and adding a Hunner's ulcers (U) domain, since these patients benefit from phenotype specific therapies (fulguration, cyclosporine). This yields 'INPUT': infection, neurologic/systemic, psychosocial, ulcers and tenderness of muscles. They applied this system retrospectively to their previously validated upointmd.com IC/PBS database. Symptoms were measured by the Genitourinary Pain Index (GUPI) (valid for men and women). The database was searched for patients with complete data to assess the INPUT domains and include GUPI. Men were included if they reported pain relieved by voiding and/or presence of Hunner's ulcers. It was concluded that the INPUT phenotype in IC/PBS appears to replicate the validity and potential clinical utility of UPOINT in CPPS. Patients have a diversity of phenotypes and more positive domains correlate with more severe symptoms. Since 95% of patients have at least 1 positive domain it may benefit patients to receive multimodal therapy up front for these extra domains (eg. pelvic floor physical therapy, fulguration of ulcers) rather than relying on a sequential tiered approach.

[WILL CESAREAN SECTION INCREASE THE RISK OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME?](#)

Chang KM, Lee MH, Lin HH, Wu SL, Wu HC. Neurourol Urodyn. 2018 May 1. doi: 10.1002/nau.23704. [Epub ahead of print] PMID: 29717503

A high number of patients with IC/PBS have a history of pelvic surgeries, and caesarean section is one of the most common pelvic surgeries in women. This study from Taiwan aimed to investigate if caesarean section increases the risk of IC/PBS. Women who exclusively gave birth through caesarean section or vaginal delivery were identified from a nationwide database between 2002 and 2013. All were followed up during the study period to detect the event of IC/PBS. The IC/PBS hazard ratio (HR) in the caesarean cohort was compared with the vaginal delivery cohort with and without matching for confounding factors. The authors found that the risk of IC/PBS was not different between caesarean and vaginal delivery after controlling the confounding

factors in this cohort study. Caesarean section has no causal effect on IC/BPS. Furthermore, delivery was not a risk factor for IC/PBS.

ENDOGENOUS H₂S SENSITIZES THE PAR4-INDUCED BLADDER PAIN.

Wang W, Bo Q, Du J, Yu X, Zhu K, Cui J, Zhao H, Wang Y, Shi B, Zhu Y. *Am J Physiol Renal Physiol.* 2018 Jan 10. doi: 10.1152/ajprenal.00526.2017. [Epub ahead of print] PMID: 29357418

Wang and colleagues from China note that hydrogen sulfide (H₂S) generated by cystathionine β-synthase (CBS) or cystathionine γ-lyase (CSE) facilitates bladder hypersensitivity. They assessed involvement of the H₂S pathway in PAR4 (protease-activated receptor 4)-induced bladder pain. Bladder pain triggered by the H₂S pathway was not accompanied by inflammation or altered micturition behaviour. Thus, endogenous H₂S generated by CBS or CSE caused referred hyperalgesia mediated through MIF in mice with PAR4-induced bladder pain, without causing bladder injury or altering micturition behaviour.

COMPARATIVE STUDY OF EFFICACY AND SAFETY BETWEEN BLADDER BODY AND TRIGONAL INTRAVESICAL ONABOTULINUM TOXINA INJECTION IN THE TREATMENT OF INTERSTITIAL CYSTITIS REFRACTORY TO CONVENTIONAL TREATMENT-A PROSPECTIVE, RANDOMIZED, CLINICAL TRIAL.

Jiang YH, Jhang JF, Lee CL, Kuo HC. *Neurourol Urodyn.* 2018 Apr;37(4):1467-1473. doi: 10.1002/nau.23475. Epub 2018 Jan 13. PMID: 29331031

Intravesical onabotulinum toxinA (BoNT-A) injection is believed to be able to relieve symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). However, the therapeutic efficacy of different injection sites is not well known. This study From Taiwan compared therapeutic efficacy and safety between bladder body and trigonal BoNT-A injection. Patients were randomly treated with 100U of BoNT-A in 10 mL saline injected into 20 bladder body sites or 10 trigonal sites. Thirty-nine patients completed the study visits. Patients in both group had significant improvement in VAS, OSS, and functional bladder capacity after treatment. There was no significant difference in changes of urinary frequency, voided volume, post-void residual volume, and bladder capacity from baseline to 8 weeks between groups. Thirteen patients in bladder body group and 10 patients in trigone group had decrease of VAS more than 2 points after treatment. Excellent symptom improvement was noted in 9 patients with bladder body injection and 10 patients with trigonal injection. Nine patients in bladder body group and 10 in trigonal group experienced dysuria after treatment. The authors concluded that no significant difference in the improvement of IC symptoms and urodynamic parameters after intravesical BoNT-A injection in the bladder body or trigone. The rate of adverse events was similar between groups.

THE EFFICACY OF BOTULINUM TOXIN A AND SACRAL NEUROMODULATION IN THE MANAGEMENT OF INTERSTITIAL CYSTITIS (IC)/BLADDER PAIN SYNDROME (BPS), WHAT DO WE KNOW? ICI-RS 2017 THINK TANK, BRISTOL.

Rahnama'i MS, Marcelissen T, Apostolidis A, Veit-Rubin N, Schurch B, Cardozo L, Dmochowski R. *Neurourol Urodyn.* 2018 Jan 24. doi: 10.1002/nau.23493. [Epub ahead of print] PMID: 29363792

This International Consultation on Incontinence (ICI) manuscript addressed the evidence available in the literature on the efficacy of Botulinum Toxin A (BoNT-A) and sacral neuromodulation (SNM) in patients suffering from IC/BPS and proposed further research to identify mechanisms of action and establish the clinical efficacy of either therapy. At the International Consultation on Incontinence-Research Society (ICI-RS) in 2017, a panel of functional urologists and urogynaecologists participated in a Think Tank (TT) discussing the management of IC/BPS by BoNT-A and SNM, using available data from both PubMed and Medicine literature searches. The role of BoNT-A and SNM in the treatment of IC/BPS are discussed and mechanisms of actions are proposed. Despite the available randomized trial data on the effect of intravesical BoNT-A treatment on symptoms of IC/BPS, a consistent conclusion of a positive effect cannot be drawn at the moment, as the published studies are small and heterogeneous in design. There is substantive evidence for the positive effects of SNM on symptoms of IC/BPS patients. However, during patient selection, it is important to distinguish the degree and the location of pain in order to tailor the best therapy to the right patients. Both intravesical BoNT-A treatment and SNM have been shown to have positive effects in patients with IC/BPS. However, firm conclusions cannot yet be drawn. Patient-reported outcomes and quality of life should be assessed in addition to urinary and pain symptoms. Since current treatments mainly focus on symptomatic relief, future research should also focus on clarifying the pathogenic mechanisms involved in IC/BPS.

NOVEL CONTRAST MIXTURE ACHIEVES CONTRAST RESOLUTION OF HUMAN BLADDER WALL SUITABLE FOR T1 MAPPING: APPLICATIONS IN INTERSTITIAL CYSTITIS AND BEYOND.

Tyagi P, Janicki J, Moon CH, Kaufman J, Chermansky C. *Int Urol Nephrol*. 2018 Feb 1. doi: 10.1007/s11255-018-1794-0. [Epub ahead of print] PMID: 29392488

Instillation of novel contrast mixture (NCM) was recently shown to improve the contrast resolution of rat bladder wall with high contrast-to-noise ratio (CNR). In this study from the USA, the clinical safety and the feasibility of NCM-enhanced MRI to achieve artifact-free visualization of human bladder wall suitable for quantitative measurement of the magnetic resonance (MR) longitudinal relaxation time (T1) was assessed. Findings demonstrate the safety and feasibility of NCM-enhanced MRI to achieve artifact-free differential contrast and spatial resolution of human bladder wall, which is suitable for measuring BWT and pixel-wise measurement of T1 in post-contrast setting.

EPSTEIN-BARR VIRUS PRESENCE AS A POTENTIAL ETIOLOGY OF PERSISTENT BLADDER INFLAMMATION IN HUMAN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Jhang JF, Hsu YH, Peng CW, Jiang YH, Ho HC, Kuo HC. *J Urol*. 2018 Apr 10. pii: S0022-5347(18)42926-6. doi: 10.1016/j.juro.2018.03.133. [Epub ahead of print] PMID: 29653163

Interstitial cystitis/bladder pain syndrome is characterized by bladder inflammation without a bacterial infection. Although viral infection is a potential etiologic cause, few studies are reported. In this study from Taiwan, bladder specimens were obtained from patients with IC/BPS and patients with stress urinary incontinence (control). Only one control specimen was Epstein-Barr positive in qPCR. All sera from IC/BPS patients showed past Epstein-Barr viral infection. Epstein-Barr infection was present in 87.5% of bladder specimens from HIC patients and in 17.4% of specimens from NHIC patients (total IC/BPS: 46.2%). Immunohistochemical staining of CD3 and CD20 revealed that Epstein-Barr infection was mainly restricted to T lymphocytes of IC/BPS bladders. The authors concluded that bladder EBV infection in T cells may be linked to the pathogenesis of persistent inflammation in patients with IC/BPS.

MORBIDITY RATE AND MEDICAL UTILIZATION IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Lee MH, Chang KM, Tsai WC. *Int Urogynecol J*. 2018 Mar 12. doi: 10.1007/s00192-018-3574-x. [Epub ahead of print] PMID: 29532129

The objective of this study from Taiwan was to calculate the morbidity rate and medical utilization of interstitial cystitis/painful bladder syndrome (IC/PBS) over 12 years using a nationwide database of Taiwan. This was a cohort study of the Longitudinal Health Insurance Database 2010 with new diagnoses of IC/PBS from 2002 through 2013. The morbidity rate of IC/PBS showed a higher incidence and prevalence in women and older patients. A new drug for the treatment of IC/PBS may be a factor of the peak in the morbidity rate. The increase in medical utilization could be explained by the awareness of physicians and patients seeking medical help.

DEPRESSION AND COPING BEHAVIORS ARE KEY FACTORS IN UNDERSTANDING PAIN IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Muere A, Tripp DA, Nickel JC, Kelly KL, Mayer R, Pontari M, Moldwin R, Carr LK, Yang CC, Nordling J. *Pain Manag Nurs*. 2018 Feb 28. pii: S1524-9042(17)30054-1. doi: 10.1016/j.pmn.2017.11.001. [Epub ahead of print] PMID: 29501360

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a urologic chronic pelvic pain syndrome with suboptimal treatment outcomes. Catastrophizing is an empirically supported risk factor for greater IC/BPS pain. In this study, a moderated multiple mediation model is tested in which several additional psychosocial risk factors (depression, illness and wellness-focused behavioural coping strategies) are proposed as mediators or moderators in the existing relationship between catastrophizing and IC/BPS pain. The present questionnaire study employed a cross-sectional design. 341 female patients with an IC/BPS diagnosis were recruited at tertiary care sites. Participants completed questionnaires assessing pain, catastrophizing, behavioural coping strategies, and depressive symptoms. Aggregate factor scores were calculated following exploratory factor analyses. It was found that patients with a greater tendency to catastrophize were more likely to engage in illness-focused coping strategies, which contributed to the reporting of greater sensory and affective pain. Furthermore, this mediating effect of illness-focused coping on affective pain was more likely to occur in those patients reporting greater depressive symptoms. Illness-focused behavioural coping is an important mechanism between maladaptive pain cognition and aspects of patient pain, with patients reporting greater depressive symptoms at increased risk for elevated pain. Patient management techniques, including screening for catastrophizing, coping, and depression, are recommended to enrich IC/BPS management.

THE EFFECTS OF CYSTOSCOPY AND HYDRODISTENTION ON SYMPTOMS AND BLADDER CAPACITY IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Kirk PS, Santiago-Lastra Y, Qin Y, Stoffel JT, Quentin Clemens J, Cameron AP. *Neurourol Urodyn*. 2018 Mar 22. doi: 10.1002/nau.23555. [Epub ahead of print] PMID: 29566264

The use of cystoscopy and hydrodistention in the management of IC/BPS varies widely between providers. Current evidence regarding the risks and benefits of hydrodistention, as well as the long-term effects of repeated hydrodistention are not well established. Kirk and colleagues sought to characterize the effects of hydrodistention on IC/BPS symptoms as well as bladder capacity. They retrospectively queried their institutional records for patients with non-ulcerative IC/BPS who underwent hydrodistention over an 11-year period to obtain demographic and clinical factors at the time of diagnosis and treatment. Symptom relief and bladder capacity changes were assessed, and multivariable models were used to predict response to treatment. There were 328 patients who underwent hydrodistention during the study period, of whom 36% received the procedure multiple times, and overall median follow-up was 38.6 months. Patients with repeated hydrodistentions were more likely to be female, have more comorbid pain disorders, and have trialed anticholinergic medications and intravesical instillations. No decrease in mean bladder capacity was observed over time. Significant decreases in symptom scores were observed following the procedure on multiple questionnaires. They concluded that hydrodistention does not decrease bladder capacity even with multiple procedures, and measurably improves symptoms in some patients with IC/BPS. Continuing efforts to better identify those patients most likely to benefit from this procedure are justified.

PIGMENTARY MACULOPATHY ASSOCIATED WITH CHRONIC EXPOSURE TO PENTOSAN POLYSULFATE SODIUM.

Pearce WA, Chen R, Jain N. *Ophthalmology*. 2018 May 22. pii: S0161-6420(17)33695-3. doi: 10.1016/j.ophtha.2018.04.026. [Epub ahead of print] PMID: 29801663

The purpose of this retrospective case series study from the USA was to describe the clinical features of a unique pigmentary maculopathy noted in the setting of chronic exposure to pentosan polysulfate sodium (PPS), a therapy for interstitial cystitis (IC). Six adult patients evaluated by a single clinician between May 1, 2015, and October 1, 2017. The authors describe a novel and possibly avoidable maculopathy associated with chronic exposure to PPS. Patients reported symptoms of difficulty reading and prolonged dark adaptation despite generally intact visual acuity and subtle funduscopic findings. Multimodal imaging and functional studies are suggestive of a primary RPE injury. Additional investigation is warranted to explore causality further.

PHARMACOLOGICAL MANAGEMENT OF INTERSTITIAL CYSTITIS /BLADDER PAIN SYNDROME AND THE ROLE CYCLOSPORINE AND OTHER IMMUNOMODULATING DRUGS PLAY.

Ogawa T, Ishizuka O, Ueda T, Tyagi P, Chancellor MB, Yoshimura N. *Expert Rev Clin Pharmacol*. 2018 May;11(5):495-505. doi: 10.1080/17512433.2018.1457435. Epub 2018 Apr 9. PMID: 29575959

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a symptomatic disorder characterized by pelvic pain and urinary frequency. Immunological responses are considered as one of the possible etiologies of IC/BPS. In this review, Ogawa and colleagues focused on emerging targets, especially on those modulating immunological mechanisms for the treatments of IC/BPS. They discussed current treatments and the drugs targeting the immune responses including CyA and other drugs with different mechanisms including NGF antibodies and P2X3 antagonists. Expert commentary: IC/BPS is often difficult to treat by current treatments. Immunosuppression agents, especially CyA are considered as effective treatments for IC/BPS with Hunner's lesion because these drugs suppress the inflammatory responses in the bladder underlying urinary symptoms of the disease. Based on the previous literatures, they are of the opinion that they should use CyA for the refractory IC/BPS, especially that with Hunner's lesion due to its side effects. New drugs targeting other mechanisms such as urothelial or afferent nerve dysfunction or new delivery systems such as sustained drug releasing devices or gene therapy techniques may be promising for the future treatments of IC/BPS.

VIDEOURODYNAMIC CHARACTERISTICS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME- THE ROLE OF BLADDER OUTLET DYSFUNCTION IN THE PATHOPHYSIOLOGY.

Kuo YC, Kuo HC. *Neurourol Urodyn*. 2018 Mar 5. doi: 10.1002/nau.23542. [Epub ahead of print] PMID: 29504632

The aim of this study from Taiwan was to investigate the characteristics of videourodynamic study (VUDS) in females with interstitial cystitis/bladder pain syndrome (IC/BPS) focusing on the etiologies of bladder outlet dysfunction (BOD) and their associations with clinical and urodynamic parameters. IC/BPS females with complete data on symptom assessment, VUDS, the potassium sensitivity test, and cystoscopic hydrodistention were reviewed retrospectively. Diagnoses of bladder dysfunction (hypersensitive bladder, HSB) and BOD including dysfunctional voiding (DV), poor relaxation of the external urethral sphincter (PRES), and bladder neck dysfunction (BND) were made by VUDS. The clinical and urodynamic parameters between patients with normal and abnormal VUDS diagnoses were analyzed. A total of 348 IC/BPS female patients (mean

age 48.8 ± 13.5) were enrolled. HSB was found in 307 (88.2%) patients and BOD in 209 (60.1%). The causes of BOD included DV in 40 (11.5%), PRES in 168 (48.3%), and BND in 1 (0.3%). Patients with DV and BND had higher, and those with PRES had lower detrusor pressures at maximum flow rate (Q_{max}) than those with normal tracings. For all BOD patients, univariate logistic regression revealed a significant positive correlation of disease duration and negative correlations of urodynamic volume parameters with BOD in IC/BPS patients. Multivariate logistic regression found a cut-off value of $Q_{max} \leq 11$ mL/s predicted BOD in IC/BPS with a receiver operating characteristic area of 0.81 (sensitivity = 82.0%, specificity = 68.5%). The authors concluded that HSB and BOD are common findings on VUDS in IC/BPS females. BOD is associated with duration and hypersensitive bladder. A $Q_{max} \leq 11$ mL/s predicts BOD in IC/BPS.

ANIMAL MODELLING OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Birder L, Andersson KE. Int Neurourol J. 2018 Jan;22(Suppl 1):S3-9. doi: 10.5213/inj.1835062.531. Epub 2018 Jan 31. PMID: 29385788

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The etiology of IC/BPS remains elusive and may involve multiple causes. To better understand its pathophysiology, many efforts have been made to create IC/BPS models. Most existing models of IC/BPS strive to recreate bladder-related features by applying noxious intravesical or systemic stimuli to healthy animals. These models are useful to help understand various mechanisms; however, they are limited to demonstrating how the bladder and nervous system respond to noxious stimuli and are not representative of the complex interactions and pathophysiology of IC/BPS. To study the various factors that may be relevant for IC/BPS, at least 3 different types of animal models are commonly used: (1) bladder-centric models, (2) models with complex mechanisms, and (3) psychological and physical stressors/natural disease models. It is obvious that all aspects of the human disease cannot be mimicked by a single model. It may be the case that several models, each contributing to a piece of the puzzle, are required to recreate a reasonable picture of the pathophysiology and time course of the disease(s) diagnosed as IC/BPS, and thus to identify reasonable targets for treatment.

SAFETY AND FEASIBILITY OF INTRAVESICAL INSTILLATION OF BOTULINUM TOXIN-A IN HYDROGEL-BASED SLOWRELEASE DELIVERY SYSTEM IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PILOT STUDY.

Rappaport YH, Zisman A, Jeshurun-Gutshat M, Gerassi T, Hakim G, Vinshtok Y, Stav K. Urology. 2018 Apr;114:60-65. doi: 10.1016/j.urology.2017.12.028. Epub 2018 Jan 4. PMID: 29307733

The purpose of this study from Israel was to assess the feasibility and the safety of a mixture instillation of TC-3 gel, a novel reverse-thermal gelation hydrogel, and botulinum toxin-A (BTX-A) for the treatment of interstitial cystitis-bladder pain syndrome (IC/BPS). TC-3 gel-BTX-A mix is instilled into the bladder as liquid, solidifies because of body heat, and gradually dissolves to release BTX-A for several hours. A single intravesical instillation of 200 U BTX-A premixed with 40 mL TC-3 gel was delivered to the bladder. Adverse events and preliminary efficacy outcome measures were assessed: bladder diary, visual analog scale (VAS) for pain, and Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) at baseline and at 2, 6, and 12 weeks. The authors concluded that intravesical instillation of a TC-3 gel-BTX-A mixture is safe and tolerable. Preliminary results suggest temporary efficacy lasting for a few weeks.

SEXUAL DYSFUNCTION IN INTERSTITIAL CYSTITIS.

Tonyali S, Yilmaz M. Curr Urol. 2017 Nov;11(1):1-3. doi: 10.1159/000447186. Epub 2017 Nov 30. PMID: 29463969

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IC/BPS is a debilitating disease characterized with urgency, frequency, and pelvic pain affecting especially women. Sexual dysfunction in female patients with IC/BPS consists of dyspareunia, altered sexual desire and orgasm frequency and insufficient lubrication is reported to negatively affect the patient's quality of life. In the present study, we aimed to determine the association between IC/BPS and sexual dysfunction and improvement in sexual dysfunction related to given treatments. However, given the used different questionnaires, study protocols, patient characteristics, previous treatments and follow-up period, it is not possible to make a head-to-head comparison of the treatment effects on sexual function. Further, randomized controlled studies are needed to confirm these results and make a comparison between effects of various treatment modalities on sexual functioning in IC/BPS.

THE X-Y FACTOR: FEMALES AND MALES WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROMES PRESENT DISTINCT CLINICAL PHENOTYPES.

Hosier GW, Doiron RC, Tolls V, Nickel JC. *Can Urol Assoc J.* 2018 Feb 23. doi: 10.5489/cuaj.4798. [Epub ahead of print] PMID: 29485033

Urological chronic pelvic pain syndrome (UCPPS) in females is often attributed to the bladder (interstitial cystitis/bladder pain syndrome), while UCPPS in males is often attributed to the prostate (chronic prostatitis/chronic pelvic pain syndrome). However, there is increasing awareness that bladder pain plays a role in both males and females and the degree of overlap of clinical characteristics in males and females with UCPPS is not well known. The objective was to compare clinical phenotypes of females and males with UCPPS. Hosier and colleagues conducted a retrospective analysis of prospectively collected data from a single-centre patient population presenting between 1998 and 2016 at their UCPPS clinic. Demographics, symptom scores, pain scales, retrospectively described clinical UPOINT (urinary, psychosocial, organ specific, infection, neurogenic, and tenderness) scoring, and presence of comorbid medical conditions were compared between females and males using comparative analyses. They found that females with UCPPS have greater prevalence of systemic disorders/symptoms and worse urinary symptoms than males with UCPPS. These findings demonstrate that females and males with UCPPS have distinct and different clinical phenotypes.

DIFFERENTIAL REGULATION OF BLADDER PAIN AND VOIDING FUNCTION BY SENSORY AFFERENT POPULATION REVEALED BY SELECTIVE OPTOGENETIC ACTIVATION.

DeBerry JJ, Samineni VK, Copits BA, Sullivan CJ, Vogt SK, Albers KM, Davis BM, Gereau IV RW. *Front Integr Neurosci.* 2018 Feb 12;12:5. doi: 10.3389/fnint.2018.00005. eCollection 2018. PMID: 29483864

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Bladder-innervating primary sensory neurons mediate reflex-driven bladder function under normal conditions and contribute to debilitating bladder pain and/or overactivity in pathological states. The goal of this study was to examine the respective roles of defined subtypes of afferent neurons in bladder sensation and function *in vivo* via direct optogenetic activation.

HUNNER LESIONS

EXTENT OF HUNNER LESIONS: THE RELATIONSHIPS WITH SYMPTOM SEVERITY AND CLINICAL PARAMETERS IN HUNNER TYPE INTERSTITIAL CYSTITIS PATIENTS.

Akiyama Y, Niimi A, Nomiya A, Yamada Y, Nakagawa T, Fujimura T, Fukuhara H, Kume H, Igawa Y, Homma Y. *Neurourol Urodyn.* 2018 Apr;37(4):1441-1447. doi: 10.1002/nau.23467. Epub 2018 Jan 9. PMID: 29315774

The purpose of this study from Japan was to assess the clinical impact of Hunner lesions in patients with Hunner type interstitial cystitis (HIC). The clinical records of 94 HIC patients who underwent their first hydrodistension (with lesion fulguration) were retrospectively reviewed. At surgery, the extent of each lesion was classified in terms of the relative involvement for the whole-bladder luminal surface. Akiyama and colleagues defined four grades of involvement: <10%, 10-24%, 25-49%, and ≥50%; and two grades of severity: <25% (focal) and ≥25% (extensive). They examined the relationships between the extent of the lesions and all demographic characteristics, symptom scores, voiding symptoms, and bladder capacity. Factors predictive of the need for repeat hydrodistension were also explored. They found that symptom severity worsened as the lesional extent rose. Those with extensive lesions scored higher on the O'Leary and Sant Symptom and Problem Index scales, the pain visual analog scale, the International Prostate Symptom Score scale, and a quality-of-life index and exhibited greater daytime urinary frequency, more nocturia, and a smaller bladder capacity than the focal group. No symptomatic or clinical parameters predicted the need for repeat hydrodistension. The authors concluded that the extent of Hunner lesions was associated with both symptom severity and bladder capacity but not with other clinical parameters, including the need for repeat hydrodistension, in patients with HIC.

DIFFERENCES IN URODYNAMIC PARAMETERS ACCORDING TO THE PRESENCE OF A HUNNER LESION IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Ahn ST, Jeong HG, Park TY, Kim JW, Park HS, Moon DG, Lee JG, Oh MM. *Int Neurourol.* 2018 Jan;22(Suppl 1):S55-61. doi: 10.5213/inj.1835044.522. Epub 2018 Jan 31. PMID: 29385787

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Differences in the severity of subjective symptoms have been noted depending on whether a Hunner lesion is present in women with interstitial cystitis/bladder pain syndrome (IC/BPS). In this study, Ahn and colleagues from Korea aimed to identify differences in objective urodynamic parameters in women with IC/BPS according to the presence of a Hunner lesion. This cross-sectional study included a total of 55 patients with IC/BPS. IC/BPS and the presence of a Hunner lesion on cystoscopy were diagnosed according to American Urological Association

guidelines. It was concluded by the authors that the differences in patients' subjective symptoms between the Hunner IC/BPS and non-Hunner IC/BPS groups were confirmed to correspond to differences in objective urodynamic parameters.

THERAPEUTIC EFFECTS OF ENDOSCOPIC ABLATION IN PATIENTS WITH HUNNER TYPE INTERSTITIAL CYSTITIS.

Ko KJ, Chung H, Suh YS, Lee SW, Kim TH, Lee KS. BJU Int. 2018 Apr;121(4):659-666. doi: 10.1111/bju.14097. Epub 2018 Jan 9. PMID: 29232035

The aim of this study from Korea was to investigate the efficacy of endoscopic ablation of Hunner lesions (HLs) in patients with interstitial cystitis (IC) and to find predictors of early recurrence of HLs. A prospective study was performed of patients with Hunner type IC who underwent transurethral ablation. Ko and colleagues repeated endoscopic ablation when symptoms and HLs recurred during the follow-up period. The primary endpoint was recurrence-free time. Secondary endpoints were a change in frequency, nocturia, and urgency episodes, and changes in visual analogue scale (VAS) pain scores and other symptom indices at follow-up visits. A total of 72 patients were analysed. There were significant improvements in the VAS pain scores, O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index, Pelvic Pain and Urgency/Frequency Patient Symptom Scale after treatment. It was concluded that endoscopic ablation is an effective treatment option for HLs and significantly reduces pain and improves voiding symptoms. Repeat ablation upon recurrence could help symptom control and bladder preservation only if the bladder capacity is maintained.

ENDOSCOPIC INJECTION OF LOW DOSE TRIAMCINOLONE: A SIMPLE, MINIMALLY INVASIVE AND EFFECTIVE THERAPY FOR INTERSTITIAL CYSTITIS WITH HUNNER LESIONS.

Funaro MG, King AN, Stern JNH, Moldwin RM, Bahlani S. Urology. 2018 May 18. pii: S0090-4295(18)30294-2. doi: 10.1016/j.urology.2018.03.037. [Epub ahead of print] PMID: 29782887

This study investigated the efficacy of low dose triamcinolone injection for effectiveness and durability in interstitial cystitis/bladder pain syndrome (IC/BPS) patients with Hunner Lesions (HL). Clinical data from patients with HL who underwent endoscopic submucosal injection of triamcinolone were reviewed: Demographics, pre/post-operative pain and nocturia scores, and long-term clinical outcomes were assessed. Duration of response was estimated by time to repeat procedure. Kaplan-Meier estimator was used to evaluate time to repeat procedure. 36 patients who received injections of triamcinolone between 2011 and 2015 were included. 26 patients (72.2%) received only 1 set of injections, 8 (22.2%) received 2 sets of injections, and 2 (5.56%) received 3 or more sets of injections. Average time between injections in those receiving more than one set of injections was 344.9 days. Pre-procedural pain scores were 8.3 ± 1.2 on Likert pain scale (0-10) and mean post-procedural pain scores at approximately one month were 3.8 ± 2.2 $p < 0.001$. Mean pre-procedural nocturia bother scores were 7.5 ± 2.0 and mean post-procedural nocturia bother scores were 5.1 ± 2.5 $p < 0.001$. It was concluded that endoscopic submucosal injection of low dose triamcinolone in IC/BPS patients with HL is an effective and durable adjunct to existing treatment modalities. This approach is associated with low morbidity and can be performed on an outpatient basis.

ELEVATED URINE LEVELS OF MACROPHAGE MIGRATION INHIBITORY FACTOR IN INFLAMMATORY BLADDER CONDITIONS: A POTENTIAL BIOMARKER FOR A SUBGROUP OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS.

Vera PL, Preston DM, Moldwin RM, Erickson DR, Mowlazadeh B, Ma F, Kouzoukas DE, Meyer-Siegler KL, Fall M. Urology. 2018 Mar 23. pii: S0090-4295(18)30271-1. doi: 10.1016/j.urology.2018.02.039. [Epub ahead of print] PMID: 29580781

The purpose of this study from the USA was to investigate whether urinary levels of macrophage migration inhibitory factor (MIF) are elevated in IC/BPS patients with Hunner lesions and also whether urine MIF is elevated in other forms of inflammatory cystitis. Urine samples were assayed for MIF by enzyme-linked immunosorbent assay. Urine samples from 3 female groups were examined: 55 IC/BPS patients without and 43 with Hunner lesions, and 100 non-IC/BPS patients (control group; no history of IC/BPS; cancer or recent bacterial cystitis). Urine samples from 3 male groups were examined: 50 patients with bacterial cystitis, 18 with radiation cystitis and 119 noncystitis patients (control group; negative for bacterial cystitis). Urine MIF was increased in female IC/BPS patients with Hunner lesions compared with IC/BPS patients without Hunner lesions or non-IC/BPS patients. Receiver operating curve analyses showed that urine MIF levels discriminated between the 2 IC groups. Male patients with bacterial and radiation cystitis had elevated urine MIF levels compared with noncystitis patients. The authors concluded that urine MIF is elevated in IC/BPS patients with Hunner lesions and also in patients with other bladder inflammatory and painful conditions. MIF may also serve as a noninvasive biomarker to select IC/BPS patients more accurately for endoscopic evaluation and possible anti-inflammatory treatment.

ASSOCIATED DISORDERS

[BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IS ASSOCIATED WITH ASTHMA: A CASE-CONTROL STUDY.](#)

Chung SD, Huang CC, Lin HC, Kao LT. *Neurourol Urodyn*. 2018 Feb 14. doi: 10.1002/nau.23520. [Epub ahead of print] PMID: 29441652

Although asthma and BPS/IC are considered to share similar pathophysiological pathways, the relationship between asthma and BPS/IC is uncertain. This case-control study aimed to investigate the relationship between prior asthma and BPS/IC using a large database in Taiwan. This study used data from the Taiwan Longitudinal Health Insurance Database 2005. Chung and colleagues identified 500 female patients with BPS/IC as cases and 500 propensity score-matched females without BPS/IC as controls. The odds ratio (OR) of prior asthma for cases was 1.61 compared to propensity score-matched controls. Additionally, the ORs of prior asthma for females with BPS/IC aged 18-59 and ≥60 years were 1.72 and 1.40, respectively, compared to controls. They concluded that prior asthma was significantly associated with BPS/IC in a female Taiwanese population.

FELINE IC

[SERUM CYTOKINE PROFILING IN CATS WITH ACUTE IDIOPATHIC CYSTITIS.](#)

Parys M, Yuzbasiyan-Gurkan V, Kruger JM. *J Vet Intern Med*. 2018 Jan 22. doi: 10.1111/jvim.15032. [Epub ahead of print] PMID: 29356123

Feline idiopathic cystitis (FIC) is a common lower urinary tract disorder of domestic cats that resembles IC/PBS in humans. Diagnosis of FIC is based on clinical signs and exclusion of other disorders because of a lack of specific pathologic findings or other objective biomarkers. Cytokines are potential noninvasive biomarkers to define the presence, severity, and progression of disease, and response to treatment. The objective of this pilot study from the USA was to determine concentrations of selected cytokines in serum from healthy cats and cats with acute FIC. Serum samples from 13 healthy cats and from 12 cats with nonobstructive acute FIC were utilized. The authors identified increased serum concentrations of pro-inflammatory cytokines and chemokines CXCL12, IL-12, IL-18, and Flt3L in FIC-affected cats. These findings suggest potential candidates for noninvasive biomarkers for diagnosis, staging, and therapeutic outcome monitoring of affected cats and provide additional insight into the etiopathogenesis of FIC.

MICROBIOME, MICROBIOTA

[THE ROLE OF THE MICROBIOME FOR HUMAN HEALTH: FROM BASIC SCIENCE TO CLINICAL APPLICATIONS.](#)

Mohajeri MH, Brummer RJM, Rastall RA, Weersma RK, Harmsen HJM, Faas M, Eggersdorfer M. *Eur J Nutr*. 2018 May 10. doi: 10.1007/s00394-018-1703-4. [Epub ahead of print] PMID: 29748817

The 2017 annual symposium organized by the University Medical Center Groningen in The Netherlands focused on the role of the gut microbiome in human health and disease. Experts from academia and industry examined interactions of prebiotics, probiotics, or vitamins with the gut microbiome in health and disease, the development of the microbiome in early-life and the role of the microbiome on the gut-brain axis. The gut microbiota changes dramatically during pregnancy and intrinsic factors (such as stress), in addition to extrinsic factors (such as diet, and drugs) influence the composition and activity of the gut microbiome throughout life. Microbial metabolites, e.g. short-chain fatty acids affect gut-brain signalling and the immune response. The gut microbiota has a regulatory role on anxiety, mood, cognition and pain which is exerted via the gut-brain axis. Ingestion of prebiotics or probiotics has been used to treat a range of conditions including constipation, allergic reactions and infections in infancy, and IBS. Fecal microbiota transplantation (FMT) highly effective for treating recurrent *Clostridium difficile* infections. The gut microbiome affects virtually all aspects of human health, but the degree of scientific evidence, the models and technologies and the understanding of mechanisms of action vary considerably from one benefit area to the other. For a clinical practice to be broadly accepted, the mode of action, the therapeutic window, and potential side effects need to thoroughly be investigated. This calls for further coordinated state-of-the art research to better understand and document the human gut microbiome's effects on human health.

URINE

[URINE: WASTE PRODUCT OR BIOLOGICALLY ACTIVE TISSUE?](#)

[Urinology Think Tank Writing Group](#). *Neurourol Urodyn*. 2018 Mar;37(3):1162-1168. doi: 10.1002/nau.23414. Epub 2018 Feb 21. PMID: 29464759

Historically, urine has been viewed primarily as a waste product with little biological role in the overall health of an individual. Increasingly, data suggest that urine plays a role in human health beyond waste excretion. For example, urine might act as an irritant and contribute to symptoms through interaction with-and potential compromise of-the urothelium. To explore the concept that urine may be a vehicle for agents with potential or occult bioactivity and to discuss existing evidence and novel research questions that may yield insight into such a role, the National Institute of Diabetes and Digestive and Kidney Disease invited experts in the fields of comparative evolutionary physiology, basic science, nephrology, urology, pediatrics, metabolomics, and proteomics (among others) to a Urinology Think Tank meeting on February 9, 2015. This report reflects ideas that evolved from this meeting and current literature, including the concept of urine quality, the biological, chemical, and physical characteristics of urine, including the microbiota, cells, exosomes, pH, metabolites, proteins, and specific gravity (among others). Additionally, the manuscript presents speculative, and hopefully testable, ideas about the functional roles of urine constituents in health and disease. Moving forward, there are several questions that need further understanding and pursuit. There were suggestions to consider actively using various animal models and their biological specimens to elaborate on basic mechanistic information regarding human bladder dysfunction.

UNDETECTED URINARY TRACT INFECTION

[RECALCITRANT CHRONIC BLADDER PAIN AND RECURRENT CYSTITIS BUT NEGATIVE URINALYSIS: WHAT SHOULD WE DO?](#)

Swamy S, Barcella W, De Iorio M, Gill K, Khasriya R, Kupelian AS, Rohn JL, Malone-Lee J. *Int Urogynecol J*. 2018 Mar 20. doi: 10.1007/s00192-018-3569-7. [Epub ahead of print] PMID: 29556674

Lower urinary tract symptoms (LUTS) may be associated with chronic urinary tract infection (UTI) undetected by routine diagnostic tests. Antimicrobial therapy might confer benefit for these patients. Over 10 years, Malone-Lee and colleagues from the UK treated patients with chronic LUTS. Pyuria was adopted as the principal biomarker of infection. Urinary leucocyte counts were recorded from microscopy of fresh midstream urine (MSU) samples. Antibiotics were prescribed and the prescription adjusted to achieve a measurable clinical response and a reduction in pyuria. They treated 624 women with chronic LUTS and pyuria. Mean duration of symptoms prior to presentation was 6.5 years. Only 16% of MSU cultures submitted were positive. Mean treatment length was 383 days. Treatment was associated with a reduction in total LUTS, 24-h frequency, urinary urgency, lower urinary tract pain, voiding symptoms, and pyuria. Full-dose first-generation antibiotics for UTI, such as cefalexin, nitrofurantoin, or trimethoprim, were combined with methenamine hippurate. They recorded 475 adverse events (AEs) during 273,762 treatment days. There was only one serious adverse event (SAE). They observed no increase in the proportion of resistant bacterial isolates. The authors concluded that this large case series demonstrates that patients with chronic LUTS and pyuria experience symptom regression and a reduction in urinary tract inflammation associated with antimicrobial therapy. Disease regression was achieved with a low frequency of AEs. These results provide preliminary data to inform a future randomized controlled trial (RCT).

KETAMINE CYSTITIS

[HISTOPATHOLOGICAL CHARACTERISTICS OF KETAMINE-ASSOCIATED UROPATHY AND THEIR CLINICAL ASSOCIATION.](#)

Jhang JF, Hsu YH, Jiang YH, Lee CL, Kuo HC. *Neurourol Urodyn*. 2018 Feb 14. doi: 10.1002/nau.23514. [Epub ahead of print] PMID: 29441609

This study by Jhang and colleagues from Taiwan investigated the histopathological findings in ketamine-associated uropathy (KU) and their clinical association. Thirty-eight KU patients had received history investigation and video urodynamic study. Twelve of them were clinically mild KU who were admitted for cystoscopic hydrodistention. The other 26 patients were severe KU who were admitted for enterocystoplasty with or without ureter reimplantation. Bladder and ureter specimens were harvested during operation, and a single pathologist reviewed all specimens under hematoxylin and eosin stain. The severity of histopathological findings was graded with a 4-point scale. Inflammatory cells infiltrations and nerve hyperplasia were found in the mucosa, muscle, and subserosal layers of KU bladders and ureter. In the mild KU bladder mucosa, the predominant component of the infiltrating inflammatory cells was lymphocytes. In contrast, neutrophils, eosinophils, lymphocytes, and plasma cells infiltration were noted in the mucosa of almost all severe KU bladders. Clinical severe KU was significantly correlated with severe to moderate lymphocytes, plasma cells,

neutrophils, eosinophils infiltration, and nerve hyperplasia in bladder mucosa. KU patients with moderate or severe neutrophils or lymphocytes infiltration in bladder mucosa had significantly more severe bladder pain and smaller bladder capacity. According to the authors, the histological findings of KU showed whole-layer inflammation and nerve hyperplasia in bladder mucosa. The severity of inflammatory cell infiltration in the bladder mucosa is associated with clinical symptoms. A histopathological examination might be a useful tool to discriminate the KU severity in patients.

CHRONIC PELVIC PAIN/CHRONIC PAIN

[AS IF ONE PAIN PROBLEM WAS NOT ENOUGH: PREVALENCE AND PATTERNS OF COEXISTING CHRONIC PAIN CONDITIONS AND THEIR IMPACT ON TREATMENT OUTCOMES.](#)

Pagé MG, Fortier M, Ware MA, Choinière M. J Pain Res. 2018 Jan 26;11:237-254. doi: 10.2147/JPR.S149262. eCollection 2018. PMID: 29416373

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The presence of multiple coexisting chronic pain (CP) conditions (eg low-back pain and migraines) within patients has received little attention in literature. The goals of this observational longitudinal study from Canada were to determine the prevalence of coexisting CP conditions, identify the most frequent ones and patterns of coexistence, investigate the relationships among patients' biopsychosocial characteristics and number of CP conditions, and determine the impact of coexisting CP conditions on treatment response. A total of 3,966 patients attending multidisciplinary pain-treatment centers who were enrolled in the Quebec Pain Registry were included. Their results highlight the need for future research that examines causes of coexistence among CP conditions across the spectrum of CP, as opposed to focusing on specific conditions, and to examine whether multiple CP conditions impact on additional domains, such as treatment satisfaction. Their results also highlight the importance of studying the pathophysiological mechanisms underlying the development of coexisting CP conditions, in order eventually to prevent/minimize their occurrence and/or develop optimal treatment and management approaches.

[MULTISPECIALTY RETROSPECTIVE REVIEW OF THE CLINICAL UTILITY OF PELVIC MAGNETIC RESONANCE IMAGING IN THE SETTING OF PELVIC PAIN.](#)

Moore JR, Pathak RA, Snowden C, Bolan CW, Young PR, Broderick GA. Transl Androl Urol. 2017 Dec;6(6):1155-1158. doi: 10.21037/tau.2017.10.02. PMID: 29354504

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Pelvic pain is a common complaint, and management of it is often difficult. The authors sought to evaluate the utility of magnetic resonance imaging (MRI) in the diagnosis of male pelvic pain. Though MRIs are commonly ordered to evaluate pelvic pain, there are very few studies obtaining the efficacy of pelvic MRI in determining a definitive diagnosis. The primary aim of this study was to evaluate the clinical utility of pelvic MRI for a diagnosis code that included pain. A total of 2,643 pelvic MRIs were ordered at this institution over a 5-year period. The increasing availability of MRI technology makes it a likely candidate to test for a clinically significant anatomic reason for pain. Though MRI is a test with minimal adverse effect and no increased risk of radiation exposure, the cost on the healthcare system should be offset by a clear clinical utility. They found total utility to be 34% across all ordering providers and an increase in positivity with concern of oncologic disease. Therefore, they would recommend pelvic MRIs in the evaluation of patients with refractory pelvic pain.

[EFFICACY AND SAFETY OF SACRAL AND PERCUTANEOUS TIBIAL NEUROMODULATION IN NON-NEUROGENIC LOWER URINARY TRACT DYSFUNCTION AND CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE.](#)

Tutolo M, Ammirati E, Heesakkers J, Kessler TM, Peters KM, Rashid T, Sievert KD, Spinelli M, Novara G, Van der Aa F, De Ridder D. Eur Urol. 2018 Jan 11. pii: S0302-2838(17)30978-8. doi: 10.1016/j.eururo.2017.11.002. [Epub ahead of print] PMID: 29336927

Neuromodulation is considered in patients with non-neurogenic lower urinary tract dysfunction (LUTD) not responsive to conservative treatment. The purpose of this study was to systematically review the available studies on efficacy and safety of sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS) in non-neurogenic LUTDs not responsive to conservative treatments. A literature research was conducted in PubMed/Medline and Scopus, restricted to articles in English, published between January 1998 and June 2017, with at least 20 patients and 6 months of follow-up. Twenty-one reports were identified. Concerning SNM, the improvement of $\geq 50\%$ in leakage episodes ranged widely between 29% and 76%. Overall dry rate ranged between 43% and 56%. Overall success/improvement rate in PTNS varied between 54% and

59%. Symptom improvement or efficacy in interstitial cystitis/bladder pain syndrome patients appeared to be lower compared with other indications in both techniques. Safety data showed fewer side effects in patients submitted to PTNS. It was concluded that neuromodulation gives good results and is a safe therapy for patients with overactive bladder or chronic nonobstructive urinary retention with long-lasting efficacy. Moreover, PTNS has been shown to have good success rates and fewer side effects compared with SNM. These data have to be confirmed with long-term follow-up.

NEUROPELVEOLOGY: AN EMERGING DISCIPLINE FOR THE MANAGEMENT OF CHRONIC PELVIC PAIN.

Possover M, Andersson KE, Forman A. Int Neurourol J. 2017 Dec;21(4):243-246. doi: 10.5213/inj.1735036.518. Epub 2017 Dec 31. PMID: 29298475

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Chronic pelvic pain (CPP) is a common condition involving multiple, organ-specific medical specialties, each with its own approach to diagnosis and treatment. Management requires knowledge of the interplay between pelvic organ function and neuro-functional anatomy, and of the neurologic and psychological aspects of CPP, but no current specialty fully encompasses this approach. Neuropelveology is an emerging discipline focusing on pathologies of the pelvic nervous system on a cross-disciplinary basis. It involves a neurological/neurosurgical approach, combining the knowledge required for a proper neurologic diagnosis, confirmation by transvaginal/transrectal examination of the pelvic nerves, and advanced laparoscopic surgery in selected cases of CPP. The management of CPP requires multidisciplinary contributions, and neuropelveology may offer an educational framework for the interdisciplinary exchange of knowledge between clinical physicians and basic researchers. See also comment: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5756813/>

CLINICAL CRITERIA OF CENTRAL SENSITIZATION IN CHRONIC PELVIC AND PERINEAL PAIN (CONVERGENCES PP CRITERIA): ELABORATION OF A CLINICAL EVALUATION TOOL BASED ON FORMAL EXPERT CONSENSUS.

Levesque A, Riant T, Ploteau S, Rigaud J, Labat JJ; for Convergences PP Network. Pain Med. 2018 Mar 7. doi: 10.1093/pm/pny030. [Epub ahead of print] PMID: 29522121

Evaluation of chronic pelvic and perineal pain (CPP) is often complex. The patient's description of the pain often appears to be disproportionate to the limited findings on physical examination and/or complementary investigations. The concept of central sensitization may allow better understanding and management of patients with CPP. The aim of this study from France was to elaborate a clinical evaluation tool designed to simply identify sensitization in pelvic pain. A list of 63 items was submitted to 22 international CPP experts according to the Delphi method. Ten clinical criteria were adopted for the creation of a clinical evaluation tool: 1) pain influenced by bladder filling and/or urination, 2) pain influenced by rectal distension and/or defecation, 3) pain during sexual activity, 4) perineal and/or vulvar pain in response to normally nonpainful stimulation, 5) pelvic trigger points (e.g., in the piriformis, obturator internus, and/or levator ani muscles), 6) pain after urination, 7) pain after defecation, 8) pain after sexual activity, 9) variable (fluctuating) pain intensity and/or variable pain distribution, 10) migraine or tension headaches and/or fibromyalgia and/or chronic fatigue syndrome and/or post-traumatic stress disorder and/or restless legs syndrome and/or temporomandibular joint dysfunction and/or multiple chemical sensitivity. This process resulted in the elaboration of a clinical evaluation tool designed to identify and appropriately manage patients with CPP comprising a sensitization component.

SMALL FIBER POLYNEUROPATHY IS PREVALENT IN PATIENTS EXPERIENCING COMPLEX CHRONIC PELVIC PAIN

Chen A, De E, Argoff C. Pain Med. 2018 Feb 13. doi: 10.1093/pm/pny001. [Epub ahead of print] PMID: 29447372

The purpose of this retrospective study of prospective database from the USA was to demonstrate the prevalence of small fiber polyneuropathy (SFPN) in patients with refractory chronic pelvic pain (CPP). Participants were complex CPP patients defined as those who were refractory to initial treatment and/or exhibited comorbid pain syndromes at initial presentation. Comprehensive treatment history for CPP was obtained. Twenty-five of 39 patients (64%) were positive for SFPN. Comorbid conditions noted in the authors' population included gastroesophageal reflux disease (46%), migraine (38%), irritable bowel syndrome (33%), lower back pain (33%), fibromyalgia (38%), endometriosis (15%), interstitial cystitis (18%), vulvodynia (5%), and other chronic pain syndromes (36%). The prevalence of SFPN in their specialty referral patients with complex CPP is remarkably high vs published general population prevalence data (53/100,000). Identification of SFPN in this complex population shifts the focus from undefined syndromes to symptom complexes with linked potentially treatable mechanisms (e.g., SFPN, central sensitization). Most CPP patients with SFPN are undiagnosed. Considering the diagnosis may expand treatment options beyond

conventional or so-called adjuvant analgesics. Treatment may expand to therapies such as IV lidocaine, IVIG, or other immunomodulatory options. In addition, the value to the patient of receiving a diagnosis for a multisystem or refractory pain syndrome, often attributed to negative psychologic factors, cannot be underestimated. Identifying SFPN should be contemplated in CPP patients who present with multisystem pain or who have not responded to initial evaluation and management.

[RESEARCH DESIGN CHARACTERISTICS OF PUBLISHED PHARMACOLOGIC RANDOMIZED CLINICAL TRIALS FOR IRRITABLE BOWEL SYNDROME AND CHRONIC PELVIC PAIN CONDITIONS: AN ACTION SYSTEMATIC REVIEW.](#)

Gewandter JS, Chaudari J, Iwan KB, Kitt R, As-Sanie S, Bachmann G, Clemens Q, Lai HH, Tu F, Verne GN, Vincent K, Wesselmann U, Zhou Q, Turk DC, Dworkin RH, Smith SM. J Pain. 2018 Feb 2. pii: S1526-5900(18)30055-5. doi: 10.1016/j.jpain.2018.01.007. [Epub ahead of print] PMID: 29412183

Chronic pain conditions occurring in the lower abdomen and pelvis are common, often challenging to manage, and can negatively affect health-related quality of life. Methodological challenges in designing randomized clinical trials (RCTs) for these conditions likely contributes to the limited number of available treatments. The goals of this systematic review of RCTs of pharmacologic treatments for irritable bowel syndrome and 3 common chronic pelvic pain conditions are to: 1) summarize the primary end points and entry criteria, and 2) evaluate the clarity of reporting of important methodological details. In total, 127 RCTs were included in the analysis. The most common inclusion criteria were a minimum pain duration (81%), fulfilling an established diagnostic criteria (61%), and reporting a minimum pain intensity (42%). Primary end points were identified for only 57% of trials. These end points, summarized in this article, were highly variable. The results of this systematic review can be used to inform future research to optimize the entry criteria and outcome measures for pain conditions occurring in the lower abdomen and pelvis, to increase transparency in reporting to allow for proper interpretation of RCT results for clinical and policy applications, and to facilitate the aggregation of data in meta-analyses.

PAIN CLINICAL UPDATE

[INTERPROFESSIONAL PAIN EDUCATION—WITH, FROM, AND ABOUT COMPETENT, COLLABORATIVE PRACTICE TEAMS TO TRANSFORM PAIN CARE](#)

Gordon DB, Watt-Watson J, Hogans BB. PAIN Reports: May/June 2018 - Volume 3 - Issue 3 - p e663

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A competent, collaborative, interprofessional team centred on the patient is necessary for quality pain care; however, interprofessional collaborative practice is not yet an integral part of all health professions education programs. Interprofessional education involves 2 or more professions learning “with, from, and about” to enable effective collaborative practice and improve health outcomes. Core competencies and curricular resources are available for interprofessional education and pain and can be adapted for use at all levels of health professions education.

PUDENDAL NEURALGIA

[A NEW ENDOSCOPIC MINIMAL INVASIVE APPROACH FOR PUDENDAL NERVE AND INFERIOR CLUNEAL NERVE NEUROLYSIS: AN ANATOMICAL STUDY.](#)

Ploteau S, Robert R, Bruyninx L, Rigaud J, Jottard K. Neurourol Urodyn. 2018 Mar;37(3):971-977. doi: 10.1002/nau.23435. Epub 2017 Oct 26. PMID: 29072775

The purpose of this study from France and Belgium was to describe a new minimal invasive approach of the gluteal region which will allow neurolysis of the pudendal and cluneal nerves in cases of perineal neuralgia due to entrapment of these nerve trunks. Ten transgluteal approaches were performed on five cadavers. Relevant anatomic structures were dissected and further described. Neurolysis of the pudendal nerve or cluneal nerves were performed. Landmarks for secure intraoperative navigation were indicated. The authors found that a reliable exploration of the gluteal region including identification of the sciatic, pudendal, and posterior femoral cutaneous nerves is feasible using a minimal invasive transgluteal procedure. Consequently, the transposition of the pudendal nerve and the liberation of the cluneal nerves can be performed.

NEUROGENIC INFLAMMATION

[ROLE OF NEUROGENIC INFLAMMATION IN LOCAL COMMUNICATION IN THE VISCERAL MUCOSA.](#)

Birder LA, Kullmann FA. *Semin Immunopathol.* 2018 Mar 26. doi: 10.1007/s00281-018-0674-0. [Epub ahead of print] PMID: 29582112

Intense research has focused on the involvement of the nervous system in regard to cellular mechanisms underlying neurogenic inflammation in the pelvic viscera. Evidence supports the neural release of inflammatory factors, trophic factors, and neuropeptides in the initiation of inflammation. However, more recently, non-neuronal cells including epithelia, endothelial, mast cells and paraneurons are likely important participants in nervous system functions. For example, the urinary bladder urothelial cells are emerging as key elements in the detection and transmission of both physiological and nociceptive stimuli in the lower urinary tract. There is mounting evidence that these cells are involved in sensory mechanisms and can release mediators. Further, localization of afferent nerves next to the urothelium suggests these cells may be targets for transmitters released from bladder nerves and that chemicals released by urothelial cells may alter afferent excitability. Modifications of this type of communication in a number of pathological conditions can result in altered release of epithelial-derived mediators, which can activate local sensory nerves. Taken together, these and other findings highlighted in this review suggest that neurogenic inflammation involves complex anatomical and physiological interactions among a number of cell types in the bladder wall. The specific factors and pathways that mediate inflammatory responses in both acute and chronic conditions are not well understood and need to be further examined. Elucidation of mechanisms impacting on these pathways may provide insights into the pathology of various types of disorders involving the pelvic viscera.

NEURAL CROSSTALK

ROLE OF MICROGLIA IN THE SPINAL CORD IN COLON-TO-BLADDER NEURAL CROSSTALK IN A RAT MODEL OF COLITIS.

Majima T, Funahashi Y, Kawamorita N, Takai S, Matsukawa Y, Yamamoto T, Yoshimura N, Gotoh M. *Neurourol Urodyn.* 2018 Jan 19. doi: 10.1002/nau.23484. [Epub ahead of print] PMID: 29350427

Majima and colleagues investigated whether spinal cord microglia are involved in colon-to-bladder neural crosstalk in a rat model of colitis. Adult female SD rats were divided into A) control, B) colitis, and C) colitis + minocycline groups. Experimental colitis was induced by administering 50% trinitrobenzene sulfonic acid into the distal colon in the colitis group and the minocycline group. Minocycline, a microglial inhibitor, was continuously infused into the intrathecal space in the minocycline group. The following investigations were performed on day 7: (1) continuous cystometry (CMG) in an awake condition; (2) nociceptive behavior observation induced by intravesical instillation of resiniferatoxin; (3) toluidine blue staining in the bladder; (4) Immunofluorescence staining for the microglial marker, CD11b, in L6 spinal cord sections; and (5) quantitative RT-PCR to investigate interleukin-1 β (IL-1 β), chemokine ligand 3 (CCL3), and brain-derived neurotrophic factor (BDNF) gene expression in the L6 spinal cord. In comparison with the control group, the colitis group showed significant increases in (1) micturition frequency during cystometry; (2) resiniferatoxin-induced freezing behavior (bladder pain); (3) the number of total and degranulated mast cells in the bladder; (4) the number of microglia in the L6 spinal cord, and (5) the expression of IL-1 β , CCL3, and BDNF mRNA in the L6 spinal cord. Moreover, intrathecal administration of minocycline alleviated these pathophysiological findings caused by experimental colitis. The authors concluded that spinal microglia may play an important role in colitis-induced bladder overactivity and enhanced bladder pain sensitivity in colitis rats.

ENDOMETRIOSIS

ENDOMETRIOSIS INCREASED THE RISK OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A POPULATION-BASED STUDY.

Wu CC, Chung SD, Lin HC. *Neurourol Urodyn.* 2018 Apr;37(4):1413-1418. doi: 10.1002/nau.23462. Epub 2018 Jan 10. PMID: 29318645

Previous studies have suggested an association between bladder pain syndrome/interstitial cystitis (BPS/IC) and endometriosis. However, no nation-wide population study has yet reported an association between them. In this study from Taiwan, Wu and colleagues examined the risk of BPS/IC among subjects with endometriosis during a 3-year follow-up in Taiwan using a population-based dataset. This study comprised 9191 subjects with endometriosis, and 27 573 subjects randomly selected as controls. They individually followed-up each subject for a 3-year period to identify subjects subsequently diagnosed with BPS/IC. Incidences of BPS/IC during the 3-year follow-up period was 0.2% and 0.05% for subjects with and without endometriosis, respectively. The hazard ratio for developing BPS/IC over a 3-year period for subjects with endometriosis compared to subjects without endometriosis was 4.43. After adjusting for co-morbidities

like diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraines, sicca syndrome, allergies, endometriosis, asthma, tobacco use, and alcohol abuse, the Cox proportional hazards regressions revealed that the hazard ratio for BPS/IC among subjects with endometriosis was 3.74 compared to that in controls. The authors concluded that this study provides epidemiological evidence of an association between endometriosis and a subsequent diagnosis of BPS/IC.

VULVODYNIA/VULVAL PAIN SYNDROME

[EARLY EXPERIENCE WITH TOPICAL MELOXICAM AND LIDOCAINE COMBINATION FOR THE TREATMENT OF VULVODYNIA.](#)

Kim R, Kelly KL, Olsen M, Nickel JC. Can Urol Assoc J. 2018 Apr 6. doi: 10.5489/cuaj.4976. [Epub ahead of print] PMID: 29629863

Kim and colleagues from Canada report on their early clinical observations on the use of topical meloxicam and lidocaine gel for patients with vulvodynia. This is an early experience in participants with a history of vulvodynia evaluated and treated at the Queen's University Pelvic and Bladder Pain Clinic. Combination meloxicam 0.3% and lidocaine 5% were provided to the participants and they were instructed to apply 5 cc to the vulvar area twice daily. Standardized assessment was conducted for each participant before the start of the topical therapy and again at one week included Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), and pain scoring (Likert) for vulvar pain, in addition to a subjective global assessment after a week of treatment. Of the eight participants, six had a subjective improvement in their symptoms with the use of the combination gel. They reported between one- and four-point reductions on the Likert pain scale and mild to moderate improvement of symptoms. Common side effects reported were burning and stinging. The authors concluded that the results from this early experience are promising for a potentially effective topical treatment for vulvodynia.

FIBROMYALGIA

[WHAT YOU CAN DO FOR YOUR FIBROMYALGIA PATIENT.](#)

Gota CE. Cleve Clin J Med. 2018 May;85(5):367-376. doi: 10.3949/ccjm.85gr.18002. PMID: 29733785

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Patients with fibromyalgia typically have pain "all over," tender points, generalized weakness and fatigue, nonrestorative sleep, and a plethora of other symptoms. In contrast to inflammatory and autoimmune conditions, laboratory tests and physical examination findings are usually normal. American College of Rheumatology guidelines facilitate diagnosis. Management requires a multifaceted, long-term strategy that emphasizes improving function rather than reducing pain.

E-HEALTH

[SMARTPHONE APP USING MINDFULNESS MEDITATION FOR WOMEN WITH CHRONIC PELVIC PAIN \(MEMPHIS\): PROTOCOL FOR A RANDOMIZED FEASIBILITY TRIAL.](#)

Ball E, Newton S, Kahan BC, Forbes G, Wright N, Cantalapiedra Calvete C, Gibson HAL, Rogozinska E, Rivas C, Taylor SJC, Birch J, Dodds J. JMIR Res Protoc. 2018 Jan 15;7(1):e8. doi: 10.2196/resprot.7720. PMID: 29335232

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Female chronic pelvic pain (CPP) is defined as intermittent or constant pelvic or lower abdominal pain occurring in a woman for at least 6 months. Up to a quarter of women are estimated to be affected by CPP worldwide and it is responsible for one fifth of specialist gynecological referrals in the United Kingdom. Psychological interventions are commonly utilized. As waiting times and funding capacity impede access to face-to-face consultations, supported self-management (SSM) has emerged as a viable alternative. Mindfulness meditation is a potentially valuable SSM tool, and in the era of mobile technology, this can be delivered to the individual user via a smartphone app. The purpose of this study was to assess the feasibility of conducting a trial of a mindfulness meditation intervention delivered by a mobile phone app for patients with CPP. This feasibility trial will inform the design of a large multicentred trial to assess the clinical effectiveness of mindfulness meditation delivered via a smartphone app for the treatment of CPP.

[DEVELOPMENT AND FEASIBILITY ASSESSMENT OF A 3 DAY ELECTRONIC BLADDER DIARY AS AN APP FOR SMART-PHONE.](#)

Mateu Arrom L, Peri Cusi L, Franco de Castro A, López-Fando L, Jiménez Cidre MÁ, Alcaraz Asensio A. *Neurourol Urodyn*. 2018 Jan 22. doi: 10.1002/nau.23494. [Epub ahead of print] PMID: 29356063

The purpose of this study from Spain was to develop a 3 day bladder diary (BD) as an easy-to-use application for smart-phone (eDM3d). To test its feasibility and acceptance in a reduced number of patients. An external agency developed the eDM3d following the structure of the Spanish validated 3 day BD (DM3d©), which includes a frequency-volume chart, the assessment of the grade of urgency, the incontinence events and fluid intake. The eDM3d consisted in a main interface of four buttons ("wake up," "go to bed," "urinate," "drink") which had to be clicked to create an event. Results were automatically transferred to an internet server to obtain an electronic report. The authors recruited 25 patients with overactive bladder syndrome or nocturia and previous experience on paper BD. They were asked to complete the eDM3d. Finally, a direct question about satisfaction was answered: "If you had to complete a BD again, would you choose the paper or the app version?" Three patients did not complete the eDM3d, 1 patient completed 2 days of the eDM3d and did not register volumes of micturition nor fluid intake, 1 patient completed all 2 days variables and 20 patients completed all 3 day variables. Regarding satisfaction, 19 patients (86.4%) would choose the app version, 2 patients would choose a paper version and 1 patient would choose either indistinctly. The authors concluded that the eDM3d is a useful tool easily filled in by patients with a high satisfaction rate. Adequate validation of the eDM3d is required.

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