International Painful Bladder Foundation

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

IPBF e-Newsletter and Research Update
Issue 50, February 2019

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:

REVIEW OF ESSIC MEETING - 29 NOVEMBER-1 DECEMBER 2018, FLORENCE, ITALY

The Auditorium al Duomo in the historic heart of Florence formed the setting for the ESSIC 2018 annual meeting. ESSIC is the International Society (originally the European Society) for the Study of Bladder Pain Syndrome/Interstitial Cystitis and its associated disorders. Its President is Professor Jean-Jacques Wyndaele from Belgium. The ESSIC annual meeting provides an opportunity for clinicians, researchers, patient advocates and other stakeholders with a special interest in BPS/IC and associated disorders to discuss the current situation, present their research or ideas and make suggestions for the future. This year's meeting in Florence, Italy, chaired by Professor Giulio Del Popolo with Professor Mauro Cervigni as ESSIC Coordinator, was attended by 180 delegates from 18 countries including Australia! There were no fewer than 17 patient representatives from different countries who played an active part in the meeting with a number of presentations, including on the very concerning issue of non-reimbursement of vital treatment for IC/BPS by health authorities and insurances. Speakers in Florence looked at different aspects of diagnosis, treatment, guidelines and presented new research. There was also time for discussion of the many problems faced by the IC/BPS world. This included the all-important issue of splitting off Hunner lesion IC from non-lesion disease, phenotyping and guideline issues.
The IPBF review of this meeting takes a look at some of the highlights. Click here to read more.
Or go to: http://www.painful-bladder.org/pdf/2018-11_ESSIC_Florence.pdf

The 2019 annual meeting of ESSIC will be held in Amsterdam, the Netherlands towards the end of 2019. Further information will be available soon on the ESSIC website: www.essic.org. If you would like to be added to the ESSIC mailing list for information about the 2019 conference, please contact essic@defoe.it.

CHRONIC PAIN AND ICD-11

A task force from the International Association for the Study of Pain (IASP) has been working for some time on the World Health Organization's new update of the International Classification of Diseases, ICD-11, in the field of chronic pain. ICD-11 will be the first version to include chronic pain. The link below provides information about the six categories of chronic pain and from there it is possible to link to a series of 10 papers published in the January 2019 issue of PAIN which provide a general overview of the classification and explain the fundamental distinction between chronic primary and chronic secondary pain. Chronic primary pain represents chronic pain as a disease in itself. Chronic secondary pain is chronic pain where the pain is a symptom of an underlying condition.

https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=8340&navItemNumber=643
In Pain: January 2019 - Volume 160 - Issue 1, you will find a number of open access articles on ICD-11 and pain.
https://journals.lww.com/pain/pages/currenttoc.aspx

4TH WORLD CONGRESS ON ABDOMINAL AND PELVIC PAIN (WCAPP) 11-12 May 2019, London UK

The 4th WCAPP to be held in London at the Hilton London Metropole Hotel will be a global event and will focus on pain from a life course and lifestyle approach. Topics will include: Childhood/Adolescence, Reproductive Age, Post-Reproductive Age, Diet and the Microbiome, Sleep and Stress, and Exercise. Further information can be obtained at: https://www.iasp-pain.org/WCAPP/home?navItemNumber=8149

RESEARCH : IMI-PainCare: "IMPROVING THE CARE OF PATIENTS SUFFERING FROM ACUTE OR CHRONIC PAIN"

Improving the care of patients suffering from acute or chronic pain is the ambitious research goal of the IMI-PAINCARE Consortium which addresses three important topics:
•Patient reported outcome measures to improve management of acute and chronic pain (PROMPT);
•Pharmacological validation of functional pain biomarkers in healthy subjects and animals (BioPain);
•Improving translation in chronic pelvic pain (TRiPP).
Information about the project as a whole can be found at: https://www.imi-paincare.eu/
Information on the TRiPP project (which includes IC/BPS) can be found at: https://www.imi-paincare.eu/PROJECT/TRIPP/

CALENDAR OF UPCOMING EVENTS

SUFU 2019 WINTER MEETING
February 26 – March 2, 2019
InterContinental Miami Hotel
Miami, Florida
https://sufuorg.com/meetings/upcoming-sufu/meeting-information.aspx

EAU 2019
15-19 March 2019 Barcelona, Spain
https://eaucongress.uroweb.org/

AUA 2019
3-6 May, Chicago, USA
http://www.aua2019.org/

4th World Congress on Abdominal and Pelvic Pain (WCAPP)
11-12 May 2019, London UK
https://www.iasp-pain.org/WCAPP/home?navItemNumber=8149

EULAR Congress 2019
European Rheumatology Congress
12-15 June 2019
Madrid, Spain
https://www.congress.eular.org

Global Interstitial Cystitis Bladder Pain Society (GIBS) of India
Annual Conference, 24-25 August 2019. Theme: "Beyond Horizon",
Mumbai, India
https://gibsociety.com/#

ICS 2019
3-6 September 2019
Gothenburg, Sweden
https://www.ics.org/2019

EFIC CONGRESS: PAIN IN EUROPE XI
4-7 September 2019, VALENCIA, SPAIN
https://efic-congress.org/welcome-messages/

ISSVD INTERNATIONAL SOCIETY FOR THE STUDY OF VULVOVAGINAL DISEASE
XXV WORLD CONGRESS & INTERNATIONAL POSTGRADUATE COURSE

16-17 September 2019, Torino, Italy
https://www.issvd.org/event/xxv-world-congress-postgraduate-course/

ESSIC ANNUAL MEETING 2019
End of year. Amsterdam, Netherlands
www.essic.org

PUBLICATIONS AND INFORMATION

IPBF REVIEW ICICJ 2018

An IPBF review of the 4TH International Consultation on Interstitial Cystitis Japan (ICICJ) and the annual meeting of the Society of Interstitial Cystitis of Japan (SICJ), held17-18 April 2018, Kyoto, Japan is available on the IPBF website: http://www.painful-bladder.org/pdf/2018_ICICJ4_Kyoto.pdf

It is hoped that an International Journal of Urology (IJU) supplement on ICICJ 2018 will be published in the spring.

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.

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.

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.

MANAGEMENT OF SYMPTOM FLARES AND PATIENT-REPORTED FLARE TRIGGERS IN INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME (IC/BPS) - FINDINGS FROM ONE SITE OF THE MAPP RESEARCH NETWORK.

Lai HH, Vetter J, Song J, Andriole GL, Colditz GA, Sutcliffe S. Urology. 2019 Jan 22. pii: S0090-4295(19)30074-3. doi: 10.1016/j.urology.2019.01.012. [Epub ahead of print] PMID: 30682464

The purpose of this study was to document patient-reported interstitial cystitis/ bladder pain syndrome (IC/BPS) flare management strategies and triggers. 24 male and 29 female participants enrolled at the Washington University site of the MAPP Research Network completed a questionnaire on strategies they utilized to manage flares and factors they believed triggered their flares (e.g., specific food items, physical activities, sexual activities, infections, and stress). Participants were also asked about the diurnal timing of their flares. 96.2% of participants reported having ever experienced a symptom flare. Participants treated or managed their flares using a wide variety of strategies, ranging from common strategies, such as drinking additional water or fluid (74.5%), to less common strategies, such as acupuncture/acupressure (5.9% of participants). Participants also reported a wide range of perceived flare triggers, including previously reported factors (citrus fruits, tomatoes, spicy food, alcoholic and caffeinated beverages, driving/sitting in forms of transportation, urinary tract infections, stress, and tight clothing), as well as some less common, previously undocumented factors (e.g.,

certain foods, non-genitourinary infections, wearing high-heeled shoes/boots or perfume, hair dye, and toothpaste). In general, female participants and those with somatic sensory hypersensitivity reported greater numbers of therapies and triggers. Finally, flares were reported most commonly in the afternoon or evening. IC/BPS participants reported diverse flare management strategies and numerous perceived triggers. These findings, together with those from the small body of literature to date, provide a wide array of candidates and hypotheses for future global and tailored flare management and prevention interventions.

SYMPTOM DURATION IN PATIENTS WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS) IS NOT ASSOCIATED WITH PAIN SEVERITY, NON-UROLOGIC SYNDROMES AND MENTAL HEALTH SYMPTOMS: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) NETWORK STUDY.

Rodríguez LV, Stephens AJ, Clemens JQ, Buchwald D, Yang C, Lai HH, Krieger JN, Newcomb C, Bradley CS, Naliboff B; MAPP Research Network. Urology. 2018 Nov 16. pii: S0090-4295(18)31206-8. doi: 10.1016/j.urology.2018.11.015. [Epub ahead of print] PMID: 30452963

The purpose of this MAPP Network study was to evaluate if patients with urologic chronic pelvic pain syndromes (UCPPS) with longer duration of symptoms experience more severe pain and urologic symptoms, higher rates of chronic overlapping pain conditions (COPC) and psychosocial comorbidities than those with a more recent onset of the condition. The authors evaluated cross-sectional associations between UCPPS symptom duration and 1) symptom severity, 2) presence of COPC, and 3) mental health comorbidities. They analyzed baseline data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP). Symptom severity, COPC and mental health comorbidities were compared between patients with symptom duration of < 2 versus ≥ 2 years. Symptom severity was assessed by the Genitourinary Pain Index (GUPI), the Interstitial Cystitis Symptom and Problem Index (ICSI and ICPI), and Likert scales for pelvic pain, urgency and frequency. Depression and anxiety were evaluated with the Hospital Anxiety and Depression Scale (HADS) and stress with the Perceived Stress Scale (PSS). Males (but not females) with UCPPS symptom duration ≥ 2 years had more severe symptoms than those with < 2 years. Participants with short (< 2 years) and longer (≥ 2 years) symptom duration were as likely to experience COPC. It was concluded that longer UCPPS symptom duration was associated with more severe symptoms only in limited patient subpopulations. Symptom duration was not associated with risk for COPC or mental health comorbidities. Females with longer UCPPS duration had decreased distress, but the association was largely attributable to age.

UROLOGIC CHRONIC PELVIC PAIN SYNDROME: INSIGHTS FROM THE MAPP RESEARCH NETWORK.

Clemens JQ, Mullins C, Ackerman AL, Bavendam T, van Bokhoven A, Ellingson BM, Harte SE, Kutch JJ, Lai HH, Martucci KT, Moldwin R, Naliboff BD, Pontari MA, Sutcliffe S, Landis JR; MAPP Research Network Study Group. Nat Rev Urol. 2018 Dec 18. doi: 10.1038/s41585-018-0135-5. [Epub ahead of print] PMID: 30560936

Urologic chronic pelvic pain syndrome (UCPPS), which encompasses interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, is characterized by chronic pain in the pelvic region or genitalia that is often accompanied by urinary frequency and urgency. Despite considerable research, no definite aetiological risk factors or effective treatments have been identified. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network uses a novel integrated strategy to characterize UCPPS as a systemic disorder that potentially involves multiple aetiologies. The first phase, MAPP I, included >1,000 participants who completed an intensive baseline assessment followed by a 12-month observational follow-up period. MAPP I studies showed that UCPPS pain and urinary symptoms co-vary, with only moderate correlation, and should be evaluated separately and that symptom flares are common and can differ considerably in intensity, duration and influence on quality of life. Longitudinal clinical changes in UCPPS correlated with structural and functional brain changes, and many patients experienced global multisensory hypersensitivity. Additionally, UCPPS symptom profiles were distinguishable by biological correlates, such as immune factors. These findings indicate that patients with UCPPS have objective phenotypic abnormalities and distinct biological characteristics, providing a new foundation for the study and clinical management of UCPPS.

CHANGES IN BRAIN WHITE MATTER STRUCTURE ARE ASSOCIATED WITH URINE PROTEINS IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS): A MAPP NETWORK STUDY.

Woodworth DC, Dagher A, Curatolo A, Sachdev M, Ashe-McNalley C, Naliboff BD, Labus JS, Landis JR, Kutch JJ, Mayer EA, Lee RS, Moses MA, Ellingson BM; MAPP Research Network. PLoS One. 2018 Dec 5;13(12):e0206807. doi: 10.1371/journal.pone.0206807. eCollection 2018. PMID: 30517112

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The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network has yielded neuroimaging and urinary biomarker findings that highlight unique alterations in brain structure and in urinary

proteins related to tissue remodelling and vascular structure in patients with Urological Chronic Pelvic Pain Syndrome (UCPPS). The authors hypothesized that localized changes in diffusion tensor imaging (DTI) measurements might be associated with corresponding changes in urinary protein levels in UCPPS. To test this hypothesis, we created statistical parameter maps depicting the linear correlation between DTI measurements (fractional anisotropy (FA) and apparent diffusion coefficient (ADC)) and urinary protein quantification (MMP2, MMP9, NGAL, MMP9/NGAL complex, and VEGF) in 30 UCPPS patients from the MAPP Research Network, after accounting for clinical covariates. Results identified a brainstem region that showed a strong correlation between both ADC and FA with urinary MMP9 levels as well as a correlation between both ADC and FA and urinary MMP9/NGAL complex. Results also identified significant correlations between FA and urinary MMP9 in white matter adjacent to sensorimotor regions, as well as a correlation in similar sensorimotor regions when examining ADC and urinary MMP2 levels as well as FA and urinary MMP9/NGAL complex. A large, diffuse cluster of white matter was identified as having a strong correlation between both ADC and FA with urinary NGAL levels. In contrast, no significant association between DTI measurements and VEGF was observed. Results suggest that elevated MMP9 or MMP9/NGAL in UCPPS may be related to degenerative neuronal changes in brainstem nuclei through excitotoxicity, while also facilitating synaptic plasticity in sensorimotor regions.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

MECHANISMS UNDERLYING OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Grundy L, Caldwell A, Brierley SM. Front Neurosci. 2018 Dec 12;12:931. doi: 10.3389/fnins.2018.00931. eCollection 2018. PMID: 30618560

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In this review, Grundy and colleagues from Australia write that the bladder is innervated by extrinsic afferents that project into the dorsal horn of the spinal cord, providing sensory input to the micturition centres within the central nervous system. Under normal conditions, the continuous activation of these neurons during bladder distension goes mostly unnoticed. However, for patients with chronic urological disorders such as overactive bladder syndrome (OAB) and interstitial cystitis/painful bladder syndrome (IC/PBS), exaggerated bladder sensation and altered bladder function are common debilitating symptoms. Whilst considered to be separate pathological entities, there is now significant clinical and pre-clinical evidence that both OAB and IC/PBS are related to structural, synaptic, or intrinsic changes in the complex signalling pathways that mediate bladder sensation. This review discusses how urothelial dysfunction, bladder permeability, inflammation, and cross-organ sensitisation between visceral organs can regulate this neuroplasticity. Furthermore, they discuss how the emotional affective component of pain processing, involving dysregulation of the HPA axis and maladaptation to stress, anxiety and depression, can exacerbate aberrant bladder sensation and urological dysfunction. This review reveals the complex nature of urological disorders, highlighting numerous interconnected mechanisms in their pathogenesis. To find appropriate therapeutic treatments for these disorders, it is first essential to understand the mechanisms responsible, incorporating research from every level of the sensory pathway, from bladder to brain.

GAG REPLENISHMENT THERAPY FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Wyndaele JJ, Riedl C, Taneja R, Lovász S, Ueda T, Cervigni M. Neurourol Urodyn. 2018 Dec 28. doi: 10.1002/nau.23900. [Epub ahead of print] PMID: 30592544

The aim of this study was to present a rationale for the inclusion of urothelial coating dysfunction in the etipathogenesis of bladder pain syndrome/interstitial cystitis (BPS/IC) and the preclinical and clinical evidence in support of glycosaminoglycan (GAG) replenishment therapy in the treatment of BPS/IC, supplemented by the clinical experience of medical experts in the field and patient advocates attending a symposium on GAG replenishment at ESSIC'17, the annual Meeting of the International Society for the Study of Bladder Pain Syndrome, held in Budapest, Hungary in 2017. The urothelial GAG layer has a primary role in providing a permeability barrier to prevent penetration of urinary toxins and pathogens into the bladder wall. Disruption of the GAG layer contributes to the development of BPS/IC. The evidence shows that replenishment of GAGs can restore the GAG layer in BPS/IC, reducing inflammation, pain, and other symptoms. Although data from large randomized controlled studies are limited, long clinical observation and the experience of clinicians and patients support the beneficial effects of intravesical GAG replenishment therapy for providing symptomatic relief for patients with BPS/IC.

SAFETY AND EFFICACY OF INTRAVESICAL HYALURONIC ACID/CHONDROITIN SULFATE IN THE TREATMENT OF REFRACTORY PAINFUL BLADDER SYNDROME.

Sherif H, Sebay A, Kandeel W, Othman T, Fathi A, Mohey A, Eshazly A. Turk J Urol. 2018 Nov 21:1-6. doi: 10.5152/tud.2018.63600. [Epub ahead of print] PMID: 30475699

This study evaluated the safety and efficacy of intravesical instillation of hyaluronic acid/chondroitin sulfate in the treatment of refractory painful bladder syndrome. Forty patients were subjected to intravesical instillations of hyaluronic acid/chondroitin sulfate weekly for 4 weeks and at 6., 8., 12. and 16. weeks, afterwards. The authors then evaluated the efficacy of this treatment modality by determining the mean changes in visual analogue scale (VAS) pain score, the pelvic pain and urgency/frequency questionnaire, the O'Leary-Sant interstitial cystitis symptoms index/problems index and 3 day-voiding diary results including daily number of voids and mean voided volume at 2 weeks, 3, and 9 months after the last dose (4th month) and urodynamic studies including cystometric capacity, 1st sensation of urination, and Q-max at 9 months after the last dose. Thirty-seven patients (6 males 16.2%, 31 females 83.8%) completed the entire follow-up protocol of this study. Age of the patients ranged from 22 to 37 years and their body mass indexes (BMIs) ranged between 29 and 37 kg/m2. An initial response to treatment in all parameters at variable degrees was noticed at 2 weeks after the last instillation when compared to the baseline, and these changes were statistically significant. Progressive improvement in all test parameters was noticed at 3 months after treatment, and this improvement was statistically significant compared with baseline and 2 weeks after treatment, respectively. It was concluded that intravesical instillation with both hyaluronic acid/chondroitin sulfate in the treatment of refractory painful bladder syndrome is safe, effective and well tolerated by all patients with no recorded side effects.

DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING: A NEW TOOL FOR THE DIAGNOSIS OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Charlanes A, Boudghene F, Chesnel C, Ciofu C, Le Breton F, Jousse M, Amarenco G, Manceau P. Urol Int. 2018 Nov 14:1-4. doi: 10.1159/000493507. [Epub ahead of print] PMID: 30428470

The purpose of this study was to determine whether diffusion-weighted magnetic resonance imaging (DWMRI), a non-invasive procedure, can contribute to the diagnosis of bladder pain syndrome/interstitial cystitis (BPS/IC). The pelvic DWMRI of patients with chronic pelvic pain syndrome was selected between January 2012 and June 2017. A radiologist analysed the bladder wall signal; he was blinded to the patients' clinical data. According to the 2008 European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis criteria, 2 groups of patients were determined: BPS/IC and no BPS/IC. The association between BPS/IC and the wall signal intensity was compared. In the 106 patients included, 82 had criteria for BPS/IC and 24 did not. A significant difference in the distribution of the signal was found between the 2 groups. High signal intensity of the bladder wall was related to the presence of a BPS/IC with a sensitivity of 28% and a specificity of 88%. No signal intensity of the bladder wall was related to the absence of a BPS/IC with a sensitivity of 96% and a specificity of 29%. It was concluded that in DWMRI, high bladder wall signal intensity helps to affirm a BPS/IC, whereas the absence of signal helps to exclude the diagnosis. Further studies are needed to confirm these preliminary results.

ROLE OF NLRP3 INFLAMMASOME IN THE DEVELOPMENT OF BLADDER PAIN SYNDROME INTERSTITIAL CYSTITIS.

Tudrej KB, Piecha T, Kozłowska-Wojciechowska M. Ther Adv Urol. 2019 Jan 8;11:1756287218818030. doi: 10.1177/1756287218818030. eCollection 2019 Jan-Dec. PMID: 30671141

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Although it has been proposed that NOD-like receptor protein 3 (NLRP3) inflammasome activation may have an important contribution to the onset of bladder pain syndrome/interstitial cystitis (BPS/IC), as of today there is still insufficient evidence to accept or to reject this hypothesis. However, taking into consideration that inflammasomes have been already shown as important mediators of cyclophosphamide-induced bladder inflammation and that some studies have also revealed human bladder epithelium expresses high levels of NLRP3, such a hypothesis seems to be reasonable. The purpose of this review from Poland is to discuss a scenario that NLRP3 inflammasome is a crucial player in the development of this disease. Identification of a novel mediator of bladder inflammation and pain could lead to emerging new therapeutic strategy and the first causative therapy.

LONG-TERM FOLLOW-UP AFTER CYSTECTOMY FOR BLADDER PAIN SYNDROME: PAIN STATUS, SEXUAL FUNCTION AND QUALITY OF LIFE.

Mateu Arrom L, Gutiérrez Ruiz C, Mayordomo Ferrer O, Martínez Barea V, Palou Redorta J, Errando Smet C. World J Urol. 2018 Nov 3. doi: 10.1007/s00345-018-2554-6. [Epub ahead of print] PMID: 30390128

This study assessed the long-term complications, pain status, sexual function and quality of life after cystectomy for bladder pain syndrome (BPS). The authors retrospectively reviewed functional variables for 35 patients (34 women/1 man, 67 ± 9 years old) who underwent cystectomy due to BPS since 1993 in their department. Cystectomy was offered to patients with BPS refractory to conservative treatments. Six cystectomies with ileal conduit (17.1%) and 29 supratrigonal cystectomies with enterocystoplasty (82.9%) were performed. Prospectively, patients completed questionnaires on pain [BPIC-SS, visual analogue scale (VAS) for pain], health-related quality of life (EQ-5D) and sexual function (FSFI; 2-36), rated satisfaction with surgery (0-10) and reported whether they would undergo the same surgery again. Mean follow-up was 107 ± 83 months. In two (5.7%) patients, pain persisted and in one patient (2.8%) pain recurred after 20 months. Significant improvements in daytime and night-time frequency and bladder capacity were observed postoperatively. 21 patients completed questionnaires. Mean BPIC-SS was 7.5 ± 8.4, mean VAS score 2.5 ± 2.8. 14 (66.7%) patients reported no problems related to pain on the EQ-5D, similar to our regional reference population. 13 (61.9%) patients had sexual intercourse after surgery, ten of them without pain. Mean FSFI score was 9.5 ± 9. Satisfaction with surgery was 8.8 ± 1.7 and 20 (95.2%) patients would undergo the same surgery again. Pain persistence or recurrence after cystectomy for BPS is infrequent. Quality of life related to pain is similar to that in the general population and patients can resume sexual activity without pain.

URINE GENE EXPRESSION PROFILES IN BLADDER PAIN SYNDROME PATIENTS TREATED WITH TRIAMCINOLONE.

Izquierdo L, Mateu L, Lozano JJ, Montalbo R, Ingelmo-Torres M, Gómez A, Peri L, Mengual L, Franco A, Alcaraz A. Eur Urol Focus. 2018 Oct 11. pii: S2405-4569(18)30294-3. doi: 10.1016/j.euf.2018.10.001. [Epub ahead of print] PMID: 30318464

The purpose of this study was to gain detailed insight into the disease pathobiology of BPS through comparative gene expression analysis of urine from BPS patients versus control individuals and, furthermore, to determine the efficacy of triamcinolone treatment in BPS patients in terms of the gene expression profiles in urine. A prospective pilot study including 21 urine samples from patients with Hunner's lesions (n=6) and controls (n=9) between January and August 2017. Urine samples from BPS patients were collected before (pretreatment group) and 2 wk after triamcinolone treatment (post-treatment group). Gene expression of urine sediment was analyzed using RNA sequencing. Pathways and biological processes in which differentially expressed genes are involved were analyzed. A total of 3745 genes were found to be differentially expressed between the three groups tested. Gene expression differences between controls and BPS samples (630 differentially expressed genes) were more pronounced than the differences between pre- and post-treatment BPS samples (197 differentially expressed genes). Gen Set Enrichment Analysis showed that differentially expressed genes in BPS patients (pretreatment), compared with controls, were enriched for some functional gene networks associated with several metabolic processes and ribosome biogenesis. However, the limited number of patients included may not accurately represent the BPS population. The authors show that triamcinolone induces changes in urine gene expression profiles. In this report, they looked at gene expression profiles of urine sediment from patients with Hunner's lesions, before and after triamcinolone treatment, and control individuals. They found that urine gene expression profiles are able to discriminate Hunner's lesions patients from controls. Furthermore, they report, for the first time, that triamcinolone treatment of patients with Hunner's lesions induces changes in bladder gene expression profiles that can be observed in urine samples.

SPINAL MECHANISMS OF PUDENDAL NERVE STIMULATION-INDUCED INHIBITION OF BLADDER HYPERSENSITIVITY IN RATS.

Ness TJ, DeWitte C, McNaught J, Clodfelder-Miller B, Su X. Neurosci Lett. 2018 Nov 1;686:181-185. doi: 10.1016/j.neulet.2018.08.041. Epub 2018 Sep 12. PMID: 30218768

Bilateral electrical pudendal nerve stimulation (bPNS) reduces bladder hypersensitivity in rat models of bladder pain and anecdotally reduces pain in humans with pelvic pain of urologic origin. The spinal neurochemical mechanisms of this antinociception are unknown. In the present study, bladder hypersensitivity was produced by neonatal bladder inflammation in rat pups coupled with a second inflammatory insult as an adult. Visceromotor responses (VMRs; abdominal muscle contractions) to urinary bladder distension (UBD) were used as a nociceptive endpoint under urethane-isoflurane anesthesia. bPNS consisted of bilateral biphasic electrical stimulation of the mixed motor/sensory component of the pudendal nerves. Following determination of the inhibitory effect of bPNS on VMRs, pharmacological antagonists were administered via an intrathecal catheter onto the lumbosacral spinal cord and bPNS effects on VMRs redetermined. bPNS resulted in statistically significant inhibition of VMRs to UBD in hypersensitive rats that was statistically reduced by the intrathecal administration of methysergide, WAY100636, CGP35348 and strychnine but was unaffected by naloxone, bicuculline, phentolamine, ondansetron and normal saline. This study suggests that inhibitory effects of bPNS

may include serotonergic, GABA-B-ergic and glycinergic mechanisms suggesting the potential for interaction of the neuromodulatory effect with concomitant drug therapies.

ATTENUATED LIPOPOLYSACCHARIDE-INDUCED INFLAMMATORY BLADDER HYPERSENSITIVITY IN MICE DEFICIENT OF TRANSIENT RECEPTOR POTENTIAL ANKILIN1.

Kamei J, Aizawa N, Nakagawa T, Kaneko S, Kume H, Homma Y, Igawa Y. Sci Rep. 2018 Oct 23;8(1):15622. doi: 10.1038/s41598-018-33967-x. PMID: 30353098

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Transient receptor potential ankyrin 1 (TRPA1) channel expressed by urothelial cells and bladder sensory nerve fibers might act as a bladder mechanosensor and nociceptive transducer. To disclose the role of TRPA1 in bladder function and inflammation-associated hypersensitivity, the authors evaluated in vitro and in vivo bladder function and inflammatory mechanosensory and nociceptive responses to intravesical lipopolysaccharide (LPS)-instillation in wild type (WT) and TRPA1-knock out (KO) mice. At baseline before treatment, no significant differences were observed in frequency volume variables, in vitro detrusor contractility, and cystometric parameters between the two groups in either sex. LPS-instillation significantly increased voiding frequency and decreased mean voided volume at 24-48 hours after instillation in WT but not in TRPA1-KO mice. LPS-instillation also significantly increased the number of pain-like behaviour at 24 hours after instillation in WT mice, but not in TRPA1-KO mice. Cystometry 24 hours after LPS-instillation revealed shorter inter-contraction intervals in the WT mice compared with TRPA1-KO mice. In contrast, inflammatory cell infiltration in the bladder suburothelial layer was not significantly different between the two groups. These results indicate that TRPA1 channels are involved in bladder mechanosensory and nociceptive hypersensitivity accompanied with inflammation but not in physiological bladder function or development of bladder inflammation.

INVESTIGATIONS OF URETHRAL SPHINCTER ACTIVITY IN MICE WITH BLADDER HYPERALGESIA BEFORE AND AFTER DRUG ADMINISTRATION OF GABAPENTIN.

Yeh JC, Do R, Choi H, Lin CT, Chen JJ, Zi X, Chang HH, Ghoniem G. Int Urol Nephrol. 2018 Nov 1. doi: 10.1007/s11255-018-2021-8. [Epub ahead of print] PMID: 30387068

This study investigated the effect of gabapentin on lower urinary tract dysfunction focusing on urethral activities and cystitis-induced hyperalgesia in a mouse model of painful bladder syndrome/interstitial cystitis (PBS/IC). The electromyography (EMG) of external urethral sphincter (EUS) was difficult to obtain but contained useful information to examine the drug effect in mice. Female C57BL/6J mice were intraperitoneally (ip) administration with either saline or 200 mg/kg of cyclophosphamide (CYP) 48 h before experimental evaluation. Cystitis mice were treated with administration of gabapentin (25 or 50 mg/kg, ip). Cystometry and EUS EMG were obtained and analysed during continuous bladder infusion. The visceral pain-related visceromotor reflex (VMR) was recorded in response to isotonic bladder distension. Cystitis mice showed shorter inter-contraction intervals and increased occurrence of non-voiding contractions during bladder infusion, with increased VMR during isotonic bladder distension, indicating cystitis-induced bladder hyperalgesia. Gabapentin (50 mg/kg) suppressed effects of CYP on cystometry, but not on EUS EMG activity, during bladder infusion. The effect on urodynamic recordings lasted 4 h. VMR was significantly reduced by gabapentin. The present study showed that CYP-induced cystitis in mice is a model of visceral hyperalgesia affecting detrusor contractions, not urethral activations. The technique of using EUS EMG to evaluate the drug effects on urethral activities is novel and useful for future investigations. Gabapentin can be as a potential treatment for detrusor overactivity and PBS/IC.

LONG-TERM RELIEF OF PAINFUL BLADDER SYNDROME BY HIGH-INTENSITY, LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OF THE RIGHT AND LEFT DORSOLATERAL PREFRONTAL CORTICES.

Nizard J, Esnault J, Bouche B, Suarez Moreno A, Lefaucheur JP, Nguyen JP. Front Neurosci. 2018 Dec 11;12:925. doi: 10.3389/fnins.2018.00925. eCollection 2018. PMID: 30618554

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The aim of this study was to show the value of low-frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) to treat bladder pain syndrome (BPS), characterized by suprapubic pain, urgency and increased micturition frequency. A 68-year-old woman with BPS underwent 16 sessions of high-intensity, low-frequency (1 Hz) rTMS of the DLPFC, first on the right hemisphere (one daily session for 5 days, followed by one weekly session for 5 weeks), and then on the left hemisphere (one monthly session for 6 months). At the end of the rTMS protocol, suprapubic pain completely vanished, micturition frequency dramatically decreased (by 60-80%), while fatigue and sleep quality improved (by 57-60%). The patient reported an overall satisfaction rate of 80% and her activities of daily living tending to normalize. This is the first report

showing that high-intensity, low-frequency rTMS delivered on the DLPFC region of both hemispheres can relieve most symptoms of BPS (pain, urinary symptoms, and interference with physical functioning) in clinical practice.

RESULTS OF SACRAL NEUROMODULATION THERAPY FOR URINARY VOIDING DYSFUNCTION: FIVE-YEAR EXPERIENCE OF A RETROSPECTIVE, MULTICENTER STUDY IN CHINA.

Zhang P, Wang JY, Zhang Y, Liao L, Lv JW, Ling Q, Wei ZQ, Zhong T, Xu ZH, Wen W, Li JY1, Luo DY. Neuromodulation. 2019 Jan 4. doi: 10.1111/ner.12902. [Epub ahead of print] PMID: 30609180

This five-year, retrospective, multicentre study evaluated the long-term safety and efficiency of sacral neuromodulation (SNM) in Chinese patients with urinary voiding dysfunction. This is a Chinese national, multicentre, retrospective study that included 247 patients (51.2% female) who received an implantable pulse generator (IPG) (InterStim, Medtronic, Minneapolis, MN, USA) between 2012 and 2016. Success was considered if the initial ≥50% improvement in any of primary voiding diary variables persisted compared with baseline. The results were further stratified by identifying patients who showed >50% improvement and those although showed <50% improvement but still wanted to receive IPG; these data were collected and analyzed for general improvement. Following test stimulation, 187 patients (43%) declined implantation and 247 (57%) underwent implantation using InterStim®. Among 247 patients, 34 (13.7%) had overactive bladder (OAB), 59 (23.8%) had interstitial cystitis/bladder pain syndrome (IC/BPS), 47 (19%) had idiopathic urinary retention (IUR), and 107 (44.1%) had neurogenic bladder (NB). IPG efficiency rate for OAB, interstitial cystitis/bladder pain syndrome, idiopathic urinary retention, and neurogenic bladder were 42.5, 72.4, 51.6, and 58.8%, respectively. The mean duration of follow-up was 20.1 ± 12.8 months. It was concluded that SNM appears effective in the long term, with a total IPG implantation rate of approximately 57% (ranging between 42.5 and 72.4% depending on indication). Interstitial cystitis/bladder pain syndrome appear to be the best indication for stage I testing. Chinese neurogenic bladder patients are most inclined to choose SNM. SNM is relatively safe, with low post-operation adverse events of 16.1% and reoperation rate of 3.2% during the follow-up period.

MOLECULAR PATHOGENESIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME BASED ON GENE EXPRESSION.

Karamali M, Shafabakhsh R, Ghanbari Z, Eftekhar T, Asemi . J Cell Physiol. 2019 Jan 4. doi: 10.1002/jcp.28009. [Epub ahead of print] PMID: 30609029

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic bladder inflammation that leads to chronic bladder pain and urinary urgency and frequency. The presentation of IC/PBS is heterogeneous, and it is classified as ulcerative IC/PBS and nonulcerative IC/PBS. The main cause of IC/PBS is thought to be a persistent inflammatory condition in the bladder, though the actual pathophysiology has not been identified yet. Although the underlying pathophysiology of IC/PBS is not completely understood, several theories for the etiology of this syndrome have been suggested, including deficiency of the glycosaminoglycan covering urothelium surface that results in leaky urothelium infection, immunological etiology, activated mast cells, neural changes, and inflammation. In addition, there are no gold standards for the detection of this disorder to date. So, determination of gene expression and its role in different signaling pathways in the pathogenesis of this heterogeneous disorder contribute to the more efficient cognition of the pathophysiology of this disease and to the design of effective treatments and molecular diagnostic methods for IC/PBS.

FELINE INTERSTITIAL CYSTITIS ENHANCES MUCOSA-DEPENDENT CONTRACTILE RESPONSES TO SEROTONIN.

Ikeda Y, Wolf-Johnston A, Roppolo JR, Buffington CAT, Birder L. Int Neurourol J. 2018 Dec;22(4):246-251. doi: 10.5213/inj.1836276.138. Epub 2018 Dec 31. PMID: 30599495

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This study looked at whether responses to serotonin are altered in bladder strips from cats diagnosed with a naturally occurring form of bladder pain syndrome/interstitial cystitis termed feline interstitial cystitis (FIC). Full thickness bladder strips were isolated from aged matched healthy control cats and cats with clinically verified FIC. Bladder strips were mounted in an organ bath and connected to a tension transducer to record contractile activity. A serotonin dose response (0.01-10μM) was determined for each strip with the mucosa intact or denuded. Bladder strips from control and FIC cats contracted in response to serotonin in a dose-dependent manner. The normalized force of serotonin-evoked contractions was significantly greater in bladder strips from cats with FIC (n=7) than from control cats (n=4). Removal of the mucosa significantly decreased serotonin-mediated responses in both control and FIC bladder preparations. Furthermore, the contractions in response to serotonin were abolished by 1μM atropine in both control and FIC bladder strips. The effect of serotonin on contractile force, but not sensitivity, was potentiated in bladder strips from cats with FIC, and was dependent upon the presence of the mucosa in control and FIC groups. As atropine inhibited these effects of serotonin, the

authors hypothesize that serotonin enhances acetylcholine release from the mucosa of FIC cat bladder strips, which could account for the increased force generated. In summary, FIC augments the responsiveness of bladder to serotonin, which may contribute to the symptoms associated with this chronic condition.

INHIBITION OF MICRORNA-132 ATTENUATES INFLAMMATORY RESPONSE AND DETRUSOR FIBROSIS IN RATS WITH INTERSTITIAL CYSTITIS VIA THE JAK-STAT SIGNALING PATHWAY.

Song YJ, Cao JY, Jin Z, Hu WG, Wu RH, Tian LH, Yang B, Wang J, Xiao Y, Huang CB. J Cell Biochem. 2018 Dec 23. doi: 10.1002/jcb.28190. [Epub ahead of print] PMID: 30582204

Interstitial cystitis (IC) is a heterogeneous syndrome with unknown etiology, and microRNAs (miRs) were found to be involved in IC. In this study, the authors aim to explore the role of miR-132 in the inflammatory response and detrusor fibrosis in IC through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling pathway in rat models. A rat model of IC was established and treated with the miR-132 mimic, miR-132 inhibitor, and/or JAK-STAT signalling pathway inhibitor AG490. Enzyme-linked immunosorbent assay was applied to measure the expression of interleukin (IL)-6, IL-10, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), and intercellular adhesion molecule-1 (ICAM-1). The urodynamic test was performed to assess urodynamic parameters, and reverse transcription quantitative polymerase chain reaction and Western blot analysis for the expression of miR-132, STAT4, suppressors of cytokine signalling 3 (SOCS3), JAK2, vascular endothelial growth factor (VEGF), IFN-γ, and TNF-α. IC rats treated with miR-132 inhibitor and AG490 had decreased collagen fiber, inflammatory cell infiltration, and mast cells, lower expression of IL-6, IL-10, IFN-γ, TNF-α, ICAM-1, collagens I and III, and alleviated urodynamic parameters and decreased expression of STAT4, VEGF, JAK2, IFN-γ, TNF-α, and increased expression of SOCS3. Taken together, the authors are of the opinion that their data indicate that downregulation of miR-132 alleviates inflammatory response and detrusor fibrosis in IC via the inhibition of the JAK-STAT signalling pathway.

INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA IS EFFECTIVE AND SAFE IN TREATMENT OF INTERSTITIAL CYSTITIS REFRACTORY TO CONVENTIONAL TREATMENT-A PROSPECTIVE CLINICAL TRIAL.

Jhang JF, Lin TY, Kuo HC. Neurourol Urodyn. 2018 Dec 21. doi: 10.1002/nau.23898. [Epub ahead of print] PMID: 30576011

This study investigated the clinical efficacy of platelet-rich plasma (PRP) intravesical injections on IC/BPS patients refractory to conventional therapies. Forty patients received four monthly intravesical injections of 10 mL PRP extracted from 50 mL of whole blood. The primary end-point was Global Response Assessment (GRA) at 3 months after the 4th PRP injection. Secondary endpoints included changes in O'Leary-Sant symptom score (OSS), visual analog scale (VAS) of pain, daily frequency, nocturia, functional bladder capacity (FBC), maximum flow rate, voided volume, post-void residual volume (PVR) from baseline to 3 months after the 4th PRP injection. All 40 patients (37 women and 3 men, aged 55.5 ± 11.1 years) completed the four injections and follow-up visits. GRA improved after the 1st PRP injection and the satisfaction persists till the primary end-point. The success rate was 45%, 52%, 70%, 70%, and 67.5% after the 1st, 2nd, 3rd, 4th, and 3 months after the 4th PRP injection, respectively. OSS and VAS also significantly decreased. The PVR did not change after repeated PRP injections, FBC increased, frequency, and nocturia were decreased after PRP injections. All patients were free of urinary tract infection or difficulty urinating. The study demonstrated that repeated intravesical injections of autologous PRP can increase bladder capacity and provide IC symptom improvement in patients with IC/BPS refractory to conventional therapy. Autologous PRP injection is safe and effective in selected patients.

LONGITUDINAL INTRAVITAL IMAGING OF TRANSPLANTED MESENCHYMAL STEM CELLS ELUCIDATES THEIR FUNCTIONAL INTEGRATION AND THERAPEUTIC POTENCY IN AN ANIMAL MODEL OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Ryu CM, Yu HY, Lee HY, Shin JH, Lee S, Ju H, Paulson B, Lee S, Kim S, Lim J, Heo J, Hong KS, Chung HM, Kim JK, Shin DM, Choo MS1. Theranostics. 2018 Nov 9;8(20):5610-5624. doi: 10.7150/thno.27559. eCollection 2018. PMID: 30555567

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Mesenchymal stem cell (MSC) therapy may be a novel approach to improve interstitial cystitis/bladder pain syndrome (IC/BPS). Unfortunately, the properties of transplanted stem cells have not been directly analysed in vivo, which hampers elucidation of the therapeutic mechanisms of these cells and optimization of transplantation protocols. Here, the authors monitored the behaviour of multipotent stem cells (M-MSCs) derived from human embryonic stem cells (hESCs) in real time using a novel combination of in vivo confocal endoscopic and microscopic imaging and demonstrated their improved therapeutic potency in a chronic IC/BPS animal model. A novel combination of longitudinal intravital confocal fluorescence imaging and microcystoscopy

in living animals, together with immunofluorescence analysis of bladder tissues, demonstrated that transplanted M-MSCs engrafted following differentiation into multiple cell types and gradually integrated into a perivascular-like structure until 30 days after transplantation. The beneficial effects of transplanted M-MSCs on bladder voiding function and the pathological characteristics of the bladder were efficient and long-lasting due to the stable engraftment of these cells. The authors concluded that this longitudinal bioimaging study of transplanted hESC-derived M-MSCs in living animals reveals their long-term functional integration, which underlies the improved therapeutic effects of these cells on IC/BPS.

EFFICACY AND SAFETY OF NONINVASIVE INTRAVESICAL INSTILLATION OF ONABOTULINUM TOXIN-A FOR OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS.

Lee HY, Doo SW, Yang WJ, Song YS, Sun HY, Nho EJ, Lee B, Kim JH. Urology. 2018 Dec 12. pii: S0090-4295(18)31307-4. doi: 10.1016/j.urology.2018.11.037. [Epub ahead of print] PMID: 30552935

The purpose of this study was to investigate the efficacy and safety of noninvasive intravesical instillation of onabotulinum toxin-A (OBTX-A) through systematic review and meta-analysis. Recently, several studies of noninvasive intravesical instillation of OBTX-A have been published. However, its efficacy is not well validated yet, compared to well-known efficacy of minimally invasive intravesical injection of OBTX-A. Systematic review and meta-analysis were performed to evaluate the efficacy of noninvasive intravesical instillation of OBTX-A in patients with overactive bladder and interstitial cystitis/bladder pain syndrome by measuring outcomes such as urgency episode per 72 hours, frequency per 72 hours, urgency urinary incontinence, voided volume (VV), postvoided residual volume, maximum flow rate, and patient perception of bladder condition. Six trials in 4 studies that compared instillation of OBTX-A and placebo involving 248 patients (121 experimental and 127 controls) were included for final data extraction. Instillation of OBTX-A significantly increased VV, with a mean difference of 38.48 (95% confidence interval: 76.05, 0.92) compared to the placebo group. However, other outcomes showed statistically insignificant changes. Major adverse events were not reported in the group receiving intravesical instillation of OBTX-A. It was concluded that intravesical instillation of OBTX-A showed limited efficacy with improvement of VV for treatment of overactive bladder or interstitial cystitis/bladder pain syndrome. More studies are needed.

AN OVERVIEW OF THE PATHOLOGY AND EMERGING TREATMENT APPROACHES FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Ali A, Ali NS, Malik MB, Sayyed Z, Ahmad MQ. Cureus. 2018 Sep 17;10(9):e3321. doi: 10.7759/cureus.3321. PMID: 30473954

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This article from Pakistan discusses diagnosis and treatment of bladder pain syndrome (BPS), looking at three different guidelines (The European Association of Urology (EAU) Guidelines 2017, the American Urology Association (AUA) Guidelines 2014, and The Royal College of Obstetricians and Gynecologists (RCOG) in conjunction with the British Society of Urogynaecologists (BSUG) Guidelines 2016). All propose different types of therapy, including conservative, medical, and surgical treatment.

RECENT ADVANCES IN IMAGING AND UNDERSTANDING INTERSTITIAL CYSTITIS.

Tyagi P, Moon CH, Janicki J, Kaufman J, Chancellor M, Yoshimura N, Chermansky C. F1000Res. 2018 Nov 9;7. pii: F1000 Faculty Rev-1771. doi: 10.12688/f1000research.16096.1. eCollection 2018. PMID: 30473772

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating condition associated with intense pelvic pain and bladder storage symptoms. Since diagnosis is difficult, prevalence estimates vary with the methodology used. There is also a lack of proven imaging tools and biomarkers to assist in differentiation of IC/BPS from other urinary disorders (overactive bladder, vulvodynia, endometriosis, and prostatitis). Current uncertainty regarding the etiology and pathology of IC/BPS ultimately impacts its timely and successful treatment, as well as hampers future drug development. This review covers recent developments in imaging methods, such as magnetic resonance imaging, that advance the understanding of IC/BPS and guide drug development.

CYSTOSCOPIC EVALUATION AND CLINICAL PHENOTYPING IN INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME.

Acar Ö, Tarcan T. J Turk Ger Gynecol Assoc. 2018 Nov 20. doi: 10.4274/jtgga.2018.0102. [Epub ahead of print] PMID: 30457110

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The authors review, report and discuss the role of cystoscopy and clinical phenotyping in interstitial cystitis/bladder pain syndrome (IC/BPS). For this purpose; a comprehensive nonsystematic review of the relevant literature was conducted. Data regarding the indications for, technique and possible findings of cystoscopy with hydrodistension (HD) and biopsy, as well as clinical implications of cystoscopic information and the concept and utility of clinical phenotyping within the context of IC/BPS were extracted and discussed. IC/BPS is diagnosed based on symptomatic assessment and exclusion of confusable diseases. There is no universal agreement on evaluation and diagnostic algorithm of IC/BPS. The majority of the guidelines recommend cystoscopy with HD and biopsy as a diagnostic prerequisite. Various different techniques have been described for cystoscopy with HD. Cystoscopy with HD and biopsy enables more objective exclusion of confusable diseases. It also provides the basis of European Society for the Study of Interstitial Cystitis classification. IC/BPS patients who demonstrate positive cystoscopic (glomerulations and/or Hunner lesion) and histologic findings have a more severe symptomatology and may benefit from lesion-targeted endoscopic treatments. Clinical phenotyping has been implemented for IC/BPS and may be used for individualized assessment and treatment.

ANALYSIS OF KEY GENES AND MICRO-RNA-MRNA REGULATORY NETWORKS IN WOMEN WITH ULCERATIVE INTERSTITIAL CYSTITIS/PAIN BLADDER SYNDROME.

Liu S, Feng S, Luo D. Int Urogynecol J. 2018 Nov 19. doi: 10.1007/s00192-018-3817-x. [Epub ahead of print] PMID: 30456462

This aim of this study was to better understand ulcerative interstitial cystitis/painful bladder syndrome (IC/PBS) at the molecular level and provide new clues related to diagnosis and treatment. The microarray data set GSE11783, including the mRNA and miRNA profiles of bladder tissue obtained at cystoscopic biopsy from patients with ulcerative IC/PBS (presence of at least one Hunner's ulcer) and normal controls, was downloaded from the GEO (Gene Expression Omnibus) database (National Center for Biotechnology Information). These were evaluated using Greenspring GX and Ingenuity Pathway Analysis (IPA) software. The differentially expressed genes (DEGs) and miRNAs (DEMs) in these two groups were identified. Subsequently, the DEGs were subjected to functional analysis, and a protein-protein interaction (PPI) network was constructed. Finally, the miRNA-mRNA regulatory network was visualized using Cystoscope software. The results of this data mining and integration provide further information on the possible molecular basis of IC/PBS pathogenesis as well as potential biomarkers and therapeutic targets for ulcerative IC/PBS diagnosis and treatment.

EXTRACORPOREAL SHOCKWAVE AGAINST INFLAMMATION MEDIATED BY GPR120 RECEPTOR IN CYCLOPHOSPHAMIDE-INDUCED RAT CYSTITIS MODEL.

Chen YL, Lin YP, Sun CK, Huang TH, Yip HK, Chen YT. Mol Med. 2018 Nov 27;24(1):60. doi: 10.1186/s10020-018-0062-1. PMID: 30482157

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Chen and colleagues tested the hypothesis that extracorporeal shockwave treatment (ESWT) can abolish inflammation and restore urothelial barrier integrity in acute interstitial cystitis by upregulating the fatty acid receptor GPR120. A total of 30 female Sprague-Dawley rats were categorized into five groups: (1) sham-operated rats (SC); (2) rats treated with ESWT (SC + ESWT); (3) rats with bladder irritation using 150 mg/kg cyclophosphamide through intraperitoneal injection; (4) cyclophosphamide rats treated with ESWT (cyclophosphamide+ESWT); (5) cyclophosphamide rats treated with GPR120 agonist (cyclophosphamide+GW9508). Their findings suggest that GPR120, the sensing receptor for ESWT, may be useful in the treatment of interstitial cystitis by inhibiting inflammatory response in bladder cells.

HYPERBARIC OXYGEN SIGNIFICANTLY IMPROVES FREQUENT URINATION, HYPERALGESIA, AND TISSUE DAMAGE IN A MOUSE LONG-LASTING CYSTITIS MODEL INDUCED BY AN INTRAVESICAL INSTILLATION OF HYDROGEN PEROXIDE.

Minami A, Tanaka T, Otoshi T, Kuratsukuri K, Nakatani T. Neurourol Urodyn. 2019 Jan;38(1):97-106. doi: 10.1002/nau.23822. Epub 2018 Nov 9. PMID: 30411813

The aim of this study was to investigate whether hyperbaric oxygen (HBO) is effective for the pathophysiological findings in an IC/PBS-like mouse model induced by intravesical hydrogen peroxide (H2 O2). Six-week-old ICR female mice (N = 16) were divided into four experimental groups: (1) sham control with intravesical vehicle instillation twice, and without subsequent treatment (N = 4); (2) H2 O2 instillation twice, followed by HBO (100% O2 , 2 ATA, 30 min per session) (N = 4); (3) H2 O2 instillation twice, followed by dummy hyperbaric treatment (air, 2ATA, 30 min per session) (N = 4); and (4) H2 O2 instillation twice, followed by no treatment (N = 4). The HBO-treated group showed significant improvement in voiding frequency, tidal voiding volume, and the individual bladder pain threshold. Moreover, HBO markedly suppressed H2 O2 -induced inflammation, edema,

and fibrosis in bladder wall, concomitant with a significant decrease in mRNA expressions of inflammation biomarkers and a significant increase in endothelial nitric oxide synthase expression. HBO also inhibited the expression of transient receptor potential channels induced by H2 O2 instillation. The authors are of the opinion that their results suggest that HBO contributes to elimination of H2 O2 -induced long-lasting cystitis through the repair of chronically inflamed bladder tissue and inhibition of the bladder sensory system.

THE POTENTIAL ROLE OF FOLATE METABOLISM IN INTERSTITIAL CYSTITIS.

Keagy CD. Int Urogynecol J. 2018 Oct 6. doi: 10.1007/s00192-018-3771-7. [Epub ahead of print] PMID: 30293165

The topic of interstitial cystitis (IC), also known as painful bladder syndrome (PBS), and folate/one carbon metabolism has previously been unaddressed in research. This narrative review highlights a potential connection for those with mast cell-related IC and histamine-mediated pain that is explored through four conceptual sections. The first section focuses on the nature of mast cell involvement and histamine-mediated pain in some interstitial cystitis patients. The second section reviews the literature on folate status in wider allergic conditions. The third section addresses the role of folate and methylation in general in histamine excretion. Finally, folate metabolism and vascular function are addressed because of the vascular abnormalities present in some IC bladders.

STRATIFICATION OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME ACCORDING TO THE ANATOMICAL BLADDER CAPACITY.

Mazeaud C, Rigaud J, Levesque A, Madec FX, Le Clerc QC, Wack M, Le Normand L, Riant T, Perrouin-Verbe MA. Urology. 2019 Jan;123:87-92. doi: 10.1016/j.urology.2018.07.046. Epub 2018 Aug 28. PMID: 30170094

The purpose of this study was to compare the data of score symptoms (Interstitial Cystitis Problem Index, Interstitial Cystitis Symptom Index, Pelvic Pain and Urgency/Frequency Patient Symptom Scale and SF-36quality of life), voiding diaries, urodynamic studies, and cystoscopy under general anaesthesia according to the anatomical bladder capacity for patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Single-centre descriptive observational epidemiological study based on retrospective review of 134 patients managed for IC/BPS between January 2010 and December 2016. Patients were stratified into 2 groups according to anatomical bladder capacity measured under general anaesthesia: ≤400 mL and >400 mL. Patients with an anatomical bladder capacity less than 400 of mL presented significantly different results for voiding diary data: higher total frequency especially at night, lower functional bladder capacity and lower maximum bladder capacity; urodynamic data: earlier onset of painful urge during bladder filling, lower maximum bladder filling capacity and lower compliance; and the findings of cystoscopy under general anaesthesia: more Hunner's lesions. These patients presented poorer Pelvic Pain and Urgency/Frequency Patient Symptom Scale symptom scores but associated with better overall quality of life as assessed by SF-36. The anatomical bladder capacity, measured under general anaesthesia, can be used objectively to define 2 distinct groups of patients with symptoms of IC/BPS.

TETRODOTOXIN-SENSITIVE VOLTAGE-GATED SODIUM CHANNELS REGULATE BLADDER AFFERENT RESPONSES TO DISTENSION.

Grundy L, Erickson A, Caldwell A, Garcia-Caraballo S, Rychkov G, Harrington A, Brierley SM. Pain. 2018 Dec;159(12):2573-2584. doi: 10.1097/j.pain.0000000000001368. PMID: 30157135

IC/BPS is a prevalent, chronic bladder disorder that negatively impacts the quality of life for ∼5% of the western population. Hypersensitivity of mechanosensory afferents embedded within the bladder wall is considered a key component in mediating IC/BPS symptoms. Bladder infusion of voltage-gated sodium (Nav) channel blockers show clinical efficacy in treating IC/BPS symptoms; however, the current repertoire of Nav channels expressed by and contributing to bladder afferent function is unknown. The authors used single-cell reverse-transcription polymerase chain reaction of retrogradely traced bladder-innervating dorsal root ganglia (DRG) neurons to determine the expression profile of Nav channels, and patch-clamp recordings to characterise the contribution of tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) Nav channels to total sodium current and neuronal excitability. They determined the TTX-S and TTX-R contribution to mechanosensitive bladder afferent responses ex vivo and spinal dorsal horn activation in vivo. Single-cell reverse-transcription polymerase chain reaction of bladder-innervating DRG neurons revealed significant heterogeneity in Nav channel coexpression patterns. However, TTX-S Nav channels contribute the vast majority of the total sodium current density and regulate the neuronal excitability of bladder DRG neurons. Furthermore, TTX-S Nav channels mediate almost all bladder afferent responses to distension. In vivo intrabladder infusion of TTX significantly reduces activation of dorsal horn neurons within the spinal cord to bladder distension. These data provide the first comprehensive analysis of Nav channel expression within sensory afferents innervating the bladder. The authors also

demonstrate an essential role for TTX-S Nav channel regulation of bladder-innervating DRG neuroexcitability, bladder afferent responses to distension, and nociceptive signalling to the spinal cord.

A WIRELESS CLOSED-LOOP SYSTEM FOR OPTOGENETIC PERIPHERAL NEUROMODULATION.

Mickle AD, Won SM, Noh KN, Yoon J, Meacham KW, Xue Y, McIlvried LA, Copits BA, Samineni VK, Crawford KE, Kim DH, Srivastava P, Kim BH, Min S, Shiuan Y, Yun Y, Payne MA, Zhang J, Jang H, Li Y, Lai HH, Huang Y, Park SI, Gereau RW 4th, Rogers JA. Nature. 2019 Jan;565(7739):361-365. doi: 10.1038/s41586-018-0823-6. Epub 2019 Jan 2. PMID: 30602791

The fast-growing field of bioelectronic medicine aims to develop engineered systems that can relieve clinical conditions by stimulating the peripheral nervous system. This type of technology relies largely on electrical stimulation to provide neuromodulation of organ function or pain. One example is sacral nerve stimulation to treat overactive bladder, urinary incontinence and interstitial cystitis (also known as bladder pain syndrome). Conventional, continuous stimulation protocols, however, can cause discomfort and pain, particularly when treating symptoms that can be intermittent (for example, sudden urinary urgency). Direct physical coupling of electrodes to the nerve can lead to injury and inflammation. Furthermore, typical therapeutic stimulators target large nerve bundles that innervate multiple structures, resulting in a lack of organ specificity. Here the authors introduce a miniaturized bio-optoelectronic implant that avoids these limitations by using (1) an optical stimulation interface that exploits microscale inorganic light-emitting diodes to activate opsins; (2) a soft, high-precision biophysical sensor system that allows continuous measurements of organ function; and (3) a control module and data analytics approach that enables coordinated, closed-loop operation of the system to eliminate pathological behaviours as they occur in real-time. In the example reported here, a soft strain gauge yields real-time information on bladder function in a rat model. Data algorithms identify pathological behaviour, and automated, closed-loop optogenetic neuromodulation of bladder sensory afferents normalizes bladder function. This all-optical scheme for neuromodulation offers chronic stability and the potential to stimulate specific cell types.

ROLE OF NLRP3 INFLAMMASOME IN THE DEVELOPMENT OF BLADDER PAIN SYNDROME INTERSTITIAL CYSTITIS.

Tudrej KB, Piecha T, Kozłowska-Wojciechowska M. Ther Adv Urol. 2019 Jan 8;11:1756287218818030. doi: 10.1177/1756287218818030. eCollection 2019 Jan-Dec. PMID: 30671141

Although it has been proposed that NOD-like receptor protein 3 (NLRP3) inflammasome activation may have an important contribution to the onset of bladder pain syndrome/interstitial cystitis (BPS/IC), as of today there is still insufficient evidence to accept or to reject this hypothesis. However, taking into consideration that inflammasomes have been already shown as important mediators of cyclophosphamide-induced bladder inflammation and that some studies have also revealed human bladder epithelium expresses high levels of NLRP3, such a hypothesis seems to be reasonable. The purpose of this review from Poland is to discuss a scenario that NLRP3 inflammasome is a crucial player in the development of this disease. Identification of a novel mediator of bladder inflammation and pain could lead to emerging new therapeutic strategy and the first causative therapy.

COMPARISON OF VOIDING DYSFUNCTION PHENOTYPES IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN AND MYOFASCIAL PELVIC PAIN: RESULTS FROM THE ICEPAC TRIAL.

Petrikovets A, Veizi IE, Hijaz A, Mahajan ST, Daneshgari F, Buffington C, McCabe P, Chelimsky T. Urology. 2019 Jan 22. pii: S0090-4295(19)30077-9. doi: 10.1016/j.urology.2019.01.015. [Epub ahead of print] Urology. PMID: 30682465

The authors evaluated whether voiding parameters differ in patients with the common overlapping pelvic pain disorders, interstitial cystitis/bladder pain syndrome (IC/BPS) and myofascial pelvic pain (MPP). Uroflow and voiding diary assessed voiding phenotypes in this prospective cohort study (ICEPAC) of women comparing IC/BPS, IC/BPS +MPP, MPP, and healthy control (HC) subjects. This quantitative evaluation of voiding diary and uroflow metrics reveals distinct voiding phenotypes, which can aid in the diagnosis of chronic pelvic pain syndromes. Patients with IC/BPS had more pain with a full bladder despite similar overall pain scores. Peak and average flow rates do not provide any differentiating power between IC/BPS and MPP patients. A longer time to peak flow may favor MPP though this finding needs confirmation.

TERMINOLOGY REPORTS/GUIDELINES

INTERNATIONAL CONTINENCE SOCIETY (ICS) REPORT ON THE TERMINOLOGY FOR NOCTURIA AND NOCTURNAL LOWER URINARY TRACT FUNCTION.

Hashim H, Blanker MH, Drake MJ, Djurhuus JC, Meijlink J, Morris V, Petros P, Wen JG, Wein A. Neurourol Urodyn. 2019 Jan 15. doi: 10.1002/nau.23917. [Epub ahead of print] PMID: 30644584

The terminology for nocturia and nocturnal lower urinary tract function is reviewed and updated in a clinically and practically-based consensus report. This report has been created by a Working Group under the auspices and guidelines of the International Continence Society (ICS) Standardisation Steering Committee (SSC). All relevant definitions were updated on the basis of research over the last 16 years since the publication of the first nocturia standardization document in 2002. An extensive process of 16 rounds of internal and external reviews was involved to examine each definition exhaustively, with decision-making by collective opinion (consensus). A clinically-based terminology report for nocturia and nocturnal lower urinary tract function, encompassing five key definitions divided into signs and symptoms has been developed. Clarity and user-friendliness have been key aims to make it interpretable by healthcare professionals and allied healthcare practitioners involved in the care of individuals with nocturnal lower urinary tract function. A consensus-based terminology report for nocturia and nocturnal lower urinary tract function has been produced to aid clinical practice and research.

THE FUNDAMENTALS OF CHRONIC PELVIC PAIN ASSESSMENT, BASED ON INTERNATIONAL CONTINENCE SOCIETY RECOMMENDATIONS.

Rana N, Drake MJ, Rinko R, Dawson M, Whitmore KE. Neurourol Urodyn. 2018 Aug;37(S6):S32-S38. doi: 10.1002/nau.23776. PMID: 30614061

Chronic pelvic pain (CPP) is defined as a noncyclical pain that has duration of at least 6 months and can lead to decreased quality of life and physical performance. The pain can be attributed to problems in the pelvic organs and/or problems in related systems, and possible psycho-social attributes may contribute to the manifestation. Due to the complex nature, CPP syndromes are multifactorial and the terminology needs to reflect the setting. The current review is a synthesis of key aspects of the recent International Continence Society Standardization for Terminology in CPP Syndromes. Nine domains can be used for a detailed description of CPP. They include four domains specific to the pelvic organs (lower urinary tract, female genital, male genital, gastrointestinal), two related to other sources of pain which may be perceived in the pelvis (musculoskeletal, neurological) and three which may influence the response to the pain or its impact on the individual (psychological, sexual, and comorbidities). For an individual patient with CPP, each domain should be reviewed in terms of symptoms and signs, noting that positive findings could reflect either a primary cause or a secondary consequence. The findings will guide further evaluations and subsequent treatment. The authors present a synthesis of the standard for terminology in CPP syndromes in women and men, which serves as a systematic framework to consider possible sources of pain (pelvic organs or other sources) and the individual responses and impact.

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; Convergences PP Network. Collaborators (19) Pain Med. 2018 Oct 1;19(10):2009-2015. doi: 10.1093/pm/pny030. PMID: 29522121

The 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 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.

LOWER URINARY TRACT

CROSS-OVER DATA SUPPORTING LONG-TERM ANTIBIOTIC TREATMENT IN PATIENTS WITH PAINFUL LOWER URINARY TRACT SYMPTOMS, PYURIA AND NEGATIVE URINALYSIS.

Swamy S, Kupelian AS, Khasriya R, Dharmasena D, Toteva H, Dehpour T, Collins L, Rohn JL, Malone-Lee J. Int Urogynecol J. 2018 Dec 18. doi: 10.1007/s00192-018-3846-5. [Epub ahead of print] PMID: 30564872

This study measured the effects of an unplanned, sudden cessation of treatment in an unselected group of patients with chronic painful LUTS managed with protracted antimicrobial treatment and reported these observational data collected from a cross-over process. The imposition of a guideline resulted in the immediate cessation of antibiotic treatment in a cohort of patients with chronic painful LUTS and microscopic pyuria. Patients were assessed before treatment withdrawal, whilst off treatment, and following reinstatement. Outcome measures included a validated symptom score, microscopic enumeration of urinary white cells and uroepithelial cells, and routine urine culture. These patients had reported treatment-resistant, painful LUTS for a mean of 6.5 years before treatment at this centre. Treatment was stopped in 221 patients. Sixty-six per cent of women were post-menopausal. After unplanned treatment cessation, 199 patients reported deterioration. Eleven patients required hospital care in association with disease recurrence, including acute urinary tract infection (UTI) and urosepsis. Symptom scores increased after cessation and recovered on reinitiating treatment and urothelial cells counts mirrored symptomatic changes. Routine urine culture results did not reflect changes in disease status. These data support the hypothesis that treating painful LUTS associated with pyuria with long-term antimicrobial courses, despite negative urine culture, is effective. The microscopy of fresh unspun, unstained urine to count white cells and epithelial cells offers a valid method of monitoring disease. An unplanned cessation of antibiotic therapy produced a resurgence of symptoms and lower urinary tract inflammation in patients with chronic LUTS, supporting an infective aetiology below the level of routine detection.

VISCERAL PAIN

VISCERAL PAIN.

Grundy L, Erickson A, Brierley SM. Annu Rev Physiol. 2018 Oct 31. doi: 10.1146/annurev-physiol-020518-114525. [Epub ahead of print] PMID: 30379615

Most of us live blissfully unaware of the orchestrated function that our internal organs conduct. When this peace is interrupted, it is often by routine sensations of hunger and urge. However, for >20% of the global population, chronic visceral pain is an unpleasant and often excruciating reminder of the existence of our internal organs. In many cases, there is no obvious underlying pathological cause of the pain. Accordingly, chronic visceral pain is debilitating, reduces the quality of life of sufferers, and has large concomitant socioeconomic costs. In this review, Grundy and colleagues from Australia highlight key mechanisms underlying chronic abdominal and pelvic pain associated with functional and inflammatory disorders of the gastrointestinal and urinary tracts. This includes how the colon and bladder are innervated by specialized subclasses of spinal afferents, how these afferents become sensitized in highly dynamic signalling environments, and the subsequent development of neuroplasticity within visceral pain pathways. They also highlight key contributing factors, including alterations in commensal bacteria, altered mucosal permeability, epithelial interactions with afferent nerves, alterations in immune or stress responses, and cross talk between these two adjacent organs.

CHRONIC PELVIC PAIN/CHRONIC UROLOGIC PAIN/CHRONIC PAIN

PELVIC PAIN IN ADOLESCENTS.

Smorgick N, As-Sanie S. Semin Reprod Med. 2018 Mar;36(2):116-122. doi: 10.1055/s-0038-1676088. Epub 2018 Dec 19. PMID: 30566977

Dysmenorrhea and noncyclic pelvic pain (chronic pelvic pain) are common in adolescents. The evaluation of teens with dysmenorrhea or chronic pelvic pain is aimed to diagnose possible gynecologic conditions (endometriosis, pelvic inflammatory disease, ovarian cysts, and obstruction of the reproductive tract) and nongynecologic conditions (irritable bowel syndrome, interstitial cystitis, and myofascial pain). The management of chronic pelvic pain in adolescents is often more complex than in adult women because both the adolescent and her parents are counselled and addressed, and her long-term emotional and physical health, fertility, and sexuality are considered. Dysmenorrhea and chronic pelvic pain are often associated with depression and anxiety in adolescents. Thus, psychosocial counselling plays an important role in the management of these patients. This review presents a systematic approach to the evaluation and treatment of dysmenorrhea and chronic pelvic pain in adolescents.

ELUCIDATING THE CAUSE OF PELVIC PAIN.

Dubin A. Phys Med Rehabil Clin N Am. 2018 Nov;29(4):777-782. doi: 10.1016/j.pmr.2018.06.011. Epub 2018 Aug 3. PMID: 30293630

Chronic pelvic pain is a common condition. Establishing a diagnosis can be complicated by the interplay between various organ systems, including urologic, gynecologic, gastrointestinal, neurologic, endocrinological, psychological, and musculoskeletal. Frequently, the patient will have seen multiple providers and undergone multiple tests, as well as invasive procedures, before the musculoskeletal system is even considered in the differential diagnosis. Typically, the musculoskeletal and nervous systems become suspected culprits only once all other potential etiologies have been eliminated.

IRRITABLE BOWEL SYNDROME

IS THERE AN APPROPRIATE STRATEGY FOR TREATING CO-MORBID IRRITABLE BOWEL SYNDROME AND BLADDER PAIN SYNDROME?

Dellis AE, Mozaffari S, Nikfar S, Papatsoris AG, Abdollahi M. Expert Opin Pharmacother. 2018 Dec 27:1-4. doi: 10.1080/14656566.2018.1559821. [Epub ahead of print] PMID: 30589379

Two of the most frequent components of chronic pelvic pain syndrome (CPPS) are irritable bowel syndrome (IBS) and bladder pain syndrome (BPS), characterized by considerable overlapping symptoms and pathophysiology. Currently, its management is challenging meaning there is high the demand for novel efficient therapeutics to aid patient care and to tackle the socioeconomic burden of IBS and BPS. As there are presently no sufficient treatment strategies, identifying the mechanisms that result in their main symptoms is the opportunity for developing appropriate therapies. The authors from Greece and Iran explore the potential common treatment strategies for co-morbid IBS and BPS and highlight the absolute need for further research of these deliberating clinical entities. In the future, the authors surmise that the discovery of predictive molecular biomarkers combined with clinical phenotypic categorization will likely allow for more definitive differentiation of patients and thus for better treatment options. Furthermore, it has been suggested that effective IBS treatment strategies would be of great value to co-morbid IBS and BPS therapy.

CHRONIC LINACLOTIDE TREATMENT REDUCES COLITIS-INDUCED NEUROPLASTICITY AND REVERSES PERSISTENT BLADDER DYSFUNCTION.

Grundy L, Harrington AM, Castro J, Garcia-Caraballo S, Deiteren A, Maddern J, Rychkov GY, Ge P, Peters S, Feil R, Miller P, Ghetti 5, Hannig G, Kurtz CB, Silos-Santiago I, Brierley SM. JCI Insight. 2018 Oct 4;3(19). pii: 121841. doi: 10.1172/jci.insight.121841. [Epub ahead of print] PMID: 30282832

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Irritable bowel syndrome (IBS) patients suffer from chronic abdominal pain and extraintestinal comorbidities, including overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome (IC-PBS). Mechanistic understanding of the cause and time course of these comorbid symptoms is lacking, as are clinical treatments. Here, Grundy and colleagues from Australia report that colitis triggers hypersensitivity of colonic afferents, neuroplasticity of spinal cord circuits, and chronic abdominal pain, which persists after inflammation. Subsequently, and in the absence of bladder pathology, colonic hypersensitivity induces persistent hypersensitivity of bladder afferent pathways, resulting in bladder-voiding dysfunction, indicative of OAB/IC-PBS. Daily administration of linaclotide, a guanylate cyclase-C (GC-C) agonist that is restricted to and acts within the gastrointestinal tract, reverses colonic afferent hypersensitivity, reverses neuroplasticity-induced alterations in spinal circuitry, and alleviates chronic abdominal pain in mice. Intriguingly, daily linaclotide administration also reverses persistent bladder afferent hypersensitivity to mechanical and chemical stimuli and restores normal bladder voiding. Linaclotide itself does not inhibit bladder afferents, rather normalization of bladder function by daily linaclotide treatment occurs via indirect inhibition of bladder afferents via reduced nociceptive signalling from the colon. These data support the concepts that cross-organ sensitization underlies the development and maintenance of visceral comorbidities, while pharmaceutical treatments that inhibit colonic afferents may also improve urological symptoms through common sensory pathways.

VULVODYNIA

DIFFERENTIATING OVERLAPPING SYMPTOMS OF VULVODYNIA AND PUDENDAL NEURALGIA.

Ghizzani A, Carta S, Casoni A, Ferrata P, Luisi S, Fortina M. Br J Pain. 2019 Feb;13(1):54-58. doi: 10.1177/2049463718776692. Epub 2018 May 15. PMID: 30671239

Vulvodynia is defined as a chronic vulvar pain non-associated with infectious, inflammatory, neoplastic or hormonal disorders. The authors present a case demonstrating the difficulty in assessing concomitant disease in vulvodynia. A 26-year-old woman presented with persistent vulvodynia. She received oral and topical medications and behavioural interventions to lessen sexual pain and restore sexuality. As sexual pain decreased, the patient reported symptoms previously not mentioned: continuous, intense periclitoral pain and numbness at the perineum when sitting for a long time. These new symptoms suggest the involvement of the peripheral neural system. The physical evaluation confirmed right-side pelvic distortion, and pathological increase in lumbar lordosis, which caused neuralgia radiating to the external genitalia and perineum, overlapping with sexual pain. After diagnosing pudendal neuralgia according to the Nantes criteria, physical treatment and relaxation exercises to de-contract the spine were added to the vulvodynia regimen. During treatment, vulvodynia was sometimes present but never unbearable, allowing satisfactory sex. With physical therapy, the symptoms of pudendal neuralgia decreased. It was concluded that differentiating the presence of two conditions with overlapping symptoms is difficult because the vestibular pain had shadowed pudendal neuralgia symptoms at initial assessment. Syndromes of chronic pain tend to associate with each other and one syndrome may shadow symptoms of the concomitant condition affecting adjacent anatomical areas. Only accurate identification of all the syndromes involved allows the correct treatment to be adopted.

DYSPAREUNIA

THE CLINICAL ANATOMY OF DYSPAREUNIA: A REVIEW.

Alimi Y, Iwanaga J, Oskouian RJ, Loukas M, Tubbs RS. Clin Anat. 2018 Oct;31(7):1013-1017. doi: 10.1002/ca.23250. Epub 2018 Oct 26. PMID: 30113086

Dyspareunia can be described as continuous unremitting or intermittent pain associated with intercourse. It can be classified based on the location of the pain - entry or deep dyspareunia or based on when the pain was first experienced - primary or secondary dyspareunia. There are different causes of dyspareunia and some of the most important causes include the following: vulvodynia, postpartum dyspareunia, endometriosis, inadequate vaginal lubrication or arousal, and other anogenital causes such as hemorrhoids and anal fissures. In this review, the authors' objective is to apply the anatomical knowledge of dyspareunia to patient care, increase awareness among clinicians about the diverse etiology of dyspareunia and ensure that the whole patient, not just the pain of dyspareunia is being treated as the causes of dyspareunia can be due to various pathologies.

LUPUS CYSTITIS

SYSTEMIC LUPUS ERYTHEMATOSUS OF THE URINARY TRACT: FOCUS ON LUPUS CYSTITIS.

Liberski S, Marczak D, Mazur E, Miętkiewicz K, Leis K, Gałązka P. Reumatologia. 2018;56(4):255-258. doi: 10.5114/reum.2018.77978. Epub 2018 Aug 31. PMID: 30237631

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Systemic lupus erythematosus (SLE) frequently manifests as urinary tract disease, most commonly in the form of lupus nephritis. Bladder involvement in the disease course takes a subclinical form and may affect both children and adults. Lupus cystitis can precede SLE diagnosis and may present with very unspecific urinary and digestive tract symptoms or no symptoms at all. The exact mechanism of bladder inflammation in lupus is not fully understood; however, histopathological studies suggest a possible role of immune complex-mediated small vessel vasculitis. Lupus cystitis is a rare SLE manifestation, but poses a challenge for physicians, due to its complex diagnostics and treatment.

SJÖGREN'S SYNDROME

RENAL TUBULAR ACIDOSIS AND HYPOKALEMIC PARALYSIS AS A FIRST PRESENTATION OF PRIMARY SJÖGREN'S SYNDROME.

Sedhain A, Acharya K, Sharma A, Khan A, Adhikari S. Case Rep Nephrol. 2018 Oct 16;2018:9847826. doi: 10.1155/2018/9847826. eCollection 2018. PMID: 30410805

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Sjögren's syndrome is an autoimmune disease with multisystem involvement and varying clinical presentation. We report the clinical course and outcome of a case who presented with repeated episodes of hypokalemia mimicking hypokalemic periodic paralysis and metabolic acidosis, which was later diagnosed as distal renal tubular acidosis secondary to primary Sjögren's syndrome. A 50-year-old lady, who was previously diagnosed as hypokalemic periodic paralysis, presented with generalized weakness and fatigue. She was found to have severe

hypokalemia with normal anion-gap metabolic acidosis consistent with distal renal tubular acidosis. Subsequent evaluation revealed Sjögren's syndrome as the cause of her problems. Kidney biopsy done to evaluate significant proteinuria revealed nonproliferative morphology with patchy acute tubular injury and significant chronic interstitial nephritis. The patient responded well to potassium supplementation and oral prednisolone. Presentation of this case highlights the necessity of close vigilance while managing a case of repeated hypokalemia, which could be one of the rare clinical manifestations of Sjögren's syndrome.

OVERACTIVE BLADDER SYMPTOM BOTHER AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND PRIMARY SJÖGREN SYNDROME.

Pereira E Silva R, Romão VC, Neves M, Garcia R, Oliveira S, Brites J, Ramos FO, Canhão H, Palma Dos Reis J, Pereira da Silva JA, Lopes T. Lupus. 2018 Nov 12:961203318811605. doi: 10.1177/0961203318811605. [Epub ahead of print] PMID: 30419773

The objective of this paper was to assess overactive bladder (OAB) symptom bother (SB) and health-related quality of life (HRQL) among patients with systemic lupus erythematosus (SLE) and primary Sjögren syndrome (pSS). The authors recruited adult SLE and pSS patients and two groups of age- and sex-matched controls. They applied the OAB questionnaire-short form (OABq-SF) to all participants to assess SB and HRQL and collected clinical information relevant for OAB. They compared the OABq-SF scores for SB and HRQL between patients and controls using univariate and multivariate linear regression analysis. They recruited 95 rheumatic patients (68 SLE, 27 pSS) and 231 controls. Compared to controls SLE patients showed higher OABq-SF SB scores and lower HRQL scores. On multivariate analysis SLE was significantly associated with a higher SB score (ß-coefficient 7.13, p = 0.008) and tended to be associated with worse HRQL values. Patients with pSS had numerically higher mean SB scores and lower HRQL scores, although these differences were not statistically significant. Diagnosis of pSS was not significantly associated with SB or HRQL scores on univariate or multivariate analysis. It was concluded that patients with SLE have significantly worse OAB-SB and poorer HRQL compared to controls. A similar trend was seen for pSS patients, especially for SB. These findings suggest that clinically subtle OAB symptoms may be present in rheumatic patients for whom, later on, bladder pain syndrome may occur.
Editorial note: could this possibly have been hypersensitive bladder rather than overactive bladder?

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