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 51, May 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:

UPCOMING MEETINGS

INTERNATIONAL SOCIETY FOR THE STUDY OF BPS/IC (ESSIC) ANNUAL MEETING TO BE HELD IN AMSTERDAM 5-7 DECEMBER 2019

The 2019 annual meeting of ESSIC will be held 5-7 December in the heart of Amsterdam, The Netherlands, at the DoubleTree by Hilton Hotel (Oosterdoksstraat 4, 1011 DK Amsterdam), adjacent to Amsterdam Central Station with a direct rail link to Amsterdam's Schiphol Airport. Meeting chair is Dr Dick Janssen from Radboud University, Nijmegen. The theme of this 2019 international meeting will be the multidisciplinary approach to IC/BPS healthcare. Expert speakers will discuss state of the art clinical diagnosis and treatment, including phenotyping and subtyping in order to achieve optimum treatment per patient and to minimize the current trial and error situation. This not-to-be-missed meeting will also include an update on hot topics, the latest developments and research in this field, physical therapy for these patients, the problems of comorbidities and much more besides.
The ESSIC congress website will provide further information as it becomes available, click here. Add this important opportunity to your diary! If you would like to be added to the ESSIC mailing list for the latest information about the 2019 conference, please contact essic@defoe.it.

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY (GIBS) INDIA

The 4th Annual Meeting on Interstitial Cystitis/Bladder Pain Syndrome (GIBS 2019: "Beyond Horizon") will be held 24th & 25th August 2019, Orchid Hotel Vile Parle, Mumbai, India. The direct link for registration is:
https://gibsociety.com/2019/01/gibs-2019-click-here-to-register/
For further updates, visit the GIBS website : www.gibsociety.com
To access the GIBS e-newsletter, please click: https://gibsociety.com/news-letter/

JOINT EAU/ICS ELUTS 2019 EUROPEAN LOWER URINARY TRACT SYMPTOMS MASTERCLASS MEETING 31/10/2019 TO 2/11/2019, PRAGUE

The 3rd edition of the European Lower Urinary Tract Symptoms (ELUTS19) masterclass meeting will be organised in collaboration with the International Continence Society (ICS). It will be held 31 October – 2 November 2019 at the Clarion Congress Hotel, Freyova 33, Prague 9, Czech Republic. There will be a session on Interstitial Cystitis/Bladder Pain Syndrome on the first day. Further information is available at https://eluts.uroweb.org/.

PATIENT SUPPORT GROUP NEWS

INTERSTITIAL CYSTITIS INDIA (ICI)

The new Interstitial Cystitis India support group is progressing by leaps and bounds. Balaka Basu has kindly sent us an update on their activities:

"We at Interstitial Cystitis India (ICI) are here to help patients suffering from Interstitial Cystitis in India and neighbouring countries. We are a group of IC patients who have come together to help other IC patients suffering from this disease. ICI is a non-profit voluntary organization which promotes knowledge and awareness of interstitial cystitis (IC). We help connect patients with doctors, guide them regarding IC diet and exercises, we provide knowledge and emotional support to patient and their family members and caregivers. Apart from this we are working to get a disability and washroom access card for patients so that they can get easy access to washrooms in public places and also their workplaces. We are currently doing a nationwide survey to create a database of patients. We helped to conduct and took part in a marathon called "racefor7" to raise awareness about rare diseases. This year is an important year for patient advocacy in India and ICI is grateful to have the opportunity to be part of both workshops where decisions were taken to raise issues regarding rare diseases to the authority."

The email address is icindiaorg@gmail.com
Website www.interstitialcystitisinindia.org
Facebook page: Interstitial Cystitis India Forum
Instagram https://t.co/4sFJitNc1X
Twitter (@CystitisIndia): https://twitter.com/CystitisIndia?s=08
YouTube channel : https://www.youtube.com/channel/UC6kTJ2A2-CUGZOLPATGOdyQ

ROMANIA

Dr Andrei Manu-Marin from Romania has informed us that in addition to the interstitial cystitis website for IC patients (http://www.cistita.ro/) there is now also a Romanian association for interstitial cystitis and perineal disorders currently under construction. Take a look at http://perineuperfect.ro/.

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

The 4th World Congress on Abdominal and Pelvic Pain (WCAPP) was held in London at the Hilton London Metropole Hotel and focused on pain from a life course and lifestyle approach. The Abdominal & Pelvic Pain (APP) Special Interest Group of the International Association for the Study of Pain (IASP) was responsible for organizing this 4th WCAPP, 11-12 May 2019, at the Hilton London Metropole Hotel in London in collaboration with Convergences in PelviPerineal Pain (Convergences PP), the International Pelvic Pain Society (IPPS) and the European Society of Neurogastroenterology and Motility (ESNM). Many thanks are due to the organising committee chaired by Katy Vincent together with Sandy Hilton, Qasim Aziz and Frank Tu for a most interesting international programme with new insights into this difficult and complex field of chronic pelvic pain, as well as an update on the chronic visceral pain section proposals for ICD-11. The IPBF and the Pelvic Pain Support Network were represented at this conference. There were around 130 attendees from many different countries and disciplines. This review takes a brief look at some of the highlights. Click here to read more.

GERMAN IC/BPS GUIDELINE NOW AVAILABLE IN AN ENGLISH VERSION

The new German Guideline "Diagnosis and Treatment of Interstitial Cystitis (IC/BPS)", initiated and written by the "Deutsche Gesellschaft für Urologie" (German Society of Urology), is now also available online in an English version.

To access this important guideline, please go to:
https://www.awmf.org/leitlinien/detail/ll/043-050.html
then select: Diagnosis and Treatment of Interstitial Cystitis > weiterlesen
Alternatively, go directly to:
https://www.awmf.org/fileadmin/user_upload/Leitlinien/043_D_Ges_fuer_Urologie/043-050e_S2k_Diagnosis_Treatment_Interstitial_Cystitis_2019-03.pdf

CALENDAR OVERVIEW

2019

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/#

INTERNATIONAL CONTINENCE SOCIETY (ICS) 2019 ANNUAL SCIENTIFIC MEETING
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/

ELUTS 2019 : JOINT EAU/ICS EUROPEAN LOWER URINARY TRACT SYMPTOMS MEETING
31 October – 2 November 2019, Clarion Congress Hotel, Freyova 33, Prague, Czech Republic.
https://eluts.uroweb.org/

SOCIETAL IMPACT OF PAIN: INTERNATIONAL SIP 2019 SYMPOSIUM
7 November 2019, Concert Noble, Rue d'Arlon 82, 1000 Brussels, Belgium
https://www.sip-platform.eu/resources/details/save-the-date-sip-2019-symposium-on-november-7-in-brussels?utm_source=newsletter&utm_medium=email&utm_campaign=SIP+Newsletter+March+2019

CONVERGENCES pp
14-16 November 2019, Madrid, Spain.
contact@convergencespp.com

4TH ANNUAL MEETING OF THE SOCIETY FOR PELVIC RESEARCH (SPR 2019)
16/17 November 2019 Charleston, USA
www.pelvicresearch.com

ESSIC ANNUAL MEETING 2019
5-7 December, DoubleTree by Hilton Hotel, Amsterdam, The Netherlands
https://www.essicmeeting.eu/

2020

EAU 2020
20-24 March 2020, RAI Amsterdam, Europaplein 24, 1078 GZ Amsterdam, The Netherlands
https://eaucongress.uroweb.org/eau20/

18TH WORLD CONGRESS ON PAIN
August 4-8, 2020, Amsterdam, The Netherlands
https://www.iaspworldcongressonpain.org/amsterdam/

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.

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. 2019 Mar;16(3):187-200. doi: 10.1038/s41585-018-0135-5. 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.

QUANTITATIVE ASSESSMENT OF NON-PELVIC PRESSURE PAIN SENSITIVITY IN UROLOGICAL CHRONIC PELVIC PAIN SYNDROME: A MAPP RESEARCH NETWORK STUDY.

Harte SE, Schrepf A, Gallop R, Kruger GH, Lai HH, Sutcliffe S, Halvorson M, Ichesco E, Naliboff BD, Afari N, Harris RE, Farrar JT, Tu F, Landis JR, Clauw DJ; MAPP Research Network. Pain. 2019 Jan 29. doi: 10.1097/j.pain.0000000000001505. [Epub ahead of print] PMID: 31050659

Experimental pain sensitivity was assessed in individuals with urologic chronic pelvic pain syndrome (UCPPS) as part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. A series of computer-controlled pressure stimuli were delivered to the thumbnail bed, an asymptomatic site distant from the area of UCPPS pain that is considered to be indicative of overall body pain threshold. Stimuli were rated according to a standardized magnitude estimation protocol. Pain sensitivity in UCPPS participants was compared to healthy controls and a mixed pain group composed of individuals with other chronic overlapping pain conditions, including fibromyalgia, chronic fatigue, and irritable bowel syndromes. Data from six participating MAPP testing sites were pooled for analysis. UCPPS participants exhibited an intermediate pain sensitivity phenotype: they were less sensitive relative to the mixed pain group but significantly more sensitive than healthy controls. Increased pain sensitivity in UCPPS patients was associated with both higher levels of clinical pain severity and more painful body areas outside the pelvic region. Exploratory analyses in UCPPS participants revealed that pain sensitivity increased during periods of urological symptom flare and that less pressure pain sensitivity at baseline was associated with a greater likelihood of subsequent genitourinary pain improvement one year later. The finding that individuals with UCPPS demonstrate non-pelvic pain hypersensitivity that is related to clinical symptoms suggests that central nervous system mechanisms of pain amplification contribute to UCPPS.

URINARY FUNGI ASSOCIATED WITH URINARY SYMPTOM SEVERITY AMONG WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS).

Nickel JC, Stephens A, Landis JR, Mullins C, van Bokhoven A, Anger JT, Ackerman AL, Kim J, Sutcliffe S, Krol JE, Sen B, Hammond J, Ehrlich GD; Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. World J Urol. 2019 Apr 26. doi: 10.1007/s00345-019-02764-0. [Epub ahead of print] PMID: 31028455

The purpose of this study was to correlate the presence of fungi with symptom flares, pain and urinary severity in a prospective, longitudinal study of women with IC/BPS enrolled in the MAPP Research Network. Flare status, pelvic pain, urinary severity, and midstream urine were collected at baseline, 6 and 12 months from female IC/BPS participants with at least one flare and age-matched participants with no reported flares. Multilocus PCR coupled with electrospray ionization/mass spectrometry was used for identification of fungal species and genus. Associations between "mycobiome" (species/genus presence, relative abundance, Shannon's/Chao1 diversity indices) and current flare status, pain, urinary severity were evaluated using generalized linear mixed models, permutational multivariate analysis of variance, Wilcoxon's rank-sum test. The most specific analysis detected 13 fungal species from 8 genera in 504 urine samples from 202 females. A more sensitive analysis detected 43 genera. No overall differences were observed in fungal species/genus composition or diversity by flare status or pain severity. Longitudinal analyses suggested greater fungal diversity and a significantly greater likelihood of detecting any fungal species in high vs low urinary severity participants. Individual taxa analysis showed a trend toward increased presence and relative abundance of Candida and Malassezia (only identified in 'high' urinary severity phenotype) for high vs low urinary symptoms. This analysis suggests the possibility that greater urinary symptom severity is associated with the urinary mycobiome urine in some females with IC/BPS.

A LONGITUDINAL ANALYSIS OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME FLARES IN THE MAPP RESEARCH NETWORK.

Sutcliffe S, Gallop R, Lai HH, Andriole GL, Bradley CS, Chelimsky G, Chelimsky T, Clemens JQ, Colditz GA, Erickson B, Griffith JW, Kim J, Krieger JN, Labus J, Naliboff BD, Rodriguez LV, Sutherland SE, Taple BJ, Landis JR; MAPP Research Network. BJU Int. 2019 Apr 23. doi: 10.1111/bju.14783. [Epub ahead of print] PMID: 31012513

The purpose of this study was to describe the frequency, intensity, and duration of urologic chronic pelvic pain syndrome symptom exacerbations ("flares"), as well as risk factors for these features, in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping longitudinal study. Current flare status ("urologic or pelvic pain symptoms that are much worse than usual") was ascertained at each bi-weekly assessment. Flare characteristics, including start date, and current intensity of pelvic pain, urgency, and frequency (scales of 0-10), were assessed for participants' first three flares and at three randomly selected times when they did not report a flare. Generalized linear and mixed effects models were used to investigate flare risk factors. Of the 385 eligible participants, 24.2% reported no flares, 22.9% reported 1 flare, 28.3% 2-3 flares, and 24.6% ≥4 flares, up to a maximum of 18 during the 11-month follow-up. Pelvic pain and urologic symptoms were both significantly worse during most flares (60.6%), with considerable within-participant variability (26.2-37.8%). Flare duration varied from 1-150 days (94.3% within-participant variability). In adjusted analyses, flares were more common, symptomatic, and/or longer-lasting in female participants and those with worse non-flare symptoms, bladder hypersensitivity, and chronic overlapping pain conditions. In this foundational flare study, the authors found that pelvic pain and urologic symptom flares were common, but variable in frequency and manifestation. They also identified sub-groups of participants with more frequent, symptomatic, and/or longer-lasting flares for targeted flare management/prevention and further study.

SENSORY SENSITIVITY AND SYMPTOM SEVERITY REPRESENT UNIQUE DIMENSIONS OF CHRONIC PAIN: A MAPP RESEARCH NETWORK STUDY.

Schrepf A, Williams DA, Gallop R, Naliboff BD, Basu N, Kaplan C, Harper DE, Landis JR, Clemens JQ, Strachan E, Griffith JW, Afari N, Hassett A, Pontari MA, Clauw DJ, Harte SE; MAPP Research. Pain. 2018 Oct;159(10):2002-2011. doi: 10.1097/j.pain.0000000000001299. PMID: 29863527

Chronic overlapping pain conditions (COPCs) are characterized by aberrant central nervous system processing of pain. This "centralized pain" phenotype has been described using a large and diverse set of symptom domains, including the spatial distribution of pain, pain intensity, fatigue, mood imbalances, cognitive dysfunction, altered somatic sensations, and hypersensitivity to external stimuli. Here, Schrepf and colleagues used 3 cohorts, including patients with urologic chronic pelvic pain syndrome, a mixed pain cohort with other COPCs, and healthy individuals (total 1039) from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network to explore the factor structure of symptoms of centralized pain. Using exploratory and confirmatory factor analysis, they identified 2 general factors in all 3 cohorts, one characterized by a broad increased sensitivity to internal somatic sensations, environmental stimuli, and diffuse pain, termed Generalized

Sensory Sensitivity, and one characterized by constitutional symptoms-Sleep, Pain, Affect, Cognition, Energy (SPACE). Longitudinal analyses in the urologic chronic pelvic pain syndrome cohort found the same 2-factor structure at month 6 and 1 year, suggesting that the 2-factor structure is reproducible over time. In secondary analyses, they found that Generalized Sensory Sensitivity particularly is associated with the presence of comorbid COPCs, whereas SPACE shows modest associations with measures of disability and urinary symptoms. These factors may represent an important and distinct continuum of symptoms that are indicative of the centralized pain phenotype at high levels. Future research of COPCs should accommodate the measurement of each factor.

A CULTURE-INDEPENDENT ANALYSIS OF THE MICROBIOTA OF FEMALE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PARTICIPANTS IN THE MAPP RESEARCH NETWORK.

Nickel JC, Stephens-Shields AJ, Landis JR, Mullins C, van Bokhoven A, Lucia MS, Henderson JP, Sen B, Krol JE, Ehrlich GD; MAPP Research Network. J Clin Med. 2019 Mar 26;8(3). pii: E415. doi: 10.3390/jcm8030415. PMID: 30917614

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This MAPP Research Network team surveyed urine microbiota of females diagnosed with interstitial cystitis/bladder pain syndrome (IC/BPS) and matched control participants enrolled in the National Institutes of Health (NIH) Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network using the culture-independent methodology. Midstream urine specimens were analyzed with the Plex-ID molecular diagnostic platform that utilizes polymerase chain reaction electrospray ionization time-of-flight mass spectrometry (PCR-ESI-TOF MS) to provide a comprehensive identification of bacterial and select fungal species. IC/BPS and control participants were evaluated for differences (presence, diversity, and abundance) in species and genus. Urine specimens obtained from 181 female IC/BPS and 182 female control participants detected a total of 92 species (41 genera). Mean (SD) species count was 2.49 (1.48) and 2.30 (1.28) among IC/BPS and control participants, respectively. Overall species composition did not significantly differ between IC/BPS and control participants at any level. IC/BPS participants urine trended to an overabundance of Lactobacillus gasseri detected but had a lower prevalence of Corynebacterium compared with control participants. The relative abundance data analysis mirrored the prevalence data differences with no significant differences in most species or genus abundance other than Lactobacillus gasseri and Corynebacterium. No cause and/or effect conclusion can be drawn from this observation, but it suggests that a more comprehensive evaluation (vaginal, bowel, catheterized bladder and/or tissue-based specimens) of the lower urinary tract microbiota in IC/BPS patients is warranted.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

STRENGTH OF ASSOCIATION BETWEEN PENTOSAN POLYSULFATE AND A NOVEL MACULOPATHY.

Hanif AM, Shah R, Yan J, Varghese JS, Patel SA, Cribbs BE, O'Keefe G, Hendrick AM, Shantha JG, Hubbard GB 3rd, Patel PS, Rao P, Yeh S, Jain N. Ophthalmology. 2019 Apr 17. pii: S0161-6420(19)30721-3. doi: 10.1016/j.ophtha.2019.04.024. [Epub ahead of print] PMID: 31004677

In this retrospective study of 219 patients with interstitial cystitis at a single institution, pentosan polysulfate exposure was the sole predictor of a newly described maculopathy. All 14 affected patients had exposure to the drug. The authors report that their findings substantiate a growing concern that this newly described maculopathy represents a medication toxicity, noting that unfortunately, many patients with this condition since the 1996 FDA approval of the drug may have been misdiagnosed with age-related macular degeneration or pattern dystrophy. Bearing in mind that PPS remains the only FDA-approved oral therapy for IC, these findings have significant public health implications. The authors conclude that exposure to PPS, and no other IC-related exposure, is strongly associated with a newly described, vision-threatening macular condition.

ANXIETY SEVERITY DOES NOT INFLUENCE TREATMENT OUTCOMES IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Yu WR, Peng TC, Yeh HL, Kuo HC. Neurourol Urodyn. 2019 May 6. doi: 10.1002/nau.24019. [Epub ahead of print] PMID: 31059599

Patients with interstitial cystitis/bladder pain syndrome (IC/BPS) typically experience anxiety mood status, which is closely connected with physical and psychological status and treatment outcome. This study from Taiwan aimed to evaluate the impact of anxiety severity on therapeutic results in IC/BPS patients. Yu and colleagues prospectively enrolled IC/BPS patients who had previously undergone any kind of treatment for their disease. The primary endpoint was a change in Beck Anxiety Inventory (BAI) scores at 3 months after treatment.

Secondary endpoints included changes in the Global Response Assessment (GRA), O'Leary-Sant symptom score (OSS), and Numerical Rating Scale (NRS) at 3 months after treatment. Urodynamic studies were also compared with the clinical symptom scores. Overall, 85 IC/BPS patients were included in the study. At 3 months, changes in the GRA were not significantly different among the different anxiety severity groups. At baseline, 55 (64.7%) patients had moderate or severe anxiety. They observed a significant positive correlation between the change in BAI and the change in OSS after treatment and a significantly negative correlation with GRA at 3 months. Moreover, improvements in OSS and NRS were associated with the change in GRA. Changes in IC symptoms, but not physiological outcomes, were associated with improved anxiety status after treatment. In addition, the change in BAI was significantly associated with age, baseline BAI, and changes in OSS and GRA after treatment. The authors concluded that baseline anxiety severity does not influence treatment outcomes of IC/BPS. Patients should receive active treatment regardless of their baseline anxiety status.

INTRAVESICAL ADMINISTRATION OF XENOGENEIC PORCINE UROTHELIAL CELLS ATTENUATES CYCLOPHOSPHAMIDE-INDUCED CYSTITIS IN MICE.

Huang CP, Chen CC, Tsai YT, Wu CC, Shyr CR. Cell Transplant. 2019 Jan 24:963689718822773. doi: 10.1177/0963689718822773. [Epub ahead of print] PMID: 30675801

The urothelium of the bladder, renal pelvis, ureter and urethra is maintained through the regulated proliferation and differentiation of urothelial stem and progenitor cells. These cells provide a rich source of a novel urothelial cell therapy approach that could be used to protect, regenerate, repair and restore a damaged urothelium. Urothelial injury caused by physical, chemical and microbial stress is the pathological basis of cystitis (bladder inflammation). The loss of urothelial integrity triggers a series of inflammatory events, resulting in pain and hematuria such as hemorrhagic cystitis and interstitial cystitis. In this study from Taiwan, Huang and colleagues investigate a novel cell therapy strategy to treat cystitis by protecting the urothelium from detrimental stresses through intravesically instilling porcine urothelial cells (PUCs) into the bladder. Using a chemical-induced urothelial injury mouse model of cyclophosphamide (CPP)-induced hemorrhagic cystitis, they determined how the intravesical instillation of PUCs could protect the urothelium from toxic attack from CPP metabolites. They show that intravesical PUC instillation protected the bladder from toxic chemical attack in mice receiving CPP with reduced inflammation and edema. Compared with the vehicle control mice, the proliferative response to chemical injury and apoptotic cells within the bladder tissues were reduced by intravesical PUC treatment. Furthermore, the urothelium integrity was maintained in the intravesical PUC-treated group. After xenogeneic PUCs were introduced and adhered to the mouse urothelium, immunological rejection responses were observed with increased neutrophil infiltration in the lamina propria and higher immune-related gene expression. Their findings provide an innovative and promising intravesical PUC cell therapy for cystitis with urothelial injury by protecting the urothelium from noxious agents.

CLUSTERING OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME.

Lai HH, Thu JHL, Moh FV, Paradis A, Vetter J. J Urol. 2019 Mar 27:101097JU0000000000000250. doi: 10.1097/JU.0000000000000250. [Epub ahead of print] PMID: 30916629

The purpose of this study from the USA was to use clustering analysis of patient symptoms to discover common patient subtypes in females and males with interstitial cystitis/bladder pain syndrome (IC/BPS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Clinical variables included in the k-means clustering included the severity of urologic pain (0-10 numeric rating scale, NRS), urinary urgency (0-10 NRS), frequency (0-10 NRS), non-urologic pain (0-10 NRS), and either a yes or no to each of the six UPOINT domains. 211 UCPPS patients seeking care of their IC/BPS or CP/CPPS were included. K-means clustering algorithm identified 3 clusters of IC/BPS and CP/CPPS patients: (1) a mild pelvic symptom cluster in about 30% of patients; (2) a severe pelvic symptom cluster in about 40% of patients; and (3) a systemic symptom cluster in about 30% of patients. Patients in the systemic cluster were younger (by about 5-7 years), more likely to be female, had the most severe urinary symptoms (urgency, frequency, painful bladder filling), the most severe pelvic pain and non-pelvic pain. They were also more likely to have chronic overlapping pain conditions (COPCs), psychosocial issues (depression, anxiety, somatic symptoms), and poorer quality of life than the two other pelvic clusters. They were not less likely to have Hunner lesions inside the bladder. Symptom-based clustering has identified 3 clusters of IC/BPS and CP/CPPS patients. These patient subtypes have different pelvic and systemic presentation. Patients within the systemic cluster may benefit from interdisciplinary therapies. Future studies to elucidate the differences in pathophysiology among these clusters are needed.

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. 2019 Feb;38(2):703-709. doi: 10.1002/nau.23898. Epub 2018 Dec 21. PMID: 30576011

Current treatments for interstitial cystitis/bladder pain syndrome (IC/BPS) are usually unsuccessful in achieving long-term bladder pain relief and irritable symptom improvement. This study from Taiwan 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.

DIAGNOSIS IN A PRECLINICAL MODEL OF BLADDER PAIN SYNDROME USING A AU/ZNO NANOROD-BASED SERS SUBSTRATE.

Lee S, Namgoong JM, Yu HY, Jue M, Kim G, Jeon S, Shin DM, Choo MS, Joo J, Pack CG, Kim JK. Nanomaterials (Basel). 2019 Feb 7;9(2). pii: E224. doi: 10.3390/nano9020224. PMID: 30736472

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The purpose of this study from Korea was to evaluate the feasibility of ZnO nanorod-based surface enhanced Raman scattering (SERS) diagnostics for disease models, particularly for interstitial cystitis/bladder pain syndrome (IC/BPS). ZnO-based SERS sensing chips were developed and applied to an animal disease model. ZnO nanorods were grown to form nano-sized porous structures and coated with gold to facilitate size-selective biomarker detection. Raman spectra were acquired on a surface enhanced Raman substrate from the urine in a rat model of IC/BPS and analyzed using a statistical analysis method called principal component analysis (PCA). The nanorods grown after the ZnO seed deposition were 30 to 50 nm in diameter and 500 to 600 nm in length. A volume of gold corresponding to a thin film thickness of 100 nm was deposited on the grown nanorod structure. Raman spectroscopic signals were measured in the scattered region for nanometer biomarker detection to indicate IC/BPS. The Raman peaks for the control group and IC/BPS group are observed at 641, 683, 723, 873, 1002, 1030, and 1355 cm-1, which corresponded to various bonding types and compounds. The PCA results are plotted in 2D and 3D. The Raman signals and statistical analyses obtained from the nano-sized biomarkers of intractable inflammatory diseases demonstrate the possibility of an early diagnosis.

CHRONIC LOWER URINARY TRACT SIGNS IN CATS: CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY AND MANAGEMENT.

Westropp JL, Delgado M, Buffington CAT. Vet Clin North Am Small Anim Pract. 2019 Mar;49(2):187-209. doi: 10.1016/j.cvsm.2018.11.001. PMID: 30736893

Cats that present with chronic lower urinary tract signs are often diagnosed with feline idiopathic/interstitial cystitis, a disease syndrome that is more than just a bladder disease and can be associated with a myriad of other co-morbidities. Further, gaining a better understanding of FIC (including the most accurate descriptive terminology) may help researchers, veterinarians, pet food companies, and clients develop and tailor the best possible approaches to management of these cat's unique health and welfare needs.

PROSPECTIVE COMPARATIVE STUDY OF THE EFFECTS OF LIDOCAINE ON URODYNAMIC AND SENSORY PARAMETERS IN BLADDER PAIN SYNDROME.

Offiah I, Dilloughery E, McMahon SB, O'Reilly BA. Int Urogynecol J. 2019 Mar 14. doi: 10.1007/s00192-019-03892-2. [Epub ahead of print] PMID: 30874834

In this study from Ireland, intravesically administered lidocaine is used in patients with bladder pain syndrome (BPS) to test the hypothesis that symptoms have a peripheral versus central mechanism. A cross-sectional study of 24 female patients with BPS was performed. The Central Sensitisation Inventory (CSI) and Kings Health

Questionnaire (KHQ) were completed. Urodynamic assessment was undertaken. Women were asked to report their pain using a numeric rating scale at cystometric capacity and post void. Participants then received an intravesical instillation of either 20 ml of 2% alkalinised lidocaine or 20 ml of normal saline. These solutions were allowed to remain in situ for 20 min and pain score repeated. Urodynamics was repeated. There was a statistically significant volume increase following lidocaine treatment: maximal cystometric capacity (MCC) 192-261 ml post lidocaine. In contrast, there was no significant difference in the saline controls: MCC 190-183 ml. Individual analysis revealed five of 16 lidocaine participants did not respond to lidocaine. These five reported a significantly worse quality of life (QoL) than lidocaine responders and had a tendency towards central sensitivity syndromes. Lidocaine significantly improved MCC in 11/16 participants in this study. These patients appear to have peripherally mediated disease. However, the failure of response to treatment in five participants, as well as their tendency towards central sensitivity syndromes, implies that in this subgroup, a peripheral drive from the bladder is not critical to their pain, suggesting central nervous system (CNS) pathology. This simple and safe test could be used to stratify patients for research or therapeutic trials.

THE EFFECT OF HYDRODISTENSION IN COMBINATION WITH PENTOSAN POLYSULFATE ON TREATMENT OUTCOMES AND COMPLIANCE IN THE TREATMENT OF BLADDER PAIN SYNDROME.

Simsir A, Kizilay F, Ozyurt C. Pak J Med Sci. 2019 Jan-Feb;35(1):189-194. doi: 10.12669/pjms.35.1.172. PMID: 30881421

Free full article, click on title.

In this study from Turkey, Simsir and colleagues investigated the efficacy of bladder hydrodistension combined with pentosan polysulfate (PPS) treatment in interstitial cystitis (IC)/bladder pain syndrome (BPS). 339 patients diagnosed with IC/BPS were categorized into two groups. The first group only received 300 mg/day PPS, while the second group received 300 mg/day PPS following bladder hydrodistension. The results were evaluated at the 3rd, 6th, and 12th months after the first dose using the interstitial cystitis symptom index (ICSI), international cystitis problem index (ICPI), visual analog scale (VAS), and female sexual function index (FSFI). PPS treatment started just after hydrodistension was significantly more effective than PPS treatment alone and combined treatment significantly reduced the rate of non-compliance such that, at the end of the 3rd month, 12.1% patients in Group-1 did not continue their treatment whereas only 1.9% of patients in Group-2 did not continue. The authors concluded that their results indicate that PPS treatment started just after hydrodistension yields significantly better results in terms of both symptom improvement and treatment compliance in patients with IC/BPS.

THE SHORT-TERM EFFICACY OF INTRAVESICAL INSTILLATION OF HYALURONIC ACID TREATMENT FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Akbay E, Çayan S, Kılınç C, Bozlu M, Tek M, Efesoy O. Turk J Urol. 2018 Dec 20;45(2):129-134. doi: 10.5152/tud.2018.35920. PMID: 30875290.

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The aim of this study from Turkey was to evaluate the short-term efficacy of intravesical instillation of hyaluronic acid in patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC). The study included 54 women with BPS/IC who received intravesical instillation of hyaluronic acid treatment (120 mg/50 mL) for 6 weeks. Visual Analogue Scale (VAS), The O'Leary Sant Questionnaire (ICSI/ICPI) forms of the patients were filled by the clinician and the health technician separately before and 3 months after the treatment. Demographic characteristics of the patients were recorded, and effectiveness of the treatment was investigated according to these data. Decrease in mean VAS and mean total scores of ICSI and ICPI was observed after three months of intravesical instillation of hyaluronic acid treatment. In most of the patients, all scores of VAS, ICSI and ICPI improved (minimum: 75.9%, maximum: 94.4%). Mostly the symptoms of nocturia and pollakiuria were seen and treated after the instillation treatment. In conclusion, it was observed that in the short-term follow-up of intravesical instillation of hyaluronic acid treatment, the symptoms highly improved. Also, Turkish versions of ICSI and ICPI forms were reliable and comprehensible.

IS BLADDER BLOOD FLOW AN ETIOLOGIC FACTOR FOR THE BLADDER PAIN SYNDROME?

Özçağlayan Ö, Akgül M, Yazıcı C, Özçağlayan Tİ, Malak A, Doğru Md M. Neurourol Urodyn. 2019 Mar 7. doi: 10.1002/nau.23969. [Epub ahead of print] PMID: 30843277

Bladder pain syndrome (BPS) is a complex disease which causes cognitive, behavioral, sexual, and emotional problems. Vascular factors related to bladder blood supply may be one of the etiologic cause of BPS. This study from Turkey aims to investigate the bladder blood flow and internal iliac artery resistive indices of patients with BPS. A total of 30 female patients with the diagnosis of BPS and 30 female as control group were enrolled in the

study. Bilateral internal iliac arterial blood flow distal to uterine arteries were examined as the primary source of vesical arterial blood supply. Peak systolic velocities, end diastolic velocities, resistive indices, and flow volumes of internal iliac arteries were measured by colour Doppler ultrasonography in a single-blind fashion. The blood flows volume of the right and left internal iliac arteries during empty and full bladder were significantly lower at BPS group compared with control. Although the difference was not significant, the mean resistive index of right and left internal iliac arteries were lower at the control group. Aging decreased the bladder blood volume and both BPS and control group internal iliac artery blood volume decreased by aging. The decrease was more significant at the control group, but the internal iliac artery blood volume was still lower at patients with BPS compared with the control group. It was concluded that arterial blood flow of the bladder was lower at patients with BPS compared with the control group. The decrease in the vascular supply of the bladder might be one of the related factors for the BPS etiology.

RISK FACTORS FOR INTERSTITIAL CYSTITIS IN THE GENERAL POPULATION AND IN INDIVIDUALS WITH DEPRESSION.

Cepeda MS1, Reps J1, Sena AG1, Ochs-Ross R1. Int Neurourol J. 2019 Mar;23(1):40-45. doi: 10.5213/inj.1836182.091. Epub 2019 Mar 31. PMID: 30943693

The purpose of this study from the USA was to identify risk factors for interstitial cystitis (IC), a chronic bladder disorder that may have a significant detrimental impact on quality of life, in the general population and in individuals with depression. This was a comparative study using a US claims database. Adults who had records of a visit to the health system in 2010 or later were included. The outcome was the development of IC within 2 years after the index date. The index date for the general population was the first outpatient visit, and for individuals with depression, it was the date of the diagnosis of depression. IC was defined using the concepts of ulcerative and IC. The authors included all medical conditions present any time prior to the index visit as potential risk factors. They found that the incidence of IC was higher in individuals with depression. Subjects who developed IC had more chronic pain conditions, depression, malaise, and inflammatory disorders.

EFFICACY OF PENTOSAN POLYSULFATE FOR THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: RESULTS OF A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS.

Ophoven AV, Vonde K, Koch W, Auerbach G, Maag KP. Curr Med Res Opin. 2019 Mar 8:1. doi: 10.1080/03007995.2019.1586401. [Epub ahead of print] PMID: 30849922

Among the numerous therapeutic approaches used in the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) only a few have been assessed with a sufficient level of evidence. Safety and efficacy of pentosan polysulfate sodium (PPS) has been shown in several open-label and comparative clinical trials with different populations including two meta-analyses. In the context of the approval procedure of PPS for the treatment of IC/BPS by the European Medicines Agency (EMA), the authors from Germany updated the findings of the previous analyses by incorporating the results of the latest studies. Relevant studies based on a systematic review of PubMed/Medline and the Cochrane Library in June 2018 have been identified. For completeness control, clinical trial registries were also searched. Only randomized, placebo-controlled clinical trials providing sufficient information to estimate at least one relevant effect size measure to compare the efficacy of PPS versus placebo were included in an analysis. Of the studies identified in the literature search 6 randomized placebo-controlled studies met the pre-defined eligibility criteria. Analyses showed no indication of heterogeneity or publication bias. Treatment with PPS led to a statistically significant improvement in the patient's overall response assessment, pain, and urgency. The authors conclude that their meta-analyses confirmed the results of preceding meta-analyses showing that PPS is efficacious compared to placebo in the treatment of bladder pain, urinary urgency and frequency of micturition and thus an evident option for the treatment of IC/BPS symptoms.

MOLECULAR TAXONOMY OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME BASED ON WHOLE TRANSCRIPTOME PROFILING BY NEXT-GENERATION RNA SEQUENCING OF BLADDER MUCOSAL BIOPSIES.

Akiyama Y, Daichi M, Katoh H, Morikawa T, Niimi A, Nomiya A, Sato Y, Kawai T, Goto A, Fujimura T, Fukuhara H, Nakagawa T, Igawa Y, Ishikawa S, Fukayama M, Kume H, Homma Y. J Urol. 2019 Mar 13:101097JU0000000000000234. doi: 10.1097/JU.0000000000000234. [Epub ahead of print] PMID: 30865573

In this study from Japan, systematic characterization of gene expression, inflammation, and neovascularization in interstitial cystitis/bladder pain syndrome was performed to obtain biological evidence supporting diagnosis and classification. RNA obtained from bladder mucosal biopsies from 33 patients with interstitial cystitis/bladder pain syndrome (three subtypes: 12 with Hunner lesions, 11 without Hunner lesions but with glomerulations, and ten with neither Hunner lesions nor glomerulations) and nine controls was sequenced. Differentially expressed

genes for each subtype were searched to identify subtype-specific biological pathways and candidate genes important for pathogenesis. Candidate genes were validated by quantitative polymerase chain reaction and immunohistochemistry. Digital immunohistochemical quantification was performed to assess subepithelial lymphoplasmacytic cell and microvessel density. Relationships between overexpression of candidate genes and symptom severity were explored. Patients with Hunner lesions showed a distinct gene expression profile associated with significant up-regulation of biological processes involving immune responses and infection, and an increase in subepithelial lymphoplasmacytic cell and microvessel densities. Overexpression of two candidate genes, VEGF and BAFF, correlated with symptom severity. Meanwhile, the gene expression profiles of patients with the two subtypes without Hunner lesions were similar to those of controls, and no discernible differences in biological pathways or subepithelial lymphoplasmacytic cell and microvessel densities were detected between these two subtypes and controls. It was concluded that interstitial cystitis/bladder pain syndrome with Hunner lesions exhibits distinct genomic and histological features associated with immune responses and infection. In addition, VEGF and BAFF are potential disease biomarkers/therapeutic targets. This subtype should be considered separate from the syndrome.

PATTERNS AND PREDICTORS OF HUNNER LESION RECURRENCE IN PATIENTS WITH INTERSTITIAL CYSTITIS.

Han JY, Shin JH, Choo MS. Neurourol Urodyn. 2019 Apr 3. doi: 10.1002/nau.23998. [Epub ahead of print] PMID: 30945347

The purpose of this study from Korea was to evaluate the patterns and predictive factors associated with Hunner lesions (HLs) recurrence in patients with interstitial cystitis (IC). This study was a retrospective analysis of data from patients with IC who underwent transurethral resection and cauterization (TUR-C) of HLs between October 2011 and December 2017. Symptoms were evaluated using the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF), O'Leary-Sant Interstitial Cystitis Symptom Index, and Visual Analogue Scale (VAS). Patients attended follow-up visits every 3 months; cystoscopy was performed immediately in patients with aggravated symptoms. Recurrence was defined as a VAS score greater than or equal to 4 and HLs recurrence on cystoscopy. A total of 91 patients were enrolled (25 male, 66 female): median follow-up was 30.6 months. HLs recurrence occurred in 101 sites (53 patients), 21.8% in the previous TUR-C site, 18.8% de novo, and 59.4% at both previous and de novo sites. The recurrence rate was approximately 12.7%, 40%, and 55.2% at 6, 12, and 18 months, respectively. A higher PUF bother score was the only predictive factor of recurrence (odds ratio: 1.142, 95% confidence interval: 1.016-1.284, P = 0.026), with a cut-off value of 7.5 (sensitivity: 67.9%, specificity: 62.5%). In case of late recurrence (>18 months), there was no predictive factor. The HLs recurrence pattern was unpredictable, involving both previous TUR-C and de novo areas. More accurately defining the HLs resection margin may lead to better surgical outcomes but this remains to be proven.

WHAT IS THE ROLE OF SURGERY IN BLADDER PAIN SYNDROME?

Downey AP, Osman NI. Eur Urol Focus. 2019 Mar 20. pii: S2405-4569(19)30084-7. doi: 10.1016/j.euf.2019.03.009. [Epub ahead of print] PMID: 30904339

The role of surgery in the management of bladder pain syndrome is unclear; particularly the optimum surgical approach. Treatment refractory patients should be managed in a multi-disciplinary setting including psychological support. Further prospective studies using validated assessments and clear diagnostic criteria would be useful to guide patient selection.

BLOCKING A2Δ-1 SUBUNIT REDUCES BLADDER HYPERSENSITIVITY AND INFLAMMATION IN A CYSTITIS MOUSE MODEL BY DECREASING NF-KB PATHWAY ACTIVATION.

Boudieu L, Mountadem S, Lashermes A, Meleine M, Ulmann L, Rassendren F, Aissouni Y, Sion B, Carvalho FA, Ardid D. Front Pharmacol. 2019 Feb 26;10:133. doi: 10.3389/fphar.2019.00133. eCollection 2019. PMID: 30863309

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Bladder pain is frequently associated with bladder inflammation, as in conditions like interstitial cystitis (IC), for which current analgesic therapies have limited efficacy. The antinociceptive effect of alpha-2-delta (α2δ) ligands on inflammation-associated visceral pain like that experienced in cystitis has been poorly investigated. To investigate the effect of pregabalin (PGB), an α2δ ligand, Boudieu and colleagues from France evaluated its impact on mechanical hyperalgesia in a mouse model of cystitis induced by cyclophosphamide (CYP). They further studied its effect on inflammation and NF-kB pathway activation. Acute cystitis was induced by intraperitoneal injection of 150 mg kg-1 of CYP in C57Bl/6J male mice. PGB was subcutaneously injected (30 mg kg-1) 3 h after CYP injection. The effect of PGB on CYP-induced mechanical referred hyperalgesia (abdominal Von Frey test), inflammation (organ weight, cytokine production, α2δ subunit level, NF-kB pathway activation)

were assessed 1 h after its injection. In parallel, its effect on cytokine production, α2δ subunit level and NF-kB pathway activation was assessed in vitro on peritoneal exudate cells (PECs) stimulated with LPS. PGB treatment decreased mechanical referred hyperalgesia. Interestingly, it had an anti-inflammatory effect in the cystitis model by reducing pro-inflammatory cytokine production. PGB also inhibited NF-kB pathway activation in the cystitis model and in macrophages stimulated with LPS, in which it blocked the increase in intracellular calcium. This study shows the efficacy of PGB in hypersensitivity and inflammation associated with cystitis. It is therefore of great interest in assessing the benefit of α2δ ligands in patients suffering from cystitis.

SPINAL MACROPHAGE MIGRATION INHIBITORY FACTOR AND HIGH MOBILITY GROUP BOX 1 MEDIATE PERSISTENT BLADDER PAIN.

Ma F, Meyer-Siegler KL, Leng L, Bucala R, Vera PL. Neurosci Lett. 2019 Jan 29;699:54-58. doi: 10.1016/j.neulet.2019.01.046. [Epub ahead of print] PMID: 30708129

Repeated intravesical PAR4 (protease activated receptor 4) activation elicits persistent bladder pain lasting 5 days after the last treatment. Persistent bladder pain was fully reversed by a systemic HMGB1 (high mobility group box 1) inhibitor while a MIF (macrophage migration inhibitory factor) antagonist partly reversed it. Since there is growing evidence that spinal MIF and HMGB1 mediate inflammatory and neuropathic pain, Ma and colleagues from the USA examined whether there were spinal changes occurring during persistent bladder pain that may be responsible for maintaining bladder pain. They found that persistent bladder pain is associated with spinal changes in MIF and HMGB1 levels. Furthermore, spinal treatment with MIF monoclonal antibody and HMGB1 inhibitor temporarily reversed bladder pain. these findings suggest that spinal MIF and HMGB1 participate in persistent bladder pain induced by repeated intravesical PAR4 and may be potential therapeutic targets in chronic bladder pain conditions.

NEUREGULIN-1-ERBB SIGNALING PROMOTES MICROGLIA ACTIVATION CONTRIBUTING TO MECHANICAL ALLODYNIA OF CYCLOPHOSPHAMIDE-INDUCED CYSTITIS.

Chen JL, Zhou X, Ding HL, Zhan HL, Yang F, Li WB, Xie JC, Liu XG, Xu YC, Su MZ, Liu BL, Zhou XF. Neurourol Urodyn. 2019 Apr 15. doi: 10.1002/nau.24005. [Epub ahead of print] PMID: 30989724

Central sensitization plays important roles in cyclophosphamide (CYP)-induced cystitis. In addition, as a visceral pain, CYP-induced chronic pain shares common pathophysiological mechanisms with neuropathic pain. Previous studies demonstrated that neuregulin-1 (Nrg1)-ErbB signalling contributes to neuropathic pain, but whether and how this signalling influences mechanical allodynia in CYP-induced cystitis is unclear. This study from China aimed to determine whether and how Nrg1-ErbB signalling modulates mechanical allodynia in a CYP-induced cystitis rat model. Systemic injection with CYP was used to establish a rat model of bladder pain syndrome/interstitial cystitis (BPS/IC). An irreversible ErbB family receptor inhibitor, PD168393, and exogenous Nrg1 were intrathecally injected to modulate Nrg1-ErbB signalling. Mechanical allodynia in the lower abdomen was assessed with von-Frey filaments using the up-down method. Western blot analysis and immunofluorescence staining were used to measure the expression of Nrg1-ErbB signalling, Iba-1, p-p38, and IL-1β in the L6-S1 spinal dorsal horn (SDH). The authors observed upregulation of Nrg1-ErbB signalling as well as overexpression of the microglia activation markers Iba-1 and p-p38 and the proinflammatory factor, interleukin-1β (IL-1β), in the SDH of the cystitis group. Further, treatment with PD168393 attenuated mechanical allodynia in CYP-induced cystitis and inhibited microglia activation, leading to decreased production of IL-1β. The inhibitor PD168393 reversed the algesic effect of exogenous Nrg1 on the cystitis model. It was concluded that Nrg1-ErbB signalling may promote microglia activation, contributing to mechanical allodynia of CYP-induced cystitis and that this study showed that modulation of Nrg1-ErbB signalling may have therapeutic value for treating pain symptoms in BPS/IC.

FUNCTIONAL EFFECTS OF BLOCKING VEGF/VEGFR2 SIGNALLING IN THE RAT URINARY BLADDER IN ACUTE AND CHRONIC CYP-INDUCED CYSTITIS.

Tooke K, Girard BM, Vizzard MA. Am J Physiol Renal Physiol. 2019 Apr 17. doi: 10.1152/ajprenal.00083.2019. [Epub ahead of print] PMID: 30995112

High expression of vascular endothelial growth factor (VEGF) is associated with immature angiogenesis within the urinary bladder wall and bladder afferent nerve sensitization leading to visceral hyperalgesia and pelvic pain. Research suggests a shift in VEGF alternative splice variant (VEGF-Axxxa, VEGF-Axxxb) expression with several pathologies (e.g., neuropathic pain and inflammation), as well as exhibiting differing effects on pain. Translational studies have also demonstrated increased total VEGF expression in the bladder of women with Interstitial cystitis/Bladder pain syndrome (IC/BPS). In this study, the authors quantified VEGF alternative splice variant expression in LUT tissues under control conditions and with CYP-induced cystitis. Using conscious

cystometry, they further determined the functional effects of VEGFR2 receptor blockade on bladder function using intravesical instillation of a potent and selective VEGFR2 tyrosine kinase inhibitor (Ki8751, 1 mg/kg) in Wistar rats (male and female) with acute and chronic CYP-induced cystitis and controls (no CYP). With VEGFR2 receptor blockade, bladder capacity increased in male and female control rats, as well as male and female rats with acute or chronic CYP-induced cystitis. Void volume also increased in female control rats and female rats with acute or chronic CYP-induced cystitis, as well as in male control rats and male rats with chronic ($p \leq 0.01$) CYP-induced cystitis. These data suggest that VEGF may be a biomarker for IC/BPS and targeting VEGF/VEGFR2 signalling may be an effective treatment.

[COMPARISON OF EFFECTIVENESS AND COMPLICATIONS BETWEEN TWO DIFFERENT METHODS OF AUGMENTATION CYSTOPLASTY].

[Article in Chinese]

Liang C, Zhang WY, Hu H, Wang Q, Fang ZW, Xu KX. Beijing Da Xue Xue Bao Yi Xue Ban. 2019 Apr 18;51(2):293-297. PMID: 30996371

The purpose of this study from Beijing, China was to compare the effectiveness and complications between enterocystoplasty and small intestinal submucosa (SIS) cystoplasty through follow-ups of patients with augmentation cystoplasty in Peking University People's Hospital, offering an alternative approach for future treatment. Retrospective analyses were carried out in 10 patients who underwent enterocystoplasty or SIS cystoplasty in Peking University People's Hospital from November 2011 to December 2016. Clinical data were collected including medical history, surgical procedures, laboratory examinations and complications. Regular follow-ups were then developed. Ten patients were separated into groups of enterocystoplasty and SIS cystoplasty, to compare their outcomes. Ten patients all completed the follow-up interview. Five cases underwent augmentation cystoplasty with sigmoid colon, one with ileum and four with SIS cystoplasty successfully. The mean operative time was (302.0±66.6) min, and blood loss was (167.0±135.0) mL. The outcomes of the group of SIS cystoplasty were better in respects of the time of operation, intestinal function recovery, postoperative hospitalization duration and drainage removal. The average scores of the American Urological Association symptom score (AUASS), overactive bladder syndrome score (OABSS), International Consultation on Incontinence questionnaire short form (ICI-Q-SF), and O'Leary-Sant Questionnaire were all improved in two groups. The authors found that enterocystoplasty and SIS cystoplasty are both effective operations to improve symptoms and protect upper urinary function, with no severe complications. Cystoscopic results showed satisfactory mucosa regeneration after SIS cystoplasty in refractory interstitial cystitis/painful bladder syndrome. But the number of patients included were quite small and the follow-up period was not long enough. Prospective control study of larger number of patients with longer follow-ups are expected to find out the effectiveness and safety of SIS cystoplasty.

SINGLE NUCLEOTIDE POLYMORPHISM ANALYSIS IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Cassão VD, Reis ST, Pimenta R, Lucon M, Leite KRM, Srougi M, Bruschini H. PLoS One. 2019 Apr 11;14(4):e0215201. doi: 10.1371/journal.pone.0215201. eCollection 2019. PMID: 30973927

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Interstitial Cystitis (IC) is a chronic condition diagnosed based on the presence of symptoms, such as suprapubic/pelvic pain, pressure or discomfort in association with urgency and increased urinary frequency. Confusable diseases must be excluded. However, there is no objective test or marker to establish the presence of the disease. Diagnosis and patient management are often difficult, given the poor understanding of IC pathogenesis and its unknown etiology and genetics. As an attempt to find biomarkers related to IC, the authors from Brazil assessed the association between 20 selected single nucleotide polymorphism (SNPs) with IC and pain severity. The purpose of this case-control study was to assess the presence of SNPs in IC patients' blood samples and correlate them with the disease and chronic pain condition. The authors selected 34 female patients with IC diagnosed according to NIDDK criteria and 23 patients in the control group (previously healthy women with only stress urinary incontinence). IC patients were allocated into two groups according to reported chronic pain severity. The polymorphic allele of SNP rs11127292 exhibited a higher frequency in subjects with IC than in controls. The polymorphic allele of SNP rs6311 was more frequent in patients with severe pain (p:0.03). The frequency of the wild-type allele of SNP rs1799971 was higher in patients with mild to moderate pain (p:0.04). The results indicated differences in SNP frequency among subjects, suggesting that SNPs could serve either as a marker of IC or as a marker of pain severity in IC patients. The study showed promising results regarding IC and polymorphism associations. These associations have not been previously reported.

MOTOR CORTICAL NEUROMODULATION OF PELVIC FLOOR MUSCLE TONE: POTENTIAL IMPLICATIONS FOR THE TREATMENT OF UROLOGIC CONDITIONS.

Yani MS, Fenske SJ, Rodriguez LV, Kutch JJ. Neurourol Urodyn. 2019 May 1. doi: 10.1002/nau.24014. [Epub ahead of print] PMID: 31044482

In the human brain, supplementary motor area (SMA) is involved in the control of pelvic floor muscles (PFMs). SMA dysfunction has been implicated in several disorders involving PFMs, including urinary incontinence and urologic pain. Here, Yani and colleagues aimed to provide a proof-of-concept study to demonstrate the feasibility of modulating resting PFM activity (tone) as well as SMA activity with noninvasive stimulation of SMA. They studied six patients (3 women + 3 men) with Urologic Chronic Pelvic Pain Syndrome. Repetitive transcranial magnetic stimulation (rTMS) was applied to SMA immediately after voiding. They tested two rTMS protocols: high-frequency (HF-rTMS) which is generally excitatory, and low-frequency (LF-rTMS) which is generally inhibitory. PFM activity was measured during rTMS using electromyography. Brain activity was measured immediately before and after rTMS using functional magnetic resonance imaging. The rTMS protocols had significantly different effects on resting activity in PFMs: HF-rTMS decreased and LF-rTMS increased pelvic floor tone. SMA activity showed a clear trend toward the expected differential changes: HF-rTMS increased and LF-rTMS decreased SMA activity. The authors interpret the differential effects of rTMS at the brain and muscle level as novel support for an important inhibitory influence of SMA activity on pelvic floor tone after voiding. This preliminary study provides a framework for designing future studies to determine if neuromodulation of SMA could augment therapy for chronic urologic conditions.

TRANSPLANT IMMUNOSUPPRESSIVE DRUGS IN UROLOGY.

Crane A, Eltemamy M, Shoskes D. Transl Androl Urol. 2019 Apr;8(2):109-117. doi: 10.21037/tau.2018.07.12. PMID: 31080770

Immunosuppressive drugs are used in renal transplantation to prevent and treat rejection and their use has traditionally been limited to urologists trained in transplant surgery. However, there are other urologic conditions for which these drugs have proven efficacy. Since transplant surgery has become a small niche subspecialty within urology, most urologists are unfamiliar and uncomfortable with their use. This review focuses on the use of Cyclosporine (CyA), mycophenolate mofetil (MMF), and mammalian target of rapamycin (mTOR) inhibitors in urology outside of solid organ transplant. This includes the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) with CyA as well as the role of CyA in eosinophilic cystitis (EC) and the treatment of retroperitoneal fibrosis (RF) with MMF. Also included is the utilization of mTOR inhibitors in both advanced renal cell carcinoma (RCC) and in patients with tuberous sclerosis complex (TSC) associated angiomyolipoma (AML). Available clinical data on mTOR inhibition in autosomal dominant polycystic kidney disease (ADPKD) is also briefly presented. Specific attention is given to the indications for each agent, the available evidence surrounding their use, and the most common adverse events (AEs) and their subsequent management.

TERMINOLOGY REPORTS/GUIDELINES

VARIATIONS IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (IC) DEFINITIONS, PATHOGENESIS, DIAGNOSTICS AND TREATMENT: A SYSTEMATIC REVIEW AND EVALUATION OF NATIONAL AND INTERNATIONAL GUIDELINES.

Pape J, Falconi G, De Mattos Lourenco TR, Doumouchtsis SK, Betschart C. Int Urogynecol J. 2019 May 9. doi: 10.1007/s00192-019-03970-5. [Epub ahead of print] PMID: 31073635

Interstitial cystitis (IC) and bladder pain syndrome (BPS) are challenging and encompassing hypersensitivity disorders of the lower urinary tract. A variety of national and international guidelines have been published including guidance on nomenclature, definitions, etiopathology, diagnostics and treatment. A lack of universally established clinical guidance is apparent. The aim of this review is to evaluate key guidelines on this area of practice, identify variations, compare their recommendations and grade them using AGREE II. Literature searches were performed using the PUBMED and CINAHL database from January 1, 1983, to December 1, 2018, referring to the search strategy of AUA. Ten national and international guidelines were included in the analysis and assessed with the updated AGREE II. Symptoms congruent in all guidelines are: pain, pressure, discomfort and frequency, urgency and nocturia. Urinalysis is a prerequisite for diagnostics, cystoscopy for most and urodynamics not part of the routine assessment. Treatment options are recommended stepwise. The highest level of evidence and consensus was identified for oral therapies. Nine guidelines had an overall quality score ≥ 50% and three scored ≥ 70% (AUA, GG, RCOG). The authors concluded that the guidelines are congruent in symptom reporting, quite congruent in diagnostics and vary to a high degree in treatment recommendations.

The complexity of BPS and emerging evidence indicate the need for regular updating of the guidelines and a wider consensus.

THE IASP CLASSIFICATION OF CHRONIC PAIN FOR ICD-11: CHRONIC SECONDARY VISCERAL PAIN.

Aziz Q, Giamberardino MA, Barke A, Korwisi B, Baranowski AP, Wesselmann U, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain. Pain. 2019 Jan;160(1):69-76. doi: 10.1097/j.pain.0000000000001362. PMID: 30586073

Chronic visceral pain is a frequent and disabling condition. Despite high prevalence and impact, chronic visceral pain is not represented in ICD-10 in a systematic manner. Chronic secondary visceral pain is chronic pain secondary to an underlying condition originating from internal organs of the head or neck region or of the thoracic, abdominal, or pelvic regions. It can be caused by persistent inflammation, by vascular mechanisms or by mechanical factors. The pain intensity is not necessarily fully correlated with the disease process, and the chronic visceral pain may persist beyond successful treatment of the underlying cause. This article describes how a new classification of chronic secondary visceral pain is intended to facilitate the diagnostic process and to enable the collection of accurate epidemiological data. Furthermore, it is hoped that the new classification will improve the tailoring of patient-centered pain treatment of chronic secondary visceral pain and stimulate research. Chronic secondary visceral pain should be distinguished from chronic primary visceral pain states that are considered diseases in their own right.

LOWER URINARY TRACT

HYPERSENSITIVE OR DETRUSOR OVERACTIVITY: WHICH IS ASSOCIATED WITH FILLING SYMPTOMS IN FEMALE BLADDER OUTLET OBSTRUCTED PATIENTS?

Zhang J, Cao M, Chen Y, Liang W, Liang Y. Urol J. 2019 Mar 18. doi: 10.22037/uj.v0i0.4362. [Epub ahead of print] PMID: 30882167

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The purpose of this study from China was to investigate and compare detrusor overactivity (DO) and bladder filling sensation characteristics in female bladder outlet obstruction (FBOO) patients with or without overactive bladder (OAB) symptoms. One hundred fifty-seven FBOO patients with urodynamic testing were recruited. Patients who showed urinary urgency, with or without urinary frequency, and urge incontinence were considered to have OAB. The detrusor overactivity (DO) and bladder filling sensation measures including first sensation (FSF), first desire to void (FDV) and strong desire to void (SDV) during filling cystometry were recorded. The associations between urodynamic variables and OAB symptoms were analysed. FBOO patients had a high incidence (79%) of OAB. FBOO patients with OAB symptoms had significantly younger age, higher incidence of DO and lower bladder volumes of FSF, FDV and SDV compared to patients without OAB. In multivariate analyses, both DO and lower bladder volumes at FDV and SDV were still independently associated with OAB, after adjustment for age and other confounding factors. It was concluded that FBOO patients had a high incidence of OAB. Not only DO but also bladder hypersensitivity were independently associated with OAB symptoms in FBOO patients.

THE SEVERITY AND DISTRIBUTION OF NON-UROLOGIC PAIN AND UROGENITAL PAIN IN OVERACTIVE BLADDER ARE INTERMEDIATE BETWEEN INTERSTITIAL CYSTITIS AND CONTROLS.

Thu JHL, Vetter J, Lai HH. Urology. 2019 Apr 26. pii: S0090-4295(19)30373-5. doi: 10.1016/j.urology.2019.03.030. [Epub ahead of print] PMID: 31034917

The purpose of this study was on the one hand to compare the severity and distribution of non-urologic and urogenital pain between OAB, IC/BPS and controls, and on the other hand to examine the relationships between the severity of urogenital pain and severity of urinary symptoms among patients with OAB. 51 OAB patients, 27 IC/BPS patients, and 30 controls were recruited. Non-urologic pain was assessed using a whole-body map and Brief Pain Inventory. Urologic pain was assessed using the Interstitial Cystitis Symptom and Problem indexes, Genitourinary Pain Index, and 0-10 pain scale. Urogenital pain was assessed using a genital map, and report of pain related to bladder filling and urination. Among OAB patients, 6% reported pelvic pain only while 28% reported pelvic pain and beyond. 18% reported widespread pain. The distribution of non-urologic pain and urogenital pain in OAB patients was intermediate between IC/BPS and controls. The intensity of pain reported by OAB patients was intermediate between controls and IC/BPS. Among OAB patients, the pain severity (GUPI-pain, ICSI-pain, ICPI-pain) were positively correlated with urinary severity. OAB patients with pelvic pain have worse urinary symptoms and psychosocial health (anxiety, depression) compared to OAB patients without pelvic pain. It was concluded that a subset of OAB patients have pain in and/or outside the pelvis. The intensity and

distribution of pain in OAB was intermediate between IC/BPS and controls. Systemic processes such as central sensitization should be examined in this population.

SYMPTOMATIC OVERLAP IN OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: DEVELOPMENT OF A NEW ALGORITHM.

Ackerman AL, Lai HH, Parameshwar PS, Eilber KS, Anger JT. BJU Int. 2019 Apr;123(4):682-693. doi: 10.1111/bju.14568. Epub 2018 Oct 24. PMID: 30253040

This study addressed challenges in the diagnosis and classification of storage lower urinary tract symptoms (LUTS). Ackerman and colleagues sought to define the fundamental features of overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS), two conditions with considerable symptomatic overlap. They note that through retrospective comparison of self-reported symptoms in women with a range of clinical presentations and symptom severities, they have attempted to refine the diagnostic features of OAB and IC/BPS and to develop a novel clinical nomogram to improve patient screening and classification. They performed a univariate analysis comparing responses to the female Genitourinary Pain Index (fGUPI), the OAB Questionnaire and O'Leary-Sant Indices (the Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index) in an initial cohort of 50 patients with OAB, patients with IC/BPS and control subjects. Only eight questions differed significantly between the IC/BPS and OAB groups; they used five unique questions and three measuring bother to generate a novel composite scoring system and nomogram that included urgency incontinence, bladder pain and symptomatic bother domains to differentiate these populations, which was validated in a second cohort of 150 patients. The addition of a self-reported bother index resulted in the creation of a diagnostic algorithm to identify and classify LUTS clusters across the total population. While all validated questionnaires could distinguish between controls and patients with storage LUTS, no combined symptom scores differed significantly between the IC/BPS and OAB groups. These results are reflective of the prevalence of significant bladder pain (35%) in patients with OAB and the presence of urge incontinence (25%) in patients with IC/BPS. Only the fGUPI pain domain scores differed between patients in the OAB and IC/BPS groups, but it was not accurate enough for diagnostic evaluation (68% accuracy). Our composite scores and nomogram gave a much-improved diagnostic accuracy (94%) and demonstrated utility as a screening tool to identify storage LUTS in patients presenting for unrelated complaints, e.g. microhaematuria. There is significant overlap of urinary tract symptoms between OAB and IC/BPS. The authors present a novel algorithm that provides a binary output capable of guiding clinical diagnosis. Future studies aimed at assessing the diagnostic value of novel classification schemes that address symptoms rather than specific diagnoses may improve patient prognosis.

MICROBIOME

THE URINARY MICROBIOME AND ANTICANCER IMMUNOTHERAPY: THE POTENTIALLY HIDDEN ROLE OF UNCULTURABLE MICROBES.

Bersanelli M, Santoni M, Ticinesi A, Buti S. Target Oncol. 2019 May 9. doi: 10.1007/s11523-019-00643-7. [Epub ahead of print] PMID: 31073691

Several urinary disorders, including overactive bladder, urinary incontinence, and interstitial cystitis, are often characterized by negative urine cultures. The application of metagenomics (i.e., 16S rRNA microbial profiling or whole-genome shotgun sequencing) to urine samples has enabled the identification of previously undetected bacteria, contributing to the discovery and characterization of the urinary microbiome. The most frequent species isolated are Lactobacillus (15%), Corynebacterium (14.2%), Streptococcus (11.9%), Actinomyces (6.9%), and Staphylococcus (6.9%). Although several studies are emerging in this context, the role of urinary microbiota in the pathogenesis of infections and in tumor carcinogenesis remains unclear. Furthermore, data on the activity of gut microbiota in modulating sensitivity to immune checkpoint inhibitors in advanced cancer patients suggest that the influence of urinary microbiota on tumor response to anticancer therapy should also be investigated. Moreover, its possible relationship with tumor mutational burden, which is in turn correlated with response to immunotherapy, should be the focus of future studies. Of note, the effect of antibiotics on this complex scenario seems to deserve careful consideration.

UROBIOME UPDATES: ADVANCES IN URINARY MICROBIOME RESEARCH.

Wolfe AJ, Brubaker L. Nat Rev Urol. 2018 Dec 3. doi: 10.1038/s41585-018-0127-5. [Epub ahead of print] PMID: 30510275

Since the discovery and confirmation of the human urobiome, highly influential studies to characterize this microbial community and understand how it relates to human health and disease have been undertaken. Technological advances will improve information about the status of the urobiome for clinicians.

THE VAGINAL AND URINARY MICROBIOMES IN PREMENOPAUSAL WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AS COMPARED TO UNAFFECTED CONTROLS: A PILOT CROSS-SECTIONAL STUDY.

Meriwether KV, Lei Z, Singh R, Gaskins J, Hobson DTG, Jala V. Front Cell Infect Microbiol. 2019 Apr 8;9:92. doi: 10.3389/fcimb.2019.00092. eCollection 2019. PMID: 31024861

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Interstitial cystitis/bladder pain syndrome (ICBPS) may be related to an altered genitourinary microbiome. The aim of this study was to compare the vaginal and urinary microbiomes between premenopausal women with ICBPS and unaffected controls. This cross-sectional study screened premenopausal women with an O'Leary-Sant questionnaire (ICBPS if score ≥6 on either index; controls <6 on both). Women completed questionnaires on health characteristics, pelvic floor symptoms (OABq, PFDI-20), body image (mBIS), and sexual function (PISQ-IR). Bacterial genomic DNA was isolated from vaginal and clean-catch urinary specimens; the bacterial 16 rRNA gene was sequenced and analyzed using the QIIME pipeline. Lactobacilli was the most abundant genus in both cohorts, and anaerobic or fastidious predominance was similar between groups. For both the urine and vagina specimens, Chao1 and Simpson indices were similar between ICBPS and unaffected women. A significant correlation existed between the urinary and vaginal Simpson indices in ICBPS women, but not in unaffected women. Premenopausal women with ICBPS, despite worsened socioeconomic indicators and pelvic floor function, were not found to have significantly different urinary and vaginal microbiomes compared to women without ICBPS.

FEMALE LOWER URINARY TRACT MICROBIOTA DO NOT ASSOCIATE WITH IC/PBS SYMPTOMS: A CASE-CONTROLLED STUDY.

Bresler L, Price TK, Hilt EE, Joyce C, Fitzgerald CM, Wolfe AJ. Int Urogynecol J. 2019 Apr 16. doi: 10.1007/s00192-019-03942-9. [Epub ahead of print] PMID: 30993388

Bresler and colleagues from the USA note that the current etiology of interstitial cystitis/painful bladder syndrome (IC/PBS) is poorly understood and multifactorial. Recent studies suggest the female urinary microbiota (FUM) contribute to IC/PBS symptoms. This study was designed to determine if the FUM, analyzed using mid-stream voided urine samples, differs between IC/PBS patients and controls. This prospective case-controlled study compared the voided FUM of women with symptoms of urinary frequency, urgency, and bladder pain for > 6 months with the voided FUM of healthy female controls without pain. Bacterial identification was performed using 16S rRNA gene sequencing and EQUC, a validated enhanced urine culture approach. Urotype was defined by a genus present at > 50% relative abundance. If no genus was present above this threshold, the urotype was classified as 'mixed.' Group comparisons were performed for urotype and diversity measures. A mid-stream voided specimen was collected from 21 IC/PBS patients and 20 asymptomatic controls. The two groups had similar demographics. Urotypes did not differ between cohorts as assessed by either EQUC or 16S rRNA gene sequencing. The authors detected no significant differences between cohorts by alpha diversity. Cohorts also were not distinct using principle component analysis or hierarchical clustering. Detection by EQUC of bacterial species considered uropathogenic was high in both cohorts, but detection of these uropathogenic species did not differ between groups. It was concluded that enhanced culture and DNA sequencing methods provide evidence that IC/PBS symptoms may not be related to differences in the FUM, at least not its bacterial components. Future larger studies are needed to confirm this preliminary finding.

KETAMINE CYSTITIS

KETAMINE-INDUCED BLADDER DYSFUNCTION IS ASSOCIATED WITH EXTRACELLULAR MATRIX ACCUMULATION AND IMPAIRMENT OF CALCIUM SIGNALING IN A MOUSE MODEL.

Shen CH, Wang ST, Wang SC, Lin SM, Lin LC, Dai YC, Liu YW. Mol Med Rep. 2019 Jan 29. doi: 10.3892/mmr.2019.9907. [Epub ahead of print] PMID: 30720140

Due to the rising abuse of ketamine usage in recent years, ketamine-induced urinary tract syndrome has received increasing attention. The present study from Taiwan aimed to investigate the molecular mechanism underlying ketamine-associated cystitis in a mouse model. Female C57BL/6 mice were randomly divided into two groups: One group was treated with ketamine (100 mg/kg/day of ketamine for 20 weeks), whereas, the control group was treated with saline solution. In each group, micturition frequency and urine volume were examined to assess urinary voiding functions. Mouse bladders were extracted and samples were examined for pathological and morphological alterations using hematoxylin and eosin staining, Masson's trichrome staining

and scanning electron microscopy. A cDNA microarray was conducted to investigate the differentially expressed genes following treatment with ketamine. The results suggested that bladder hyperactivity increased in the mice treated with ketamine. Furthermore, treatment with ketamine resulted in a smooth apical epithelial surface, subepithelial vascular congestion and lymphoplasmacytic aggregation. Microarray analysis identified a number of genes involved in extracellular matrix accumulation, which is associated with connective tissue fibrosis progression, and in calcium signalling regulation, that was associated with urinary bladder smooth muscle contraction. Collectively, the present results suggested that these differentially expressed genes may serve critical roles in ketamine-induced alterations of micturition patterns and urothelial pathogenesis. Furthermore, the present findings may provide a theoretical basis for the development of effective therapies to treat ketamine-induced urinary tract syndrome.

A SURVEY FOR KETAMINE ABUSE AND ITS RELATION TO THE LOWER URINARY TRACT SYMPTOMS IN TAIWAN.
Li CC, Wu ST, Cha TL, Sun GH, Yu DS, Meng E. Sci Rep. 2019 May 10;9(1):7240. doi: 10.1038/s41598-019-43746-x. PMID: 31076629
Free full text, click on title.
Li and colleagues from Taiwan aimed to explore the correlation between ketamine abuse and lower urinary tract symptoms (LUTS) and epidemiology of ketamine cystitis. Questionnaire records of ketamine abusers, such as sex, age, and details of using ketamine, including consumption method, amount, duration of ketamine use, and LUTS, were obtained from two private rehabilitation centers. They analyzed these factors and established a severity forecasting module. One hundred and six ketamine abusers completed the questionnaires. All symptom scores were positively correlated with the duration of ketamine abuse. Ketamine snorting was significantly correlated with all symptom scores compared to smoking. Hydrodistention, intravesical hyaluronic acid instillation, intravesical injection with botulinum toxin, and hyperbaric-oxygen therapy showed better effect than oral treatment. Ketamine can induce severe storage symptoms, such as frequency or nocturia depending on the duration of abuse. Ketamine snorting may cause worse LUTS than smoking. Combining ketamine and other substances may exacerbate LUTS. Intravesical therapy may lead to better outcomes than oral treatment.

VISCERAL PAIN

PERSISTENT AUTONOMIC DYSFUNCTION AND BLADDER SENSITIVITY IN PRIMARY DYSMENORRHEA.
Oladosu FA, Hellman KM, Ham PJ, Kochlefl LE, Datta A, Garrison EF, Steiner ND, Roth GE, Tu FF. Sci Rep. 2019 Feb 18;9(1):2194. doi: 10.1038/s41598-019-38545-3. PMID: 30778114
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Menstrual pain, also known as dysmenorrhea, is a leading risk factor for bladder pain syndrome (BPS). A better understanding of the mechanisms that predispose dysmenorrheic women to BPS is needed to develop prophylactic strategies. Abnormal autonomic regulation, a key factor implicated in BPS and chronic pain, has not been adequately characterized in women with dysmenorrhea. In this study from the USA, Oladosu and colleagues examined heart rate variability (HRV) in healthy, dysmenorrheic, and BPS participants in their luteal phase across a bladder-filling task. Both dysmenorrheic and BPS participants reported increased bladder pain sensitivity when compared to controls. Similarly, dysmenorrheic and BPS participants had increased heart rate, increased diastolic blood pressure, and reduced HRV when compared to controls. Dysmenorrheic participants also exhibited little change in heart rate between maximum bladder capacity and after micturition when compared to controls. The findings demonstrate menstrual pain's association with abnormal autonomic activity and bladder sensitivity, even two weeks after menses. According to the authors, their findings of autonomic dysfunction in both early episodic and chronic visceral pain states point to an urgent need to elucidate the development of such imbalance, perhaps beginning in adolescence.

CHRONIC PELVIC PAIN/CHRONIC UROLOGIC PAIN/CHRONIC PAIN

SACRAL NEUROMODULATION TREATING CHRONIC PELVIC PAIN: A META-ANALYSIS AND SYSTEMATIC REVIEW OF THE LITERATURE.
Mahran A, Baaklini G, Hassani D, Abolella HA, Safwat AS, Neudecker M, Hijaz AK, Mahajan ST, Siegel SW, El-Nashar SA. Int Urogynecol J. 2019 Mar 14. doi: 10.1007/s00192-019-03898-w. [Epub ahead of print] PMID: 30874835
Sacral neuromodulation (SNM) is gaining popularity as a treatment option for chronic pelvic pain (CPP). In this study from the USA and Egypt, the authors hypothesized that SNM is effective in improving CPP. A systematic search was conducted through September 2018. Peer-reviewed studies using pre- and postpain intensity scores

were selected. The primary outcome was pain improvement on a 10-point visual analog scale (VAS) (adjusted or de novo) in patients with CPP. Secondary outcomes included comparing SNM approaches and etiologies and evaluating lower urinary tract symptoms (LUTS). Fourteen of 2175 studies, evaluating 210 patients, were eligible for further analysis. The overall VAS pain score improvement was significant. Regarding SNM approach, both standard and caudal approaches had significant reduction in pain scores. While significant improvement in pain was observed both in patients with and without interstitial cystitis/bladder pain syndrome (IC/BPS), the observed improvement was lower in patients with IC/BPS. SNM was effective in treating voiding symptoms (frequency, urgency, nocturia) associated with IC/BPS. It was concluded that SNM is an effective therapy for CPP in both IC/BSP and non-IC/BSP patients, with better results in non-IC/BSP patients. Outcomes of the antegrade caudal approach were comparable with the standard retrograde approach.

COMORBIDITIES

THE EMERGING ROLE OF EPIGENETICS IN HUMAN AUTOIMMUNE DISORDERS.

Mazzone R, Zwergel C, Artico M, Taurone S, Ralli M, Greco A, Mai A. Clin Epigenetics. 2019 Feb 26;11(1):34. doi: 10.1186/s13148-019-0632-2. PMID: 30808407

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Epigenetic pathways play a pivotal role in the development and function of the immune system. Over the last decade, a growing body of studies has been published out seeking to explain a correlation between epigenetic modifications and the development of autoimmune disorders. Epigenetic changes, such as DNA methylation, histone modifications, and noncoding RNAs, are involved in the pathogenesis of autoimmune diseases mainly by regulating gene expression. This paper from Italy reviews the importance of epigenetic alterations during the development of the most prevalent human autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjogren's syndrome (SS), autoimmune thyroid diseases (AITD), and type 1 diabetes (T1D), aiming to provide new insights in the pathogenesis of autoimmune diseases and the possibility to develop novel therapeutic approaches targeting the epigenome.

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. 2019 Mar;20(4):411-414. doi: 10.1080/14656566.2018.1559821. Epub 2018 Dec 27. 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 insufficient treatment strategies, identifying the mechanisms that result in their main symptoms is the opportunity for developing appropriate therapies. In this study from Greece and Iran, the authors 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.

AUTONOMIC NEUROPHYSIOLOGIC IMPLICATIONS OF DISORDERS COMORBID WITH BLADDER PAIN SYNDROME VS MYOFASCIAL PELVIC PAIN.

Chelimsky GG, Yang S, Sanses T, Tatsuoka C, Buffington CAT, Janata J, McCabe P, Dombroski MA, Ialacci S, Hijaz A, Mahajan S, Zolnoun D, Chelimsky TC. Neurourol Urodyn. 2019 Apr 4. doi: 10.1002/nau.23995. [Epub ahead of print] PMID: 30945780

The neuropathophysiology of a debilitating chronic urologic pain condition, bladder pain syndrome (BPS), remains unknown. Chelimsky and colleagues from the USA note that their recent data suggests withdrawal of cardiovagal modulation in subjects with BPS, in contrast to sympathetic nervous system dysfunction in another chronic pelvic pain syndrome, myofascial pelvic pain (MPP). They evaluated whether comorbid disorders differentially associated with BPS vs MPP shed additional light on these autonomic differences. They compared the presence and relative time of onset of 27 other medical conditions in women with BPS, MPP, both syndromes, and healthy subjects. Analysis included an adjustment for multiple comparisons. Among 107 female subjects (BPS alone = 32; BPS with MPP = 36; MPP alone = 9; healthy controls = 30), comorbidities differentially associated with BPS included irritable bowel syndrome (IBS), dyspepsia, and chronic nausea, whereas those

associated with MPP included migraine headache and dyspepsia, consistent with the distinct autonomic neurophysiologic signatures of the two disorders. PTSD (earliest), anxiety, depression, migraine headache, fibromyalgia, chronic fatigue, and IBS usually preceded BPS or MPP. PTSD and the presence of both pelvic pain disorders in the same subject correlated with significantly increased comorbid burden. According to the authors, this study suggests a distinct pattern of comorbid conditions in women with BPS. These findings further support their hypothesis of primary vagal defect in BPS as compared with primary sympathetic defect in MPP, suggesting a new model for these chronic pelvic pain syndromes. Chronologically, PTSD, migraine, dysmenorrhea, and IBS occurred early, supporting a role for PTSD or its trigger in the pathophysiology of chronic pelvic pain.

FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND MULTIPLE CHEMICAL SENSITIVITY: ILLNESS EXPERIENCES.

Alameda Cuesta A, Pazos Garciandía A, Oter Quintana C, Losa Iglesias ME. Clin Nurs Res. 2019 Mar 27:1054773819838679. doi: 10.1177/1054773819838679. [Epub ahead of print] PMID: 30917692

Fibromyalgia, chronic fatigue syndrome/myalgic encephalomyelitis, and multiple chemical sensitivity can be considered contested illnesses. The questioning of the status of these conditions as real diseases reduces feelings of legitimacy in those affected. The purpose of this study was to analyze subjectivity construction processes in people with these diseases. A qualitative exploratory study was conducted from the perspective of hermeneutic phenomenology and ethnosociology. The authors used life stories for compiling data (13 informants were interviewed face-to-face), and sociological discourse analysis was developed. Three main categories were identified: (a) self and grieving; (b) images and practices relating to fibromyalgia, chronic fatigue syndrome/myalgic encephalomyelitis, and multiple chemical sensitivity; and (c) relationships with health professionals. This study shows that daily experiences of people living with these diseases are marked by stigmatization processes. The ultimate purpose of nursing care for people with these conditions should be to reduce their vulnerability and exclusion.

IRRITABLE BOWEL SYNDROME

MIRNA-29A MODULATES VISCERAL HYPERALGESIA IN IRRITABLE BOWEL SYNDROME BY TARGETING HTR7.

Zhu H1, Xiao X1, Chai Y2, Li D3, Yan X3, Tang H4. Biochem Biophys Res Commun. 2019 Feb 28. pii: S0006-291X(19)30327-4. doi: 10.1016/j.bbrc.2019.02.126. [Epub ahead of print] PMID: 30827505

Some patients with irritable bowel syndrome (IBS) have visceral hypersensitivity, which contributes to their abdominal pain. miRNA-29 was detected to be significantly upregulated in colonic tissues of patients with IBS. However, it is unknown whether miRNA-29a is involved in the visceral hypersensitivity pathogenesis of IBS. This study from China aimed to investigate whether miRNA-29a participates in visceral hypersensitivity in IBS. Zhu and colleagues investigated miRNA-29a in intestinal biopsies collected during endoscopy of 10 patients with IBS and 10 healthy volunteers (control). In addition, a water avoidance stress (WAS)-induced visceral hypersensitivity IBS mouse model was established. The abdominal withdrawal reflex (AWR) scores of mice in response to colorectal distention were used to assess visceral sensitivity. Reverse transcription quantitative-polymerase chain reaction (RT-qPCR) was used to measure miRNA-29a levels. Immunofluorescence, RT-qPCR and western blot were used to measure 5-HT7 receptor (HTR7) levels. Bioinformatic analysis and luciferase reporter assays were used to detect the direct relationship between miRNA-29a and HTR7. Finally, alterations in the levels of HTR7 and miRNA-29a were measured in the human intestinal epithelial cell line NCM460 after transfection with miRNA-29a inhibitor or mimic. Intestinal tissues from patients with IBS and WAS-induced IBS mice had increased levels of miRNA-29a, but reduced levels of HTR7. MiRNA-29a knockout resulted in overexpression of HTR7 and attenuated visceral hyperalgesia in WAS-induced IBS mice. HTR7 was a direct target of miRNA-29a. Based on analyses of intestinal tissue samples from patients with IBS and WAS-induced miRNA-29a-/- mice, miRNA-29a plays a role in the visceral hyperalgesia pathogenesis of IBS, probably through regulating HTR7 expression.

VULVODYNIA

SENSORY PAIN CHARACTERISTICS OF VULVODYNIA AND THEIR ASSOCIATION WITH NOCICEPTIVE AND NEUROPATHIC PAIN: AN ONLINE SURVEY PILOT STUDY.

Schlaeger JM, Patil CL, Steffen AD, Pauls HA, Roach KL, Thornton PD, Hartmann D, Kobak WH, Yao Y, Suarez ML, Hughes TL, Wilkie DJ. Pain Rep. 2019 Feb 22;4(2):e713. doi: 10.1097/PR9.0000000000000713. eCollection 2019 Mar-Apr. PMID: 31041417

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The purpose of this study was to evaluate self-reported sensory pain scores of women with generalized vulvodynia (GV) and provoked vestibulodynia (PVD), characterize pain phenotypes, and assess feasibility of using the Internet for recruitment and data collection among women with vulvodynia. Data was collected using an online survey accessed via a link on the National Vulvodynia Association web site. Convenience sample, 60 women aged 18 to 45 years; 50 white, 2 black/African American, 4 Hispanic/Latino, and 4 Native American/Alaskan Native, diagnosed with vulvodynia, not in menopause. Pain assessment and medication modules from PAINReportIt. Women with GV reported severe pain, whereas those with PVD reported moderate to severe pain. Pain quality descriptors may aid a clinician's decisions about whether to prescribe adjuvant drugs vs opioids to women with vulvodynia.

SJÖGREN'S SYNDROME

HOW TO TREAT SJÖGREN'S SYNDROME.

Price EJ, Baer AN. Rheumatology (Oxford). 2019 Feb 15. pii: key363. doi: 10.1093/rheumatology/key363. [Epub ahead of print] PMID: 30770917

SS is a chronic, autoimmune disease of unknown aetiology for which there is no known curative treatment. Although dryness of the eyes and mouth are the classically described features, patients often experience drying of other mucosal surfaces and systemic manifestations, including fatigue and arthralgia. There is an association with other autoimmune diseases, especially thyroid disease, coeliac disease and primary biliary cholangitis. Systemic features may affect up to 70% and include inflammatory arthritis, skin involvement, haematological abnormalities, neuropathies, interstitial lung disease and a 5-10% lifetime risk of B cell lymphoma. Treatment should aim to empower patients to manage their condition; conserve, replace and stimulate secretions; prevent damage; and suppress underlying systemic disease activity.

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.

RARE DISEASES

RARE DISEASES IN THE YEAR 2019 - THE CZECH AND INTERNATIONAL CONTEXT.

Macek M Jr. Cas Lek Cesk. 2019 Spring;158(1):33-37. PMID: 31046390

Rare diseases (RD) are a clinically heterogeneous, predominantly inherited (or congenital) multisystem diseases with very low incidence in the general population that negatively affect the quality of life and social inclusion of affected patients and their families. The disease is defined as rare in the European Union if it affects less than 5 people out of every 10,000 citizens. There are approx. 5,000 different RD, implying an estimated total number of patients in Europe of approx. 20 million. RD most often manifest themselves soon after birth and affect up to 2-5 % of children but may occur also later in childhood or even in adulthood. About 80 % of RD have genetic pathogenesis, but most of them remain unrecognized or their causal gene remains unknown. In this summary article the author describes the current state of diagnosis and treatment of RD in the Czech Republic and at the European level and additionally presents the current issue of the development of international classification of diseases, the creation of domestic and international databases, the development of European and domestic recommendations, the implementation of a national strategy and three action plans for VO, the application of cross-border care, including the creation of European Reference Networks for these diseases and their impact on national legislation in terms of creation of highly specialized centers for RD in the country. The overall aim of this review is to not only map the state of art but also outline likely future developments in this rapidly developing field of modern medicine.

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