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 52, August 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:

PUBLICATIONS

A SELECTION OF ARTICLES AND EDITORIALS FROM THE 4TH INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS, 2018 JAPAN (ICICJ)

International Journal of Urology: Volume 26, Issue S1, Pages: I-Iv, 1-88, June 2019 - Open Access

This is a Special Open Access Issue of the International Journal of Urology with a selection of articles and editorials from the 4th International Consultation on Interstitial Cystitis, Japan (ICICJ) and the Annual Meeting of the Society of Interstitial Cystitis of Japan (SICJ), held 17–18 April 2018, Kyoto International Conference Center, Kyoto, Japan. To view all articles and editorial comments in full, go to:
https://onlinelibrary.wiley.com/toc/14422042/2019/26/S1
Or click here: View all articles

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. The theme running through 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 role of the urology nurse, the problems of comorbidities and much more besides. Deadline for abstract submission is 10 September.
Further information and preliminary programme can be found on the ESSIC congress website, click here. Add this important IC/BPS event 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. This will include presentations on Interstitial Cystitis/Bladder Pain Syndrome. Further information is available at https://eluts.uroweb.org/.

CALENDAR OVERVIEW

2019

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/

9TH GLOBAL PATIENTS CONGRESS
16-18 April 2020
Surgeons Quarter, Edinburgh, Scotland.
www.globalpatientscongress.org

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

50th INTERNATIONAL CONTINENCE SOCIETY ANNUAL MEETING 2020
26-29 August, Las Vegas, USA
https://www.ics.org/2020

PATIENT ORGANISATION NEWS

9TH GLOBAL PATIENTS CONGRESS 2020 – SAVE THE DATE!

The International Alliance of Patients' Organizations (IAPO) has announced that IAPO's 9th Global Patients Congress will be held 16-18 April 2020 at the Surgeons Quarter in Edinburgh, Scotland. At the 2020 Global Patient Congress, members, patients and partners will share their experiences of working and promoting global health. Delegates will also have the opportunity to build their capacity through a string of talks, interactive discussions and expert workshops. More information can be found at:
www.globalpatientscongress.org

COCHRANE TRAINING

Cochrane has recently launched Evidence Essentials, a new online learning module that has been co-created with patients and carers and is designed to give anyone an introduction to Evidence Based Medicine and Systematic Reviews. While many of you will probably already be familiar with these concepts, please feel free to pass on the link to Evidence Essentials to anyone you know who you feel may be interested, as the resource is free to anyone who has a Cochrane account. Ideal for patients and their organisations who want to know more about the science behind drugs.

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.

CYSTITIS-INDUCED BLADDER PAIN IS TOLL-LIKE RECEPTOR 4 DEPENDENT IN A TRANSGENIC AUTOIMMUNE CYSTITIS MURINE MODEL: A MAPP RESEARCH NETWORK ANIMAL STUDY.

Cui X, Jing X, Lutgendorf SK, Bradley CS, Schrepf A, Erickson BA, Magnotta VA, Ness TJ, Kreder KJ, O'Donnell MA, Luo Y. Am J Physiol Renal Physiol. 2019 May 15. doi: 10.1152/ajprenal.00017.2019. [Epub ahead of print] PMID: 31091120

Altered Toll-like receptor (TLR) 4 activation has been identified in several chronic pain conditions but has not been well studied in interstitial cystitis/bladder pain syndrome (IC/BPS). Cui reports that their published human studies indicated that IC/BPS patients present altered systemic TLR4-mediated inflammatory responses, which were significantly correlated with reported pain severity. In this study, they sought to determine whether altered TLR4 activation plays a role in pelvic/bladder pain seen in IC/BPS patients using our validated IC/BPS-like

transgenic autoimmune cystitis model (URO-OVA). URO-OVA mice developed responses consistent with pelvic and bladder pain after cystitis induction, which was associated with increased splenocyte production of TLR4-mediated proinflammatory cytokines interleukin (IL)-1b, IL-6 and tumor necrosis factor (TNF)-a. Increased spinal expression of mRNAs for proinflammatory cytokines IL-6 and TNF-a, glial activation markers CD11b and glial fibrillary acidic protein (GFAP), and endogenous TLR4 ligand high mobility group box 1 (HMGB1) was also observed after cystitis induction. Compared to URO-OVA mice, URO-OVATLR4-/- (TLR4-deficient URO-OVA) mice developed significantly reduced nociceptive responses, although similar bladder inflammation and voiding dysfunction, after cystitis induction. Intravenous administration of TAK-242 (a TLR4 selective antagonist) significantly attenuated nociceptive responses in cystitis-induced URO-OVA mice, which was associated with reduced splenocyte production of TLR4-mediated IL-1b, IL-6 and TNF-a as well as reduced spinal expression of mRNAs for IL-6, TNF-a, CD11b, GFAP, and HMGB1. They are of the opinion that their results indicate that altered TLR4 activation plays a critical role in bladder nociception independent of inflammation and voiding dysfunction in the URO-OVA model, providing a potential mechanistic insight and a therapeutic target for IC/BPS pain.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME/HYPERSENSITIVE BLADDER: WORLDWIDE CONFUSION! WHAT HAS GONE WRONG AND HOW CAN WE PUT IT RIGHT FOR THE SAKE OF THE PATIENTS?

Meijlink J. Int J Urol. 2019 Jun;26 Suppl 1:41-45. doi: 10.1111/iju.13973. PMID: 31144742

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The international interstitial cystitis, bladder pain syndrome and hypersensitive bladder world is facing major problems. While healthcare is ultimately about making sick people feel better, this is still not happening for our patients who are not receiving the individually tailored treatment that they need. So, what has gone wrong, and why is there so much confusion everywhere? Since the first NIDDK research criteria were published over 30 years ago, there has been no major breakthrough either in treating the patients or even in truly understanding what bladder condition(s) we are dealing with. For the sake of the patients, it is imperative to take action now and make a fresh, determined start with meaningful, international, multi-stakeholder collaboration to determine how to proceed further to take the necessary decisions, solve the problems and achieve real global consensus and real progress to help the real patients with their real symptoms.

PHENOTYPING OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Akiyama Y, Hanno P. Int J Urol. 2019 Jun;26 Suppl 1:17-19. doi: 10.1111/iju.13969. PMID: 31144756

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Interstitial cystitis/bladder pain syndrome is a chronic, potentially debilitating condition characterized by pain perceived to be related to the bladder in conjunction with lower urinary tract symptoms and includes a wide variety of clinical phenotypes with diverse etiologies. Currently the only clinically relevant proven phenotype of interstitial cystitis/bladder pain syndrome is the Hunner lesion. Whether the presence of Hunner lesions is a hallmark of a distinct disease cohort or a potentially transient feature of non-Hunner lesion phenotype has been debated but remains controversial. There are few documented examples of a patient converting between the two forms. Growing clinical and basic evidence supports eliminating the Hunner lesion phenotype from the bladder pain syndrome umbrella and considering it a distinct disease. The Hunner lesion phenotype is characterized by distinct bladder histology, including subepithelial chronic inflammatory changes and epithelial denudation, and specific clinical characteristics (older onset age, severe bladder-centric symptoms, reduced bladder capacity, and favorable response to the lesion-targeted therapies). To define the Hunner lesion phenotype, it is necessary to develop an atlas of standardized images of cystoscopic (and, if possible, pathological) appearances of Hunner lesions. A true potential and clinically relevant phenotype of interstitial cystitis/bladder pain syndrome may be patients with non-bladder-centric symptoms, characterized by the affect dysregulation and somatic symptoms, and a greater bladder capacity in absence of Hunner lesions. In the present workshop, the authors concluded that the Hunner lesion is a valid phenotype and can reasonably be considered a disease in its own right. Assessment of bladder capacity and the extent of symptoms (bladder beyond or bladder centric) may help phenotyping of interstitial cystitis/bladder pain syndrome. Proper phenotyping is essential for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome, and for facilitating research.

DEPRESSION AND HELPLESSNESS IMPACT INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PAIN OVER TIME.

Crawford A, Tripp DA, Nickel JC, Carr L, Moldwin R, Katz L, Muere A. Can Urol Assoc J. 2019 Feb 7. doi: 10.5489/cuaj.5703. [Epub ahead of print] PMID: 31364973

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a devastating urological chronic pelvic pain condition with an unknown etiology. Evidence-based psychological strategies are becoming more successful for symptom management as we learn more about the targets for intervention. Previous research has established an indirect relationship between depression and pain through catastrophizing, but there have yet to be studies examining the emerging role of emotion regulation in this relationship. Women with IC/BPS were recruited from tertiary care clinics in Canada and the U.S. between 2013 and 2018. Patients completed questionnaires, including demographics and scores for pain, depression, catastrophizing, and difficulties in emotion regulation at baseline, six months, and one year. Serial mediation was used to test models of pain, catastrophizing, and depression. A total of 135 women with IC/BPS completed all three time points. The only significant indirect path was from baseline depression to catastrophizing at six months, to pain at one year. A follow-up analysis demonstrated that helplessness was the key factor of catastrophizing driving this relationship. Reducing feelings of helplessness and increasing patient feelings of control are important ways to limit the effect of low mood on patient pain experience. De-catastrophizing interventions should be part of the referral strategy for IC/BPS symptom management.

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

Akiyama Y, Maeda D, Katoh H, Morikawa T, Niimi A, Nomiya A, Sato Y1, Kawai T, Goto A, Fujimura T, Fukuhara H, Nakagawa T, Igawa Y, Ishikawa S, Fukayama M, Kume H, Homma Y. J Urol. 2019 Aug;202(2):290-300. doi: 10.1097/JU.0000000000000234. Epub 2019 Jul 8. PMID: 30865573

Akiyama and colleagues from Japan systematically characterized gene expression, inflammation and neovascularization in patients with IC/BPS to obtain biological evidence supporting diagnosis and classification. They sequenced RNA obtained from bladder mucosal biopsies of 33 patients with 3 subtypes of IC/BPS, including Hunner lesions in 12, no Hunner lesions in 11 but with glomerulations and neither Hunner lesions nor glomerulations in 10, and 9 controls. Differentially expressed genes of 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 candidate gene over expression 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 density. Over expression of 2 candidate genes, VEGF and BAFF, correlated with symptom severity. Meanwhile, the gene expression profiles of patients with the 2 subtypes without Hunner lesions were similar to those of controls. No difference in biological pathways or subepithelial lymphoplasmacytic cell and microvessel density were detected between these 2 subtypes and controls. IC/BPS with Hunner lesions shows distinct genomic and histological features associated with immune responses and infection. In addition, VEGF and BAFF are potential disease biomarkers and therapeutic targets. This subtype should be considered separate from the syndrome.

PATHOLOGY AND TERMINOLOGY OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A REVIEW.

Akiyama Y, Homma Y, Maeda D. Histol Histopathol. 2019 Jan;34(1):25-32. doi: 10.14670/HH-18-028. Epub 2018 Jul 17. PMID: 30015351

Interstitial cystitis/bladder pain syndrome (IC/BPS) is an umbrella term of chronic debilitating conditions of unknown etiology characterized by symptoms of lower urinary tract hypersensitivity such as bladder pain/discomfort, urgency, and urinary frequency. The pathological features of IC/BPS have been generally reported as non-specific chronic inflammatory changes, with mast cell infiltration as a potential key finding. However, growing evidence reveals a histological distinction between IC/BPS with Hunner lesions and IC/BPS without Hunner lesions, and also sheds doubt on the diagnostic value of the mast cell count. Specifically, IC/BPS with Hunner lesions is an inflammatory disorder characterized by pancystitis with B cell abnormalities and epithelial denudation, while IC/BPS without Hunner lesions shows minimal histological changes. The umbrella term "IC/BPS" connects totally distinct clinical entities. Pathological evaluation thus plays an important role in the precise subtyping and clinical management of IC/BPS. In addition, terminology should be developed to refer separately to IC/BPS with Hunner lesions and IC/BPS without Hunner lesions.

HUNNER LESION VERSUS NON-HUNNER LESION INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Whitmore KE, Fall M, Sengiku A, Tomoe H, Logadottir Y, Kim YH. Int J Urol. 2019 Jun;26 Suppl 1:26-34. doi: 10.1111/iju.13971. PMID: 31144757

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Global consensus on the standardization of terminology for interstitial cystitis/bladder pain syndrome is lacking and is in the formative stages. The Workshop on Hunner lesion versus non-Hunner lesion at the 2018 International Consultation on Interstitial Cystitis Japan discussed prevalence, performance and outcome of endoscopy, the role of histopathology, and markers. A panel of experts reviewed the literature regarding Hunner lesion vs. non-Hunner lesion interstitial cystitis/bladder pain syndrome. The prevalence of Hunner lesion has been reported to be 5-57%. Older age and smaller anatomic bladder capacity were associated with Hunner lesions. Cystoscopy using local anesthesia is not adequate in diagnosing interstitial cystitis but is needed to rule out confusable diseases. Cystoscopy with hydrodistention and redistention of the bladder is considered standard. A Hunner lesion is visualized as a quite typical inflammatory reaction: a reddened mucosal area with small vessels radiating towards a central scar, splitting at distension, usually associated with a waterfall bleeding pattern. Biopsies from the inflamed area show inflammatory infiltrates, granulation tissue, detrusor mastocytosis, and fibrin deposits. Ablation of Hunner lesions includes transurethral resection of lesions, fulguration, laser ablation, and cortical steroid injections. Mast cell density is a somewhat controversial matter, described differently in different studies: marked increase in Hunner lesion vs. non-Hunner lesion in the majority of studies, no difference in a few. Nitric oxide appears to be a definitive marker in distinguishing Hunner lesion vs. non-Hunner lesion disease. Macrophage migration inhibitory factor is elevated in Hunner lesion patients. Increased level of urinary proinflammatory genes expression has also been found in Hunner lesion subjects. The panel concluded that Hunner lesion patients are clinically and pathologically distinct from non-Hunner lesion bladder pain syndrome patients.

LOW BLADDER CAPACITY IS AN IMPORTANT PREDICTOR FOR COMORBIDITY OF INTERSTITIAL CYSTITIS WITH HUNNER'S LESION IN PATIENTS WITH REFRACTORY CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME.

Ueda M, Sengiku A, Kono J, Negoro H, Saito R, Yoshimura N, Ogawa O, Ueda T. Int J Urol. 2019 Jun;26 Suppl 1:53-56. doi: 10.1111/iju.13975. PMID: 31144759

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This study evaluated the predictive factors for comorbidity of Hunner-type interstitial cystitis in patients with chronic prostatitis/chronic pelvic pain syndrome using urethrocystoscopy. Thirty-two male patients were included in this study. Between April 2012 and April 2016; they were diagnosed with chronic prostatitis/chronic pelvic pain syndrome according to the National Institutes of Health classification. Their symptoms were not improved by 3 months of behavioral and pharmacological therapies. They all underwent narrow band imaging-assisted urethrocystoscopy to assess whether the presence of Hunner's lesions correlated with other variables. Thirteen out of 32 patients (41%) had Hunner's lesions. Of the variables, maximal voided volume per micturition and bladder capacity were significantly smaller in patients with Hunner's lesions compared to those without. Other variables, apart from age, were not significantly different. Furthermore, patients with voided volume less than 150 mL were more likely to have Hunner's lesions than those with voided volume exceeding 150 mL. It was concluded that Hunner-type interstitial cystitis is a common comorbidity among patients with refractory chronic prostatitis/chronic pelvic pain syndrome. In cases where voided volume is small, performing narrow band imaging-assisted urethrocystoscopy would be very helpful for detecting bladder mucosal changes such as Hunner's lesions.

PATHOPHYSIOLOGY OF INTERSTITIAL CYSTITIS.

Birder LA. Int J Urol. 2019 Jun;26 Suppl 1:12-15. doi: 10.1111/iju.13985. PMID: 31144735

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Interstitial cystitis/bladder pain syndrome is a chronic pain syndrome whose causes remains elusive with no generally accepted treatment. A hallmark of functional pain syndromes such as interstitial cystitis/bladder pain syndrome is pain in the absence of demonstrable pathology of the viscera or associated nerves. Patients with chronic pain experience a greater impairment in quality of life than healthy controls. In addition, interstitial cystitis/bladder pain syndrome symptoms can frequently overlap with other conditions including irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, anxiety disorders, and a number of other syndromes not directly related to the urinary bladder. Because of the complex pathophysiology, a number of animal models have been studied over the years to better understand mechanisms underlying patient symptoms. These models

can include: bladder centric, complex mechanisms and psychological and physical stress models. Such animal models can aid in the investigation of aspects of interstitial cystitis/bladder pain syndrome that cannot be pursued in humans as well as to develop and test potential therapies. In addition, the search for urinary factors that may be a cause of interstitial cystitis/bladder pain syndrome has resulted in the discovery of a number of potential targets that could serve as predictive biomarkers which can aid in early diagnosis and treatment of this chronic disorder.

ANGIOGENESIS IN BLADDER TISSUES IS STRONGLY CORRELATED WITH URINARY FREQUENCY AND BLADDER PAIN IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Furuta A, Suzuki Y, Igarashi T, Koike Y, Kimura T, Egawa S, Yoshimura N. Int J Urol. 2019 Jun;26 Suppl 1:35-40. PMID: 31144750

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Furuta and colleagues examined the correlation among bladder inflammation, angiogenesis, fibrosis and urothelial denudation in biopsied bladder specimens, and O'Leary-Sant symptom indexes, O'Leary-Sant problem indexes and visual analog scale pain scores in IC/BPS patients with or without Hunner lesions (Hunner type IC or non-Hunner type IC). Bladder biopsied tissues were collected from 12 Hunner type IC female patients, 12 non-Hunner type IC female patients and 12 age-matched non-IC female patients (controls). Immunohistochemical stainings of tissue necrotic factor-α, mast cell tryptase, vascular endothelial growth factor, CD31, transforming growth factor-β, SLUG associated with epithelial mesenchymal transition and E-cadherin as well as Masson trichrome staining were evaluated. The significant correlation between the expression of tissue necrotic factor-α, mast cell tryptase, vascular endothelial growth factor, CD31, transforming growth factor-β, collagen, SLUG or E-cadherin, and O'Leary-Sant symptom indexes, O'Leary-Sant problem indexes or visual analog scale pain scores was then examined. The expression of tissue necrotic factor-α, vascular endothelial growth factor, CD31, transforming growth factor-β and SLUG was significantly increased in non-Hunner type IC and Hunner type IC patients compared with controls whereas the significant increases in the expression of mast cell tryptase and collagen were observed in Hunner type IC patients compared with controls and non-Hunner type IC patients. On the other hand, the expression of E-cadherin was significantly decreased in Hunner type IC patients compared with controls and non-Hunner type IC patients. In addition, the increased expression of CD31 in bladder tissues was strongly correlated with O'Leary-Sant symptom indexes, O'Leary-Sant problem indexes and visual analog scale pain scores. It was concluded that these results suggest that bladder angiogenesis evident as the increased expression of CD31 is strongly correlated with urinary frequency and bladder pain in patients with non-Hunner type IC and Hunner type IC.

INTRAVESICAL TACROLIMUS IN TREATMENT OF INTRACTABLE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME - A PILOT STUDY.

Mishra NN, Riedl C, Shah S, Pathak N. Int J Urol. 2019 Jun;26 Suppl 1:68-72. doi: 10.1111/iju.13978. PMID: 31144739

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Interstitial cystitis/Bladder pain syndrome (IC/BPS) is a chronic condition with limited effectiveness of current treatments without any cure. Cyclosporine A is effective in intractable cases of BPS/IC. Tacrolimus has the same mechanism of action. The purpose of this pilot study was to find out if tacrolimus instilled in bladder is effective in treating BPS/IC without side effects. From February 2013 to December 2017 tacrolimus dissolved in DMSO/sterile water was instilled in bladder of 24 patients of intractable BPS/IC. Patients received one to six cycles of therapy at interval of 14 days. Base line complete blood count, blood glucose, renal and liver function test were done and repeated after every three instillations. Serum tacrolimus level was also measured in 10 patients. The primary study endpoint was the Global Response Assessment (GRA) score. 13 out of 24 patients showed improvement in a follow up extending from 6 to 63 month. Except for post- instillation flare in symptoms no side effects were observed in the patients during follow-up. Blood levels of tacrolimus reach the same safe level irrespective of using either DMSO or water for preparing the solution. The authors concluded that intravesical tacrolimus dissolved in DMSO/water has been found effective in 54% patients of intractable BPS/IC without significant side effects in this pilot study. For the first time they have discovered that though tacrolimus is believed to be insoluble in water it gets absorbed by the bladder urothelium when a solution of tacrolimus in water is instilled in urinary bladder. It should be offered to the patients before offering surgery.

SUPLATAST TOSILATE IN PATIENTS WITH INTERSTITIAL CYSTITIS: EFFICACY AND TREATMENT POSSIBILITIES, WITH SUGGESTIONS FOR FUTURE ASSESSMENTS.

Ueda T, Homma Y, Yoshimura N. Int J Urol. 2019 Jun;26 Suppl 1:4-11. doi: 10.1111/iju.13968. PMID: 31144762

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Suplatast tosilate, a Th2 cytokine inhibitor, was predicted to relieve interstitial cystitis symptoms. Four studies with suplatast tosilate in Japanese interstitial cystitis patients have been conducted: a single-arm clinical study, a phase II dose-ranging trial, a phase III trial with placebo, and a second phase PIII trial with placebo. Treatment efficacy was observed in the first two studies; however, in the phase PIII trials, no significant difference in interstitial cystitis symptom score changes was observed between suplatast tosilate and placebo. Ueda and colleagues summarized these four studies to investigate factors causing the difference in observed efficacy. Placebo effects in the first two studies and differences regarding study design between the four studies were considered to be possible factors. Therefore, placebo effects were investigated by comparing interstitial cystitis symptom score changes, and the study designs were compared to investigate the effects on observed efficacy. Interstitial cystitis symptom score changes in the phase PII treatment groups increased in a dose-dependent manner and showed an almost linear relationship with interstitial cystitis symptom score changes observed in placebo groups of 2 phase PIII studies. A major difference regarding the phase PIII study design was the use of diagnostic hydrodistention. Diagnostic hydrodistention and its washout period were applied only in the phase PIII trials. Comparison of interstitial cystitis symptom score changes suggested that the placebo effect was very small. Use of diagnostic hydrodistention was considered to be a major difference in the population characteristics of the studies and may have resulted in different observed efficacies. Diagnostic hydrodistention, which potentially influences the treatment effect, is probably not essential for trials of suplatast in interstitial cystitis patients.

MINIMALLY INVASIVE DEVICE FOR INTRAVESICAL INSTILLATION BY UROLOGICAL SYRINGE ADAPTER (MID-II U.S.A.) FOR CATHETER-FREE INSTILLATION THERAPY OF THE BLADDER IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Lovasz S. Int J Urol. 2019 Jun;26 Suppl 1:57-60. doi: 10.1111/iju.13976. PMID: 31144753

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The intravesical instillation of bladder cocktails via catheter is a widespread, most effective way of treating interstitial cystitis/bladder pain syndrome. This disease often affects the urethra too, causing tenderness and pain. Therefore, catheterization causing superficial mucosal lesions triggers strong and long-lasting pain, sometimes bleeding, and a higher risk of infection. Lovasz and colleagues from Hungary invented an adapter fitting on both Luer-lock and Luer-slip syringes allowing the injection of "bladder cocktails" into the bladder through the urethra in a retrograde way; the injected fluid opens the bladder sphincter. Its radiused tip and the specially shaped flexible isolating collar allow drop-free instillation without catheterization. In the last 2 years, clinical evaluations were conducted in 270 IC/BPS patients (243 female, 27 male), altogether totalling 1520 instillations. In 5 of 243 female patients (2%) using the syringe adapter was unsuccessful due to the deep located urethral orifice or cicatricose vaginal opening. This made visualization of the urethral orifice impossible (success rate: 98%). All 27 male patients (100%) could be treated without any difficulties. No infection due to the instillation was observed. All treatable patients preferred the catheter-free method to conventional catheterization. They did not report any pain, long-lasting burning sensation or any other complications. This new non-invasive instillation method prevents superficial lesions of the urethra and treats urethral and bladder mucosa simultaneously. It reduces pain and the complication rate compared to conventional catheterization and at the same time reduces time, costs and inconvenience of bladder instillation.

POTENTIAL OF HYPERBARIC OXYGEN IN UROLOGICAL DISEASES.

Tanaka T, Minami A, Uchida J, Nakatani T. Int J Urol. 2019 May 13. doi: 10.1111/iju.14015. [Epub ahead of print] PMID: 3108378

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Hyperbaric oxygen therapy is a promising medical technology that delivers oxygen to targeted tissues at high pressure to increase the amount of dissolved oxygen in the blood. Over the past three decades, hyperbaric oxygen has been used in a variety of conditions, including radiation-induced tissue injuries, non-healing states with ischemia and malignant neoplasms. In the field of urology, hyperbaric oxygen has also been applied to some pathological conditions (e.g. radiation-induced hemorrhagic cystitis, Fournier gangrene, interstitial cystitis, male infertility, acute kidney injury and urological cancers). In normal and injured tissues, hyperoxia from hyperbaric oxygen therapy contributes to anti-inflammation, angiogenesis through endothelial proliferation, enhanced fibroblastic activity, increased lymphocyte and macrophage activity, and bactericidal effects with the aim of wound repair. In cancerous tissues, the enhanced supply of oxygen into the hypoxic cancer cells can exert inhibitory effects on factors that contribute to their aggressiveness (e.g. cell survival, escape from apoptosis, epithelial-to-mesenchymal transition and tumor immunotolerance), and sensitize the tumor to radiation

therapy and chemotherapy. However, further research, including multicenter clinical studies, is essential for determining the role of hyperbaric oxygen therapy in refractory urological diseases that are resistant to conventional therapies.

[EFFICACY OF ELECTROACUPUNCTURE NERVE STIMULATION THERAPY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME]. [Article in Chinese]

Lv TT, Lv JW, Wang SY, Jiang C, Gu YJ, Liu HR. Zhongguo Zhen Jiu. 2019 May 12;39(5):467-72. doi: 10.13703/j.0255-2930.2019.05.003. PMID: 31099215

The purpose of this study was to explore the clinical efficacy of electroacupuncture nerve stimulation therapy (ENST) for interstitial cystitis/painful bladder syndrome (IC/PBS). A total of 68 patients with IC/PBS were randomly divided into an observation group and a control group, 34 cases in each one. The patients in the observation group were treated with ENST; abdominal four acupoints and sacral four acupoints were connected with a pair of electrodes and treated alternately every other day. The ENST was given 50 min per times, three times a week for 3 months. The patients in the control group were treated with perfusion therapy of four-medication combination (heparin sodium, lidocaine, sodium bicarbonate, gentamicin sulfate), twice a week for the first 6-8 weeks, followed by twice per month for 3 months. The infusion fluid remained for 1 h before discharging. The O' Leary-Sant score, including interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI), 24 h urination frequency, visual analogue scale (VAS) and maximum bladder volume were observed before treatment and treatment of 1 month, 3 months and 6 months after treatment respectively; the adverse events during the treatment were also recorded. Compared before treatment, the O'Leary-Sant score (ICSI, ICPI), 24 h urination frequency, VAS and maximum bladder volume in the two groups were improved after 1, 3 months treatment and 6 months after treatment. The scores of ICSI, ICPI, VAS and 24 h urination frequency in the observation group were significantly lower than those in the control group. The maximum bladder volume in the observation group was significantly higher than that in the control group. Six months after treatment, the total effective rate in the observation group was 87.5% (28/32), which was higher than 69.7% (23/33) in the control group. No significant adverse events occurred during the treatment. It was concluded that ENST could effectively relieve the clinical symptoms of IC/PBS, but its long-term efficacy needs further observation.

A MODIFIED CLINICAL SCORING SYSTEM FOR BLADDER PAIN SYNDROME: LONG TERM EXPERIENCE.

Taneja R, Massand S. Int J Urol. 2019 Jun;26 Suppl 1:61-67. doi: 10.1111/iju.13977. PMID: 31144746

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The purpose of this study was to document a modified clinical scoring system in patients with bladder pain syndrome that increases weightage to pain and nocturia and includes measures for sexual dysfunction and psychological impact. The clinical outcome of a set combination of treatment modalities linked to the clinical score at entry was also made. The new proposed scale was used to assess and treat 190 enrolled patients from January 2009 to September 30, 2017. The patients were evaluated using the new scoring system at the time of induction, after 1, 3 and 6 months after commencement of treatment. Thereafter, they were followed every 6 months. The new scoring system included increased weightage to pain and nocturia and added domains of sexual dysfunction and psychological impact. The patients were treated with a protocol followed by the authors and published in the year 2007. A pictorial linkage of treatment modalities used with the clinical score of the patient was also described. A total of 174 evaluable patients had a follow up between 6 and 105 months (mean 64 months). The patients had age distribution between 24 and 76 years and included 19 male patients. 154 out of 174 patients (88.5%) had good or excellent response to treatment using the proposed scale at the end of 6 months. It was concluded that the proposed clinical scale appeared to aid clinical stratification of severity of the disease at the induction and during follow up. The treatment protocol could be linked with the clinical score at the time of induction.

LONG-TERM OUTCOME AND SYMPTOM IMPROVEMENT IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH OR WITHOUT REGULAR FOLLOW-UP AND TREATMENT.

Yeh HL, Jhang JF, Kuo YC, Kuo HC. Neurourol Urodyn. 2019 Jul 16. doi: 10.1002/nau.24104. [Epub ahead of print] PMID: 31310370

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disease which is difficult to treat. Patients usually seek new therapies and might not follow-up regularly. This study investigated long-term symptom changes in patients with IC/BPS, especially in those who were lost to follow-up. Yeh and colleagues enrolled patients with IC/BPS with a history of >5 years and having comprehensive medical records, baseline IC symptom index and IC problem index, O'Leary-Sant symptom score, and visual analog scale (VAS). A telephone interview was conducted to assess current symptoms with the same questionnaires. A 5-point scale (from -1 to 3) was used to

grade current treatment outcomes. A total of 198 patients with IC/BPS with a mean age of 57.4 ± 12.2 years were included. At a mean follow-up duration of 16.6 ± 9.75 years, 12% of the patients were free of symptoms and 47% exhibited symptom improvement of more than 50%. In total, 47 (23.7%) patients were lost to follow-up for >5 years, and 151 (76.3%) had regular follow-up. The patients with IC/BPS who were not regularly followed up had no Hunner lesion and had a higher bladder volume, higher urine flow, and fewer comorbidities than those who had regular follow-up. The number of treatment modalities was significantly less in the patients who were lost to follow-up. About half of the patients with IC/BPS exhibited symptom improvement with time, with or without regular follow-up and receiving a new treatment.

[A COMPARATIVE ANALYSIS OF INTRAVESICAL SODIUM HYALURONATE MONOTHERAPY AND ITS COMBINATION WITH ORAL CHONDROITIN SULFATE IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS].

[Article in Russian]

Aboyan IA, Aboyan VE, Pavlov SV, Zinkovskaya OV, Pavlov DS. Urologiia. 2019 Apr;(1):35-39. PMID: 31184015

It has been established that intravesical sodium hyaluronate and chondroitin sulfate has high efficacy in patients with bladder pain syndrome/interstitial cystitis (BPS/IC). Currently, an oral form of chondroitin sulfate is also available. The aim of study was to compare the efficacy of intravesical hyaluronic acid monotherapy and long-term oral chondroitin sulfate in combination with intravesical therapy in patients with BPS/IC. A total of 59 patients with BPS/IC were randomized in two groups. In Group 1, 30 women (mean age 57.1 years) received viscoelastic solution of sodium hyaluronate 50 ml 1 time per week for 12 weeks as intravesical monotherapy. In Group 2 , patients were prescribed to complex therapy, which included the similar intravesical therapy combined with chondroitin sulfate in a dose 0.39 g, 2 capsules 3 times a day, also for 12 weeks. All patients completed visual analogue scale (VAS), interstitial cystitis symptom index (ISCI), interstitial cystitis problems index (ICPI) and voiding diary before and 1 week after the start of therapy. In all cases a cystoscopy and urodynamic study were performed in order to exclude other bladder pathologies. At baseline, a mean VAS score in both groups was 7 points, a mean ISCI score was 17 points in Group 1 and 18 points in Group 2. The mean ICPI score in both groups was 15 points. A frequency of urination in Group 1 and 2 was 11.4 and 11.6 per day, respectively. A mean volume of urination was 138+/-24.6 and 131+/-18.6 , respectively. After 12 weeks of therapy there was significant improvement of VAS, ICSI and ICPI scores in both groups, as well as frequency and volume of urination, but in Group 2 an improvement in almost all parameters studied, except for the volume of urination, was more pronounced. It was concluded that the combined therapy of BPS/IC with intravesical hyaluronic acid and oral chondroitin sulfate provides significantly better results in comparison with intravesical hyaluronic acid as monotherapy.

SMALL FIBER POLYNEUROPATHY AS A POTENTIAL THERAPEUTIC TARGET IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Matthews CA, Deveshwar SP, Evans RJ, Badlani G, Walker SJ. Int Urogynecol J. 2019 Jun 25. doi: 10.1007/s00192-019-04011-x. [Epub ahead of print] PMID: 31240362

Interstitial cystitis/bladder pain syndrome (IC/BPS) and fibromyalgia (FM) are frequently co-occurring medical diagnoses in patients referred to the urology clinic for secondary and tertiary treatment options. Abundant literature has shown that many patients with FM have small fiber polyneuropathy (SFPN) that can be confirmed via skin punch biopsy and immunological staining to measure nerve density. This finding of SFPN provides a therapeutic target for FM and in this article the authors hypothesize and provide rationale for the idea that this same phenomenon (SFPN) might explain, in some IC/BPS patients, the finding of widespread pain and likewise provide a therapeutic target for these patients.

INTERSTITIAL CYSTITIS: ELEMENTS OF DIAGNOSIS AND PLACE OF HISTOPATHOLOGICAL EXAMINATION. ABOUT 16 CASES.

Chaieb S, Mestiri S, Bouassida K, Jmour M, Mosbah AT, Mokni M. Tunis Med. 2018 Dec;96(12):859-864. PMID: 31131865

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Interstitial cystitis (IC) is a rare disease which is difficult to diagnosis. The diagnostic utility of histopathological examination of bladder biopsy remains controversial. Chaieb and colleagues conducted a retrospective study to assess the frequency of interstitial cystitis, to analyze its clinical presentation and the data from the paraclinical examinations. They discuss the steps and criteria of diagnosis, as well as the place of histopathological examination for diagnosis. Sixteen patients diagnosed with IC were followed in the Urology Department of the Sahloul University Hospital between 1996 and 2013. The diagnosis was suggested by clinical history and

confirmed on the basis of clinical symptoms and results of the paraclinical explorations: urodynamic assessment, cystoscopy and bladder biopsy. Six men (37.5%) and ten women (62.5%), with an average age of 56 years complained of pelvic pain and urination disorders for two years on average before the diagnosis. The urodynamic study found decreased bladder compliance in 13 cases and bladder instability in nine cases. Cystoscopy demonstrated inflammatory mucosa in 13 patients (81%). Histologically, the classic ulcerative form accounted for 50% of the cases. The number of mast cells was high in both the mucosa and the muscular in 12 cases, both in the classical and non-ulcerative forms. IC remains a diagnosis of exclusion. The first line of diagnosis is patient selection based on symptoms and an exclusion of diseases with similar presentation. Vesical biopsy is useful for confirmation and classification of the disease.

TO REVEAL PHARMACOLOGICAL TARGETS AND MOLECULAR MECHANISMS OF CURCUMOL AGAINST INTERSTITIAL CYSTITIS.

Wu K, Wei P, Liu M, Liang X, Su M. J Adv Res. 2019 May 15;20:43-50. doi: 10.1016/j.jare.2019.05.003. eCollection 2019 Nov. PMID: 31193808

This study was designed to reveal the predictive targets and biological mechanisms of curcumol against interstitial cystitis (IC). By use of available databases and bioinformatic assays, pathogenetic targets of IC and functional targets of curcumol were identified respectively. A network of functional protein-protein interaction (PPI) was produced before screening the main predictive targets, biological processes and signalling pathways of curcumol against IC. In bioinformatic findings, the data of ingenuity pathway analysis (IPA) delineated that curcumol exerted anti-IC benefits through regulating multipronged signalling pathways, including tyrosine protein kinase-2 (PTK2) pathway. Further, optimal 18 biotargets of curcumol against IC were harvested through differential expression analysis. And the predictive targets of receptor tyrosine-protein kinase erbB-2 (ERBB2), epidermal growth factor receptor (EGFR) and PTK2 were the most important molecules. In further validated experiments, PTK2 and phosphorylation PTK2 (p-PTK2) were representatively selected for testing by human and animal IC samples. As results, increased immunoreactive proteins of tumor necrosis factor alpha (TNF-α), PTK2 and p-PTK2Tyr397 in human IC sections were observed, accompanied with altered urinary parameters. Interestingly, curcumol-treated IC mice showed that intracellular expressions of PTK2, p-PTK2Tyr397 in bladder samples were reduced, accompanied with lowered blood inflammatory cytokines of interleukin 6 (IL-6), TNF-α. In conclusion, the current bioinformatic data and preliminary findings unravel that the predominant targets of curcumol against IC may be the potential biological markers for screening and treating IC, such as PTK2 molecule.

BLADDER HYDRODISTENTION DOES NOT RESULT IN A SIGNIFICANT CHANGE IN BLADDER CAPACITY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS.

Walker SJ, Plair A, Hemal K, Langefeld CD, Matthews C, Badlani G, Zambon J, Heath H, Evans RJ. Urology. 2019 Jul 9. pii: S0090-4295(19)30606-5. doi: 10.1016/j.urology.2019.06.031. [Epub ahead of print] PMID: 31299328

The purpose of this study from the USA was to assess the impact of multiple (two or more) bladder hydrodistentions (HODs) on anesthetic BC in a large cohort of IC/BPS patients. Urinary bladder hydrodistention (HOD) under anesthesia is a third line therapeutic approach used to treat patients with interstitial cystitis/bladder pain syndrome (IC/BPS). There is some concern that performing multiple therapeutic HODs may be contraindicated due to the potential for contributing to a diminished bladder capacity (BC) over time. This is a retrospective chart review of IC/BPS patients from a single institution who had undergone two or more bladder HOD procedures. Patient demographic and clinical data, including BC under anesthesia, was retrieved from patient charts for analysis. Least squares regression slopes of BC under anesthesia were calculated and used to estimate within-patient BC changes over time. It was concluded that multiple therapeutic HODs, over several years, do not result in a significant change in BC in IC/BPS patients.

THERAPEUTIC POTENTIAL OF INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA IN THE TREATMENT OF LOWER URINARY TRACT DISORDERS DUE TO REGENERATIVE DEFICIENCY.

Ke QS, Jhang JF, Lin TY, Ho HC, Jiang YH, Hsu YH, Kuo HC. Ci Ji Yi Xue Za Zhi. 2019 Jul-Sep;31(3):135-143. doi: 10.4103/tcmj.tcmj_92_19. PMID: 31258287

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The bladder urothelium plays an important role of barrier function to prevent influx of urinary toxic substance and bacteria. When there is insult to the urinary bladder, the urothelium will start to regenerate on injury. However, several factors might affect the regenerative function of bladder urothelium, including aging, chronic inflammation, and system diseases such as diabetes and chronic kidney diseases (CKDs). Impairment of bladder mucosal regenerative function might result in defective urothelial cell differentiation as well as barrier function, which might be the underlying pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) and

recurrent bacterial cystitis. Our previous immunohistochemistry (IHC) study and electron microscopic study revealed that the loss of normal umbrella cells and defective junction proteins in IC/BPS and recurrent cystitis. Platelet-rich plasma (PRP) has been previously used in many medical aspects as regenerative medicine therapy. PRP is rich in many growth factors and cytokines which modulate the process of inflammation and regeneration in the wound healing process. Recent pilot studies have shown that intravesical PRP injections improve IC symptoms and yield a success rate of 70% at 3 months after treatment. The results highly suggest that PRP injection could improve urothelial regenerative function and reduce chronic inflammation in IC patients. This article reviews recently published researches on the urothelial dysfunction biomarkers, urothelial cell differentiation, and urinary regenerative and inflammatory proteins in patients with IC/BPS or recurrent bacterial cystitis. The pathophysiology of the insufficient urothelial regeneration and differentiation; and chronic inflammation may induce urothelial dysfunction and further affect the regenerative ability of the diseased bladder urothelium in IC/BPS and recurrent bacterial cystitis are discussed.

N-ACETYLCYSTEINE PREVENTS BLADDER TISSUE FIBROSIS IN A LIPOPOLYSACCHARIDE-INDUCED CYSTITIS RAT MODEL.

Ryu CM, Shin JH, Yu HY, Ju H, Kim S, Lim J, Heo J, Lee S, Shin DM, Choo MS. Sci Rep. 2019 May 31;9(1):8134. doi: 10.1038/s41598-019-44631-3. PMID: 31148586

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Therapeutic options for non-Hunner type interstitial cystitis (IC), which is histologically characterized by fibrosis and mast cell infiltration, are limited. Ryu and colleagues developed a rat model that replicates chronic inflammation and fibrosis and evaluated the therapeutic effect of N-acetylcysteine (NAC), a well-known anti-fibrotic agent, on the model. Intravesical instillation of lipopolysaccharide (LPS, 750 μg) after protamine sulfate (10 mg) was conducted twice per week for five consecutive weeks. One week after final instillation, 200 mg/kg NAC (n = 10, IC + NAC group) or phosphate-buffered saline (n = 10, IC group) was daily injected intraperitoneally once daily for 5 days. LPS instillation induced bladder fibrosis, mast cell infiltration, and apoptotic tissue damage. Functionally, LPS insult led to irregular micturition, decreased inter-contraction intervals, and decreased micturition volume. NAC significantly improved most of the voiding parameters and reversed histological damages including fibrosis. NAC inhibited the induction and nuclear localization of phospho-Smad2 protein in bladder tissues and the upregulation of genes related to fibrosis, such as Tgfb2, Tgfb3, Smad2, Smad3, Cxcl10, and Card10. This is the first study to demonstrate the beneficial effects on NAC in restoring voiding function, relieving tissue fibrosis and related bladder injuries, in the LPS-induced cystitis rat model.

MOLECULAR DETERMINANTS OF AFFERENT SENSITIZATION IN A RAT MODEL OF CYSTITIS WITH UROTHELIAL BARRIER DYSFUNCTION.

Montalbetti N1, Rooney JG2, Rued AC3, Carattino MD1. J Neurophysiol. 2019 Jul 17. doi: 10.1152/jn.00306.2019. [Epub ahead of print] PMID: 31314637

The internal surface of the urinary bladder is covered by the urothelium, a stratified epithelium that forms an impermeable barrier to urinary solutes. Increased urothelial permeability to urinary solutes is thought to contribute to symptoms generation in several forms of cystitis by promoting the sensitization of bladder afferents. In this report Montalbetti and colleagues investigated the mechanisms that mediate bladder afferent hyperexcitability in a rat model of cystitis induced by the overexpression in the urothelium of claudin-2 (Cldn2), a tight-junction associated protein upregulated in bladder biopsies from patients with interstitial cystitis/bladder pain syndrome. Patch-clamp studies showed that the overexpression of Cldn2 in the urothelium sensitizes a population of isolectin GS-IB4-negative (IB4(-)) bladder sensory neurons with tetrodotoxin-sensitive (TTX-S) action potentials. Gene expression analysis revealed a significant increase in mRNA levels of the delayed rectifier channel Kv2.2 and the accessory subunit Kv9.1 in this population of sensory neurons. Consistent with this finding, Kv2/Kv9.1 channel activity was greater in IB4(-) bladder sensory neurons from rats overexpressing Cldn2 in the urothelium than in the control counterparts. Sensitized neurons presented higher TTX-S Na+current density than the control counterparts. Significantly, guangxitoxin-1E (GxTx-1E), a selective blocker of Kv2 channels, blunted the repetitive firing of sensitized IB4(-) sensory neurons. In summary, their studies uncovered a central role for Kv2/Kv9.1 channels in facilitating the repetitive firing of sensitized sensory neurons in a model of cystitis with increased urothelial permeability.

TARGETING THE SHIP1 PATHWAY FAILS TO SHOW TREATMENT BENEFIT IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: LESSONS LEARNED FROM EVALUATING POTENTIALLY EFFECTIVE THERAPIES IN THIS ENIGMATIC SYNDROME.

Nickel JC, Moldwin R, Hanno P, Dmochowski R, Peters KM, Payne C, Wein A. J Urol. 2019 Feb 15:101097JU0000000000000192. doi: 10.1097/JU.0000000000000192. [Epub ahead of print] PMID: 31090511

In this 12-week, randomized, double-blind, placebo controlled, multicenter, 3-arm, parallel group, phase 3 trial Nickel and colleagues assessed the effects of a novel SHIP1 activator on bladder pain and urinary symptoms in patients with IC/BPS. Subjects with IC/BPS and a mean pain score of 5 or greater on an 11-point scale despite treatment were randomized to 100 or 200 mg of an oral SHIP1 activator or placebo once daily for 12 weeks. Maximum pain scores and urinary frequency were recorded in an e-diary. The ICSI (O'Leary-Sant Interstitial Cystitis Symptom Index) and BPIC-SS (Bladder Pain Interstitial Cystitis Symptom Score) questionnaires were administered. Safety was monitored through 12 weeks of treatment. A total of 298 female subjects with moderate to severe symptoms of IC/BPS were treated with 100 or 200 mg SHIP1 activator orally once daily for 12 weeks. Treatment demonstrated no difference in maximum daily bladder pain compared to placebo. There was no treatment benefit over that of placebo in the secondary end points of urinary voiding frequency, the BPIC-SS, the ICSI and a global response assessment. Exploratory analysis in 87 male subjects yielded a similar result, that is no difference from placebo. Treatment was generally well tolerated at both doses. It was concluded that SHIP1 activation is a safe but ineffective therapeutic approach to IC/BPS. Although this was a negative trial, the important lessons learned from this study in respect to inflammatory phenotype differentiation, including the potential importance of cystoscopy-based classification, will improve current treatment in patients with IC/BPS and allow for better future trial design in those with this difficult urological chronic pain syndrome.

SEXUAL PAIN AND IC/BPS IN WOMEN.

Kim SJ,2, Kim J,4, Yoon H. BMC Urol. 2019 Jun 6;19(1):47. doi: 10.1186/s12894-019-0478-0. PMID: 31170952

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Interstitial cystitis/bladder pain syndrome (IC/BPS) and female sexual dysfunction (FSD) are common conditions that substantially reduce women's health. In particular, women with IC/BPS show vulvodynia, a kind of FDS that originates from consistent pain around the vulvar area. There have been many studies attempting to find the underlying mechanisms that induce the chronic pain associated with IC/BPS and vulvodynia and explain why these two conditions often coexist. Proposed theories suggest that pain hypersensitivity is being mediated by peripheral and central sensitization. However, there are still many unknown factors, such as etiologies, that can evoke pain hypersensitivity and may be linking the casual relationship between IC/BPS and vulvodynia. At present, knowledge regarding IC/BPS and vulvodynia are insufficient when considering their clinical importance. Therefore, efforts are necessary to elucidate the issues surrounding IC/BPS and vulvodynia.

BOTTOM-UP AND TOP-DOWN PROFILING OF PENTOSAN POLYSULFATE.

Lin L, Yu Y, Zhang F, Xia K, Zhang X, Linhardt RJ. Analyst. 2019 Jul 9. doi: 10.1039/c9an01006h. [Epub ahead of print] PMID: 31287456

Pentosan polysulfate (PPS) is a semi-synthetic glycosaminoglycan (GAG) mimetic. PPS, synthesized through the chemical sulfonation of a plant-derived β-(1 → 4)-xylan, is the active pharmaceutical ingredient of the drug Elmiron™ used to treat interstitial cystitis. Unlike natural GAGs that can be enzymatically broken down into oligosaccharides for analysis, PPS is an unnatural polyanionic polysaccharide and is not amenable to such an analytical approach. Instead reactive oxygen species were used for the controlled depolymerization of PPS and the resulting oligosaccharide fragments were then analyzed by liquid chromatography-mass spectrometry (LC-MS) to obtain bottom-up information on its composition. Because PPS has an average molecular weight ranging from 4000 to 6000 Da, similar to that of low molecular weight heparin, this suggested that it might be possible to use LC-MS on its intact chains and perform top-down analysis. The bottom-up and top-down analysis of PPS provides the first detailed compositional and structural information on PPS. Lin and colleagues from China and the USA examined whether PPS would interfere with polysaccharide lyases and hydrolases, used in the analysis of natural GAGs such as chondroitin sulfates, heparan sulfate, and keratan sulfates. They found that PPS did not interfere with GAG analysis, suggesting that a combination of chemical and enzymatic treatment could be used to analyze samples containing both natural GAGs and PPS.

THERAPEUTIC POTENTIAL OF INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA IN THE TREATMENT OF LOWER URINARY TRACT DISORDERS DUE TO REGENERATIVE DEFICIENCY.

Ke QS, Jhang JF, Lin TY, Ho HC, Jiang YH, Hsu YH, Kuo HC. Ci Ji Yi Xue Za Zhi. 2019 Jul-Sep;31(3):135-143. doi: 10.4103/tcmj.tcmj_92_19.

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The bladder urothelium plays an important role of barrier function to prevent influx of urinary toxic substance and bacteria. When there is insult to the urinary bladder, the urothelium will start to regenerate on injury. However, several factors might affect the regenerative function of bladder urothelium, including aging, chronic inflammation, and system diseases such as diabetes and chronic kidney diseases (CKDs). Impairment of bladder mucosal regenerative function might result in defective urothelial cell differentiation as well as barrier function, which might be the underlying pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) and recurrent bacterial cystitis. Ke and colleagues report that their previous immunohistochemistry (IHC) study and electron microscopic study revealed that the loss of normal umbrella cells and defective junction proteins in IC/BPS and recurrent cystitis. Platelet-rich plasma (PRP) has been previously used in many medical aspects as regenerative medicine therapy. PRP is rich in many growth factors and cytokines which modulate the process of inflammation and regeneration in the wound healing process. Recent pilot studies have shown that intravesical PRP injections improve IC symptoms and yield a success rate of 70% at 3 months after treatment. The results highly suggest that PRP injection could improve urothelial regenerative function and reduce chronic inflammation in IC patients. This article reviews recently published research on the urothelial dysfunction biomarkers, urothelial cell differentiation, and urinary regenerative and inflammatory proteins in patients with IC/BPS or recurrent bacterial cystitis. The pathophysiology of the insufficient urothelial regeneration and differentiation; and chronic inflammation may induce urothelial dysfunction and further affect the regenerative ability of the diseased bladder urothelium in IC/BPS and recurrent bacterial cystitis are discussed.

HYALURONIC ACID IMPROVES PAIN SYMPTOMS MORE THAN BLADDER STORAGE SYMPTOMS IN WOMEN WITH INTERSTITIAL CYSTITIS.

Hung MJ, Tsai CP, Lin YH, Huang WC, Chen GD, Shen PS. Taiwan J Obstet Gynecol. 2019 May;58(3):417-422. doi: 10.1016/j.tjog.2018.11.033. PMID: 31122535

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Intravesical hyaluronic acid (HA) therapy is one of acceptable methods to treat bladder pain and storage symptoms (i.e. urgency, frequency and nocturia) of interstitial cystitis/bladder pain syndrome (IC/BPS). Hung and colleagues aimed to assess the impact of intravesical HA on bladder pain and storage symptoms, respectively, and to investigate their associated factors in patients with IC/BPS. In this prospective, multicenter study, 103 women with refractory IC/BPS undergoing a standard protocol of intravesical HA therapy were enrolled. A pain Visual Analog Scale (VAS) and the Interstitial Cystitis Symptom and Problem Index (ICSI & ICPI) were used to assess symptoms and bother associated with IC/BPS. The Scaled Global Response Assessment (GRA) was used to evaluate patients' perception of overall changes in bladder pain and storage symptoms, respectively, after treatment. Bladder instillation of HA seemed more efficient in improving bladder pain than storage symptoms associated with IC/BPS. The persistence of bladder storage symptoms after treatment might result from a reduced functional bladder capacity.

OUTCOMES OF INTRAVESICAL CHONDROITIN-SULFATE AND COMBINED HYALURONIC-ACID/CHONDROITIN-SULFATE THERAPY ON FEMALE SEXUAL FUNCTION IN BLADDER PAIN SYNDROME.

Arslan B, Gönültaş S, Gökmen E, Özman O, Avci MA, Özdemir E. Int Urogynecol J. 2019 Jun 28. doi: 10.1007/s00192-019-04036-2. [Epub ahead of print] PMID: 31254047

The aim of the study was to determine the efficacy of intravesical chondroitin sulfate (CS) and combined hyaluronic acid/chondroitin sufate (HA/CS) treatment and their effects on sexual function of females with interstitial cystitis/bladder pain syndrome (IC/BPS). A total of 68 female patients with IC/BPS between 2012 and 2018 were reviewed. Thirty-three patients were treated with combined HA/CS and 28 patients were treated with CS. Instillations were performed weekly for the first month, biweekly for the second month, and monthly in the third and fourth months. Before and after the sixth month of the treatment, all patients were evaluated with the Female Sexual Function Index (FSFI), visual analog pain scale (VAS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), and voiding diary, and changes were recorded. A statistically significant improvement was determined for FSFI, VAS, ICSI, and ICPI scores after treatment in both groups. Among baseline characteristics, a weak but significant negative correlation was determined only between the ICSI score improvement and age on statistical analysis. Compared with CS, combined HA/CS treatment was superior in terms of ICSI, ICPI, and daytime and nighttime frequency improvement. All domains of the sexual

function index were significantly improved at the sixth month of intravesical therapy in both groups. A statistical difference was not found between the two groups. Although it seems that intravesical HA/CS combination is superior to CS alone in terms of symptom reduction, both of them have beneficial effects on sexual function.

STUDY OF THE APOPTOTIC EFFECT IN PATIENTS WITH UROLOGICAL VERSUS GYNAECOLOGICAL CHRONIC PELVIC PAIN.

Sánchez Llopis A, Di Capua Sacoto C, O'Connor JE, Martínez Romero A, Ruiz Cerdá JL. Urol Int. 2019 May 24:1-7. doi: 10.1159/000500211. [Epub ahead of print] PMID: 31129663

The objective was to observe if it could be possible to use the apoptosis test to distinguish different aetiologies in chronic pelvic pain syndrome (CPPS). A prospective study was done in 106 patients, 57 had previously been diagnosed with urological chronic pelvic pain (UCPP)/interstitial cystitis (IC) and 49 patients with gynaecological chronic pelvic pain (GCPP). Neoplastic cells cultures were exposed to the urine of patients with UCPP/IC and patients with GCPP. The urine ability to provoke apoptosis on them was analysed. The apoptosis degree was measured by quantifying the percentage of cells in phase subG0, determined by a flow cytometry analysis. It is observed that the cell cultures exposed to urine of patients with UCPP had a significantly higher sub-G1 peak and G2 phase than those of the cells exposed to urine from patient's GCPP. The average values of apoptosis in patients with UCPP were significantly higher to that obtained in -patients having GCPP. With the apoptosis tests having a value >10%, it is considered as positive as well. This means that when we are faced with a patient who has UCPP or non-bladder chronic pelvic pain, the probability of having an UCPP increases by 45% when the apoptosis test is positive for a value >10%. Urine from patients with UCPP has significantly higher apoptotic effect over than the effect produced by urine from patients with GCPP. The apoptosis test could be useful as an illness biomarker.

A NEW LOOK AT THE ETIOLOGY OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: EXTRAORDINARY CULTIVATIONS.

Aydogan TB, Gurpinar O, Eser OK, Mathyk BA, Ergen A. Int Urol Nephrol. 2019 Jul 30. doi: 10.1007/s11255-019-02248-5. [Epub ahead of print] PMID: 31363960

So far, studies have not clearly identified infectious agents as an etiological factor for interstitial cystitis (IC). Specific microbiological diagnosis for detecting the pathogen with higher sensitivity in IC may decrease the treatment costs and increase psychosocial health of the patients. A prospective clinical study was performed in 26 IC patients and 20 controls between April and September 2017. All participants were asked to give mid-stream urine sample for routine urine cultures. Followed by the negative results, symptomatic 26 patients were evaluated for L-form pathogen existence by extraordinary cultivation methods. Biopsy samples were taken from 19 patients with ulcerative lesions in the bladder while collecting sterile urine samples from all 26 patients. PG broth, 5% sheep blood agar, EMB, Sabouraud's dextrose, LEM, and GYPA were used. Followed by the 1st day inoculations, all inoculated PG broths were subcultured into the same solid media at the 2nd and 10th days in case of any growth after incubation of 24 h under 35-37 °C. The "O'Leary Sant Symptom and Problem Index" score forms were used to evaluate response to the appropriate treatment for those patients with documented pathogens. Bacterial isolations were yielded from samples of 13 IC patients in PG broth. Eight (61.5%) P. aeruginosa, 2 (15.4%) K. pneumoniae, 2 (15.4%) C. mucifaciens, and 1 (7.7%) E. faecalis were isolated. Antibiotic susceptibility tests were performed. Somehow, the median symptom index and problem scores of those 13 IC patients were lower after the appropriate antibiotic treatment ($p < 0.05$). Extraordinary mediums with longer incubation periods may reveal a causative pathogen in the etiology of IC. Future culture techniques may have some value, because some IC/BPS patients are still describing symptomatic relief from a group of antibiotics.

THE MISDIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN A VA POPULATION.

Skove SL, Howard LE, Senechal J, De Hoedt A, Bresee C, Cunningham TJ, Barbour KE, Kim J, Freedland SJ, Anger JT. Neurourol Urodyn. 2019 Jul 14. doi: 10.1002/nau.24100. [Epub ahead of print] PMID: 31302944

The complexity of Interstitial Cystitis/bladder Pain Syndrome (IC/BPS) has led to a great deal of uncertainty around the diagnosis and prevalence of the condition. Under the hypothesis that IC/BPS is frequently misdiagnosed, Skove and colleagues sought to assess the accuracy of the ICD-9/ICD-10 code for IC/BPS using a national data set. Using the Veterans Affairs Informatics and Computing Infrastructure, they identified a random sample of 100 patients with an ICD-9/ICD-10 diagnosis of IC/BPS (595.1/N30.10) by querying all living patients in the Veterans Affairs (VA) system. They purposely sampled men and women equally to better understand gender-specific practice patterns. Patients were considered a correct IC/BPS diagnosis if they had two visits complaining of bladder-centric pain in the absence of positive urine culture at least 6 weeks apart. Patients were considered not to have IC/BPS if they had a history of pelvic radiation, systemic chemotherapy, metastatic

cancer, or bladder cancer. Of the 100 patients, 48 were female and 52 were male. Five had prior radiation, one had active cancer, and 10 had bladder cancer (all male), and an additional fifteen had insufficient records. Of the remaining 69 patients, 43% did not have IC/BPS. Of these patients who did not have IC/BPS, 43% complained only of overactive bladder (OAB) symptoms, which was more common in women (63%) than men (21%), P = .003. In their small sample from a nationwide VA system, results indicate that IC/BPS has a high misdiagnosis rate. These findings shed light on the gender-specific diagnostic complexity of IC/BPS.

HISTOLOGICAL EVIDENCE SUPPORTS LOW ANESTHETIC BLADDER CAPACITY AS A MARKER OF A BLADDER-CENTRIC DISEASE SUBTYPE IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Schachar JS, Evans RJ, Parks GE, Zambon J, Badlani G, Walker SJ. Int Urogynecol J. 2019 Jun 28. doi: 10.1007/s00192-019-04038-0. [Epub ahead of print] PMID: 31254048

Low anesthetic bladder capacity has been shown to be a biomarker for bladder-centric interstitial cystitis/bladder pain syndrome (IC/BPS). The goal of this study was to determine if histopathological evidence from bladder biopsies supports anesthetic bladder capacity (BC) as a marker to distinguish a bladder-centric IC/BPS subtype. From a review of their large IC/BPS cohort of patients undergoing hydrodistention, they identified a total of 41 patients with low BC (≤ 400 ml); an additional 41 consecutive patients with BC > 400 ml were selected as the comparator group. The original bladder mucosal biopsy pathology slides were re-reviewed by a single pathologist (blinded to patient information) using a standardized grading scale developed for this study. Histologically, the low BC subjects exhibited higher levels of acute inflammation, chronic inflammation, and erosion on microscopy; however, there was no significant difference in mast cell count between groups. There was no significant gender difference between the groups; female patients were the majority in both groups. Individuals in the low BC group were older, had a higher incidence of Hunner's lesions on cystoscopy, and had significantly higher scores, i.e., more bother symptoms, on two IC/BPS questionnaires. It was concluded that IC/BPS patients with low anesthetic bladder capacity have histological evidence of significantly more acute and chronic inflammation compared with patients with a non-low bladder capacity. These data provide additional evidence to support low bladder capacity as a marker of a distinct bladder-centric IC/BPS phenotype.

IC/BPS-ASSOCIATED ALTERATIONS OF M2 AND M3 MUSCARINIC ACETYLCHOLINE RECEPTOR TRAFFICKING IN HUMAN DETRUSOR.

Berndt-Paetz M, Herbst L, Weimann A, Gonsior A, Stolzenburg JU, Neuhaus J. Neurourol Urodyn. 2019 Jul 13. doi: 10.1002/nau.24087. [Epub ahead of print] PMID: 31301091

The aim of this study by Berndt-Paetz and colleagues was to explore caveolae- and clathrin-mediated internalization of muscarinic M2 and M3 receptors, recycling and degradation in formalin-fixed paraffin-embedded detrusor sections and to study alterations possibly involved in the pathophysiology of the bladder functional disorder IC/BPS. Samples of IC/BPS (n = 11) and cystectomy patients were analyzed. Proximity ligation assay (PLA) was used to detect interactions of M2 and M3 with endocytotic regulators (Cav-1, clathrin, Rab7, and Rab11) by Cy3 labelling. Analyses of three-dimensional (3D)-reconstructed z-stacks (63 × Oil 1.4) were done with Huygens software. They determined the object density for quantification and assessed membrane localization. Receptor/protein complexes were detected as well-demarcated 3D objects. Interactions of M2 with Cav-1, clathrin, Rab11, and Rab7 were significantly increased in IC/BPS. M3/clathrin and M3/Rab11 complexes were higher in IC/BPS, while M3/Cav-1 and M3/Rab7 were not. A significant shift of complexes from the membrane to cytoplasm was observed in conjunction with increased internalization via clathrin vesicles or caveolae in IC/BPS. It was concluded that high numbers of M3/clathrin and M3/Rab11 complexes reflect the well-documented clathrin-mediated desensitization of M3 and speak in favor with enhanced receptor protein expression in IC/BPS. Increased amounts of M2/Cav-1, M2/clathrin, and M2/Rab11 complexes represent altered M2 internalization and recycling leading to high abundance in IC/BPS. In this regard, caveolae-localized M2 could be possibly associated with the activation of nitric oxide (NO) synthase and NO production.

HYALURONIC ACID AND CHONDROITIN SULFATE, ALONE OR IN COMBINATION, EFFICIENTLY COUNTERACT INDUCED BLADDER CELL DAMAGE AND INFLAMMATION.

Stellavato A, Pirozzi AVA, Diana P, Reale S, Vassallo V, Fusco A, Donnarumma G, De Rosa M, Schiraldi C. PLoS One. 2019 Jun 25;14(6):e0218475. doi: 10.1371/journal.pone.0218475. eCollection 2019. PMID: 31237905

Interstitial cystitis and/or bladder pain syndrome (IC/BPS) are characterized by discomfort, abdominal pain, and pelvic pain, and they are often associated with chronic diseases. Pathological conditions related to IC/BPS can occur due to a defect in the integrity of the bladder lining. This defect has been ascribed to damage to the glycosaminoglycan (GAG) layer of the urinary epithelium. In addition, the incipient cascade of inflammation events might prompt extracellular matrix degradation. Several medical devices based on GAG instillation were

proposed to re-establish epithelial integrity by GAGs binding to proteoglycans or interacting with structural urothelium. However, to date, only in vitro studies have investigated the GAG, hyaluronic acid (HA). In the present study, TNFα treatment was used to mimic IC/BPS-induced damage in bladder cells in an in vitro model. Highly purified fermentative HA and pharmaceutical grade bovine chondroitin sulfate (CSb), alone or in combination, were evaluated for the ability to counteract bladder cell damage. The authors evaluated NF-κB with western blots, and analyzed interleukin 6 and 8 expression at the transcriptional and protein levels with quantitative RT-PCR, western blotting, and ELISA. They also evaluated the expression of an antibacterial peptide, human β-defensin-2. They confirmed our results in a 3D bladder epithelium model. Their results demonstrated that inflammatory status was reduced in the presence of HA, CSb, and the combination of both (HA/CSb 1.6%/2% w/v). This result suggested that these GAGs might be suitable for treating IC/BPS. All the assayed biomarkers showed that HA/CSb treatment modulated cells towards a more physiological status. Finally, they compared two commercial products suggested for the IC/BPS treatments and found that the product with more Ca++, showed enhanced anti-inflammatory activity and provided superior mucoadhesivity.

PARTNERS IN CRIME: NGF AND BDNF IN VISCERAL DYSFUNCTION.

Coelho A, Oliveira R, Antunes-Lopes T, Cruz CD. Curr Neuropharmacol. 2019 Jun 16. doi: 10.2174/1570159X17666190617095844. [Epub ahead of print] PMID: 31204623

Neurotrophins (NTs), particularly Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF), have attracted increasing attention in the context of visceral function for some years. Here, Coelho and colleagues examined current literature and produced a thorough review on the subject. After initial studies linking NGF to cystitis, it is now well-established that this neurotrophin (NT) is a key modulator of bladder pathologies, including Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). NGF is upregulated in bladder tissue and its blockade results in major improvements on urodynamic parameters and pain. Further studies expanded showed that NGF is also an intervenient in other visceral dysfunctions such as endometriosis and Irritable Bowel Syndrome (IBS). More recently, BDNF was also shown to play an important role in the same visceral dysfunctions, suggesting that both NTs are determinant factors in visceral pathophysiological mechanisms. While manipulation of NGF and BDNF improves visceral function and reduce pain, suggesting that clinical modulation of these NTs may be important, much is still to be investigated before this step is taken. Another active area of research is centred on urinary NGF and BDNF. Several studies show that both NTs can be found in the urine of patients with visceral dysfunction in much higher concentration than in healthy individuals, suggesting they could be used as potential biomarkers. However, there are still technical difficulties to be overcome, including the lack of a large multicentre placebo-controlled studies to prove the relevance of urinary NTs as clinical biomarkers.

TEMPERATURE-RESPONSIVE SILK-ELASTINLIKE PROTEIN POLYMER ENHANCEMENT OF INTRAVESICAL DRUG DELIVERY OF A THERAPEUTIC GLYCOSAMINOGLYCAN FOR TREATMENT OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Jensen MM, Jia W, Schults AJ, Isaacson KJ, Steinhauff D, Green B, Zachary B, Cappello J, Ghandehari H, Oottamasathien S. Biomaterials. 2019 Jun 20;217:119293. doi: 10.1016/j.biomaterials.2019.119293. [Epub ahead of print] PMID: 31276948

Interstitial cystitis (IC), also known as painful bladder syndrome, is a debilitating chronic condition with many patients failing to respond to current treatment options. Rapid clearance, mucosal coating, and tight epithelium create strong natural barriers that reduce the effectiveness of many pharmacological interventions in the bladder. Intravesical drug delivery (IDD) is the administration of therapeutic compounds or devices to the urinary bladder via a urethral catheter. Previous work in improving IDD for IC has focused on the sustained delivery of analgesics within the bladder and other small molecule drugs which do not address underlying inflammation and bladder damage. Therapeutic glycosaminoglycans (GAG) function by restoring the mucosal barrier within the bladder, promoting healing responses, and preventing irritating solutes from reaching the bladder wall. There is an unmet medical need for a therapy that provides both acute relief of symptoms while alleviating underlying physiological sources of inflammation and promoting healing within the urothelium. Semi-synthetic glycosaminoglycan ethers (SAGE) are an emerging class of therapeutic GAG with intrinsic anti-inflammatory and analgesic properties. To reduce SAGE clearance and enhance its accumulation in the bladder, the authors developed a silk-elastinlike protein polymer (SELP) based system to enhance SAGE IDD. They evaluated in vitro release kinetics, rheological properties, impact on bladder function, pain response, and bladder inflammation and compared their effectiveness to other temperature-responsive polymers including Poloxamer 407 and poly(lactic-co-glycolic acid)-poly(ethylene glycol). SAGE delivered via SELP-enhanced intravesical delivery

substantially improved SAGE accumulation in the urothelium, provided a sustained analgesic effect 24 h after administration, and reduced inflammation.

DIFFERENTIATION OF UROTHELIUM FROM MOUSE EMBRYONIC STEM CELLS IN CHEMICALLY DEFINED CONDITIONS.

Boumelhem BB, Fraser ST, Assinder SJ. Methods Mol Biol. 2019;2029:103-115. doi: 10.1007/978-1-4939-9631-5_9. PMID: 31273737

The urothelium of the bladder and urethra are derived from the definitive endoderm during development. Cellular signalling molecules important to the developmental specification of the urothelium are also implicated in the dysregulation of the tissue repair mechanism characteristic of bladder disease. Hence, a complete understanding of the regulation of urothelium development is central to understanding the processes of bladder disease, and in development of simple chemically defined methods for use in regenerative medicine. Key to this is a suitable in vitro model that readily allows for the prosecution of biologically pertinent questions. Here a method for differentiating urothelium from mouse embryonic stem cells in chemically defined conditions is described. The method includes a description of flow cytometry and RT-PCR analysis of definitive endoderm markers Cxcr4, c-Kit, and FoxA2, and of terminally differentiated urothelial cell markers Upk1b and Upk2.

MIF MEDIATES BLADDER PAIN, NOT INFLAMMATION, IN CYCLOPHOSPHAMIDE CYSTITIS.

Ma F, Kouzoukas DE, Meyer-Siegler KL, Hunt DE, Leng L, Bucala R, Vera PL. Cytokine X. 2019 Mar;1(1). pii: 100003. doi: 10.1016/j.cytox.2019.100003. Epub 2019 Jan 23. PMID: 31289792

Macrophage migration inhibitory factor (MIF), a proinflammatory mediator, is recognized as a player in inflammatory and neuropathic pain. Cyclophosphamide (CYP) results in bladder inflammation and pain and it's a frequently used animal model of interstitial cystitis/bladder pain syndrome (IC/BPS). Because pretreatment with a MIF inhibitor (ISO-1) prevented both CYP-induced bladder pain and inflammation the authors used genetic MIF knockout (KO) mice to further investigate MIF's role in CYP-induced bladder pain and inflammation. Abdominal mechanical threshold measured bladder pain induced by CYP in wild type (WT) and MIF KO mice at several time points (0-48 hours). End-point (48 hours) changes in micturition parameters and histological signs of bladder inflammation were also evaluated. Abdominal mechanical hypersensitivity developed within 4 hours after CYP injection (and lasted for the entire observation period: 48 hours) in WT mice. MIF KO mice, on the other hand, did not develop abdominal mechanical hypersensitivity suggesting that MIF is a pivotal molecule in mediating CYP-induced bladder pain. Both WT and MIF KO mice treated with CYP showed histological signs of marked bladder inflammation and showed a significant decrease in micturition volume and increase in frequency. Since both changes were blocked in MIF KO mice by pretreatment with a MIF inhibitor (ISO-1) it is likely these are non-specific effects of ISO-1. MIF mediates CYP-induced bladder pain but not CYP-induced bladder inflammation. The locus of effect (bladder) or central (spinal) for MIF mediation of bladder pain remains to be determined.

NEUROMODULATION IN UROLOGY, STATE OF THE ART.

Ammirati E, Giammò A, Manassero A, Carone R. Urologia. 2019 Aug 1:391560319866075. doi: 10.1177/0391560319866075. [Epub ahead of print] PMID: 31368415

Sacral neuromodulation is an approved and validated treatment for overactive bladder syndrome, chronic non-obstructive retention, and chronic pelvic pain. Percutaneous tibial nerve stimulation is a less invasive approach of neuromodulation. Ammirati and colleagues performed a literature research to assess the current evidence available about neuromodulation. Both techniques appear to be effective and safe third-line treatments. The overall success rate ranges from 43% to 85% for sacral neuromodulation and from 40% to 79.5% for percutaneous tibial nerve stimulation. Sacral neuromodulation has a higher incidence of complications in comparison to percutaneous tibial nerve stimulation, due to the more invasive surgical technique and the presence of a permanent implant. The incidence of surgical revision ranges between 9% and 33%. The most frequent complication with sacral neuromodulation is pain at implant site (15%-42%), followed by lead migration (4%-21%), pain at lead site (5.4%-19.1%), leg pain (18%), and infection (5.7%-6.1%). The quality of the studies on sacral neuromodulation and percutaneous tibial nerve stimulation in literature is quite modest, because of the shortage of good randomized clinical trials; most of the studies are prospective observational studies with mid-term follow-up.

TERMINOLOGY REPORTS/GUIDELINES

INTERSTITIAL CYSTITIS, BLADDER PAIN SYNDROME, HYPERSENSITIVE BLADDER, AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME - CLARIFICATION OF DEFINITIONS AND RELATIONSHIPS.

Homma Y. Int J Urol. 2019 Jun;26 Suppl 1:20-24. doi: 10.1111/iju.13970. PMID: 31144731

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Interstitial cystitis and interstitial cystitis-related conditions such as bladder pain syndrome and hypersensitive bladder have a similar symptomatic profile but probably different etiologies. A meaningful classification of these diseases/conditions is mandatory for clinical and investigational progress. The condition with Hunner lesions (Hunner type interstitial cystitis) is distinct from other categories in terms of histopathology, gene expression, and clinical management. Classification should clearly differentiate the presence or absence of Hunner lesions. The term covering patients as a whole should contain interstitial cystitis, since interstitial cystitis is historically a well-known name and used for insurance reimbursement. The proposed taxonomy features an umbrella term (interstitial cystitis/bladder pain syndrome) and two subgroups, Hunner type interstitial cystitis (with Hunner lesions) and bladder pain syndrome (without Hunner lesions). Interstitial cystitis/bladder pain syndrome is convenient for initial management, and subgroups can categorize the patients for specific management. The characteristic symptom profile is to be collectively termed as hypersensitive bladder symptoms.

OVERACTIVE BLADDER AND IC/BPS

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

Thu JHL, Vetter J, Lai HH. Urology. 2019 Aug;130:59-64. doi: 10.1016/j.urology.2019.03.030. Epub 2019 Apr 26. PMID: 31034917 P

The objectives of this study were (1) to compare the severity and distribution of nonurologic and urogenital pain between overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS) and controls, and (2) to examine the relationships between the severity of urogenital pain and severity of urinary symptoms among patients with OAB. Fifty-one OAB patients, 27 IC/BPS patients, and 30 controls were recruited. Nonurologic 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 nonurologic pain and urogenital pain in OAB patients were 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) was 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 has pain inside 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.

LOWER URINARY TRACT AND SYSTEMIC AUTOIMMUNE DISEASES

RISKS OF INTERSTITIAL CYSTITIS AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED COHORT STUDY.

Wen JY, Lo TS, Chuang YC, Ho CH, Long CY, Law KS, Tong YC, Wu MP. Int J Urol. 2019 Jul 16. doi: 10.1111/iju.14065. [Epub ahead of print] PMID: 31311067

The purpose of this study was to investigate whether the risk of interstitial cystitis increases among the patients with systemic lupus erythematosus. This was a nationwide population-based cohort study. Data were obtained from the National Health Insurance Research Database in Taiwan. Women aged >18 years newly diagnosed as systemic lupus erythematosus during 2001-2008 were identified as the control group. The comparison included individuals randomly selected from the National Health Insurance Research Database in the year of 2000, by matching one systemic lupus erythematosus participant with eight non-systemic lupus erythematosus participants with sex and age. These participants were followed up until being diagnosed as interstitial cystitis, or the end of 2011. Women diagnosed with lupus cystitis were excluded from this study. This study included 7240 women with systemic lupus erythematosus and 57 920 women without systemic lupus erythematosus as controls. The incidence rate of interstitial cystitis was significantly higher in the systemic lupus erythematosus group, with an incidence rate ratio of 2.26 (95% confidence interval 1.57-3.27, $P < 0.0001$). After adjustment,

the risk increased by 2.45-fold (adjusted hazard ratio 2.45, 95% confidence interval 1.57-3.27, P < 0.05). Age as a factor increases incidence rate ratios among all age groups, 2.12-, 3.32- and 4.65-fold. Age ≥45 years had an increased adjusted hazard ratio (2.07, 95% confidence interval 1.37-3.13, P < 0.05). Comorbidities, for example, hypertension, diabetes mellitus, dyslipidemia and renal disease, were insignificant. This is the first population-based cohort study showing a higher incidence of interstitial cystitis among patients with systemic lupus erythematosus. These findings support the concordance of interstitial cystitis with autoimmune diseases, and the temporal relationship to develop interstitial cystitis in patients with systemic lupus erythematosus.

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

Pereira E Silva R, Romão VC, Neves M, Garcia R, Oliveira S, Brites J, Ramos FO, Canhão H, Palma Dos Reis J, Pereira da Silva JA, Lopes T. Lupus. 2019 Jan;28(1):27-33. doi: 10.1177/0961203318811605. Epub 2018 Nov 12. PMID: 30419773

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

PAIN/CHRONIC PELVIC PAIN

GYNECOLOGICAL ASSOCIATED DISORDERS AND MANAGEMENT.

Jia X, Rana N, Crouss T, Whitmore KE. Int J Urol. 2019 Jun;26 Suppl 1:46-51. doi: 10.1111/iju.13974. PMID: 31144734

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Chronic pelvic pain syndrome is complex and involves multiple organ systems. The gynecological aspects of chronic pelvic pain syndrome can be divided into four different areas: intra-abdominal, vaginal, pelvic floor muscles and sexual pain. This article provides an overview of gynecological evaluation in patients with chronic pelvic pain and reviews the most common gynecological diagnoses and their management. An extensive review of the literature including guidelines from the International Continence Society, the European Association of Urology, and the International Association for the Study of Pain was performed. Gynecological evaluation of patients with chronic pelvic pain begins with a thorough history and physical examination. Laboratory tests, imaging studies and diagnostic procedures can be used as adjuncts to make a diagnosis. Treatment modalities include physical therapy, medications, trigger points injections, and surgery. Common gynecological diagnoses of chronic pelvic pain include endometriosis, adenomyosis, vulvodynia, high tone pelvic floor dysfunction, and genitopelvic pain/penetration disorder. Gynecology is one of the many systems that can be associated with chronic pelvic pain. Managing patients with chronic pelvic pain requires a multimodal and multidisciplinary approach.

CURRENT USAGE OF QUALITATIVE RESEARCH IN FEMALE PELVIC PAIN: A SYSTEMATIC REVIEW.

Mellado BH, Pilger TL, Poli-Neto OB, Rosa E Silva JC, Nogueira AA, Candido Dos Reis FJ. Arch Gynecol Obstet. 2019 Jun 14. doi: 10.1007/s00404-019-05212-x. [Epub ahead of print] PMID: 31201537

Qualitative research has received growing attention in the multidisciplinary investigation of patients' perceptions about chronic diseases. The purpose of this systematic review was to characterize the usage of qualitative research in women with chronic pelvic pain (CPP). The authors performed a structured search in Web of Science, Pubmed, and EMBASE platforms until June 2019. Qualitative studies on female CPP were included and the main findings combined using thematic synthesis. They found 1211 citations, of which 52 were included in this review. The majority of included studies were based on phenomenological design. The main method for

data collection was semi-structured interviews. Endometriosis was the theme of 23 studies, chronic pelvic pain of eight, dysmenorrhea of eight, dyspareunia of four, interstitial cystitis of two, vaginismus of two, vulvodynia of two, and pelvic inflammatory disease of one study. They found a wide variety of contributions. Among them, the impact of the disease on women's lives was the commonest. Qualitative research has the potential to reveal and explain several aspects of CPP in women. The medical community may better accept knowledge gained from these studies if the methods are described more transparently in published articles.

CANNABINOIDS/PAIN TREATMENT

[EVIDENCE OF THE EFFICACY AND SAFETY OF CANNABIS MEDICINES FOR CHRONIC PAIN MANAGEMENT : A METHODOLOGICAL MINEFIELD]. [Article in German]
Häuser W, Petzke F. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2019 Jul;62(7):836-844. doi: 10.1007/s00103-019-02966-2. PMID: 31139839
Recent systematic reviews (SRs) came to divergent conclusions on the efficacy and safety of medical marijuana and cannabis-based medicines for chronic pain management. This paper gives an overview and critical appraisal of the methods of recent SRs of randomized controlled trials (RCTs) with cannabis medicines for chronic pain. Selective search of the literature, incorrect data analyses and presentation in favour of cannabis medicines can be detected in both RCTs and SRs. The more detailed the search of literature (e.g. inclusion of so-called grey literature) and the higher the criteria of the inclusion of studies (such as study duration) and of the clinical relevance of the study findings, the more disappointing are the conclusions of SRs on the efficacy and safety of cannabis medicines. There is moderate quality evidence of a moderate relief of neuropathic pain. Cannabis medicines can be regarded to be third-line therapy for chronic neuropathic pain. There are signals of a lack of efficacy for all other chronic pain syndromes. New high-quality RCTs and approaches, such as network meta-analyses combining different treatments and controlled and observational including additional outcomes than pain relief, are necessary to better define the importance of cannabis medicines for chronic pain management.

CANNABIS-BASED MEDICINES FOR CHRONIC PAIN MANAGEMENT: CURRENT AND FUTURE PROSPECTS.
Sharon H1,2,3,4, Brill S1. Curr Opin Anaesthesiol. 2019 Jul 25. doi: 10.1097/ACO.0000000000000775. [Epub ahead of print] PMID: 31356363
The medicinal use of cannabis has recently become the focus of much medical, as well as political, attention. This reality of growing use but limited evidence creates unique dilemmas for the prescribing clinician. The purpose of this review is to explore current evidence and gaps in knowledge and offer some practical considerations. There is robust preclinical data regarding the relevance of the endocannabinoid system to many pain-relevant processes. However, evidence to support cannabis-based medicines clinical use is still lacking. The best evidence to date is in managing neuropathic pain, although whether effects are clinically significant remains undetermined. However, the safety profile of cannabinoids seems favorable, especially by comparison to other medications used for pain control. The endocannabinoid system is undoubtedly a new and exciting pharmaceutical target for chronic pain management, but transition from preclinical to clinical studies has so far proved difficult. Although it is reasonable to consider cannabinoids for otherwise unresponsive pain, care should be taken in frail clinical populations. As this has become a socioeconomic and political issue in which agendas often take precedence over due diligence, there is a pressing need for unbiased empirical data and high quality evidence to better inform prescribers and patients.

SJÖGREN'S SYNDROME

MANAGING FATIGUE IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME: CHALLENGES AND SOLUTIONS.
Miyamoto ST, Lendrem DW, Ng WF, Hackett KL, Valim V. Open Access Rheumatol. 2019 Apr 24;11:77-88. doi: 10.2147/OARRR.S167990. eCollection 2019. Open Access Rheumatol. 2019 Apr 24;11:77-88. doi: 10.2147/OARRR.S167990. eCollection 2019. PMID: 31118841
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Primary Sjögren's syndrome (pSS) patients identify fatigue as their most important symptom and the one most difficult to cope with, but there are still many challenges and few solutions to manage this debilitating symptom. Promising pharmacological treatments, such as rituximab, have failed in more stringent tests including randomized controlled trials (RCTs) and meta-analysis. While non-pharmacological interventions may be safer, less costly, and address other common comorbidities, to date only aerobic exercise seems to be effective at reducing fatigue in pSS. All interventions, pharmacological or not, need to be tested in high-quality RCTs. The

aim of this review is to provide an overview of fatigue management in pSS and discuss potential opportunities for future research.

FIBROMYALGIA

AAPT DIAGNOSTIC CRITERIA FOR FIBROMYALGIA.

Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, Fitzcharles MA, Paiva ES, Staud R, Sarzi-Puttini P, Buskila D, Macfarlane G. J Pain. 2018 Nov 16. pii: S1526-5900(18)30832-0. doi: 10.1016/j.jpain.2018.10.008. [Epub ahead of print] PMID: 30453109

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Fibromyalgia (FM) is a common chronic pain disorder that presents diagnostic challenges for clinicians. Several classification, diagnostic and screening criteria have been developed over the years, but there continues to be a need to develop criteria that reflect the current understanding of FM and are practical for use by clinicians and researchers. The Analgesic, Anesthetic and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the U.S. Food and Drug Administration (FDA) and the American Pain Society (APS) initiated the ACTTION-APS Pain Taxonomy (AAPT) to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders. The AAPT established an international FM working group consisting of clinicians and researchers with expertise in FM to generate core diagnostic criteria for FM and apply the multidimensional diagnostic framework adopted by AAPT to FM. The process for developing the AAPT criteria and dimensions included literature reviews and synthesis, consensus discussions, and analyses of data from large population-based studies conducted in the United Kingdom. The FM working group established a revised diagnosis of FM and identified risk factors, course, prognosis, and pathophysiology of FM. Future studies will assess the criteria for feasibility, reliability, and validity. Revisions of the dimensions will also be required as research advances our understanding of FM. PERSPECTIVE: The ACTTION-APS FM taxonomy provides an evidence-based diagnostic system for FM. The taxonomy includes diagnostic criteria, common features, comorbidities, consequences, and putative mechanisms. This approach might improve the recognition of FM in clinical practice.

RETHINKING THE CRITERIA FOR FIBROMYALGIA IN 2019: THE ABC INDICATORS

Stewart JA, Mailler-Burch S, Müller D, Studer M, von Känel R, grosse Holtforth M, Schwegler K, Egloff N. Dove Med Press 10 July 2019 Volume 2019:12 Pages 2115—2124

Diagnostic criteria for fibromyalgia have been subject to debate and controversy for many years. The preliminary diagnostic criteria introduced in 2010 and 2011 have been criticized for different reasons, including questionable diagnostic specificity and a lack of an etiopathogenetic foundation. The “ABC indicators” presented in this Swiss study reflect a further development of the 2011 criteria and refer to (A) algesia, (B) bilateral, axial-symmetric pain distribution, and (C) chronic distress. Stewart and colleagues compared the diagnostic performance of the ABC indicators with that of the 2011 criteria by analyzing the data of 409 inpatients with chronic functional pain divided into two subgroups of pain patients: Those with whole-body pain and those with pain not involving the whole body. Under the premise that FM phenotypically represents a whole-body pain disorder, sensitivity, specificity, correct classification and diagnostic odds ratios were calculated. The 2011 criteria demonstrated a specificity of 68.1%, a sensitivity of 75.5%, a correct classification of 71.0% and a diagnostic odds ratio of 6.56 (CI: 4.17–10.31). The ABC indicators achieved a specificity of 88.3%, a sensitivity of 62.3%, a correct classification of 78.6%, and a diagnostic odds ratio of 12.47 (CI: 7.30–21.28). It was concluded that the ABC fibromyalgia indicators demonstrated better specificity, lower sensitivity, and better overall diagnostic effectiveness than the original 2011 criteria.

IRRITABLE BOWEL SYNDROME

MANY PATIENTS WITH IRRITABLE BOWEL SYNDROME HAVE ATYPICAL FOOD ALLERGIES NOT ASSOCIATED WITH IMMUNOGLOBULIN E.

Fritscher-Ravens A, Pflaum T, Mösinger M, Ruchai Z, Röcken C, Milla PJ, Das M, Böttner M, Wedel T, Schuppan D. Gastroenterology. 2019 May 14. pii: S0016-5085(19)34636-0. doi: 10.1053/j.gastro.2019.03.046. [Epub ahead of print] PMID: 31100380

Confocal laser endomicroscopy (CLE) is a technique that permits real-time detection and quantification of changes in intestinal tissues and cells, including increases in intraepithelial lymphocytes and fluid extravasation through epithelial leaks. Using CLE analysis of patients with irritable bowel syndrome (IBS), the authors found that more than half have responses to specific food components. Exclusion of the defined food led to long-term

symptom relief. The authors used results of CLE to detect reactions to food in a larger patient population, and analyzed duodenal biopsies and fluid from patients to investigate mechanisms of these reactions. In a prospective study, 155 patients with IBS received 4 challenges with each of 4 common food components via the endoscope, followed by CLE, at a tertiary medical center. Classical food allergies were excluded by negative results from immunoglobulin E serology analysis and skin tests for common food antigens. Duodenal biopsies and fluid were collected 2 weeks before and immediately following CLE, and analyzed by histology, immunohistochemistry, reverse transcription PCR, and immunoblots. Results from patients who had a response to food during CLE (CLE+) were compared with results from patients who did not have a reaction during CLE (CLE-) or healthy individuals (controls). In a CLE analysis of patients with IBS, it was found that more than 50% of patients could have nonclassical food allergy, with immediate disruption of the intestinal barrier upon exposure to food antigens. Duodenal tissues from patients with responses to food components during CLE had immediate increases in expression of claudin-2 and decreases in occludin. CLE+ patients also had increased eosinophil degranulation, indicating an atypical food allergy characterized by eosinophil activation.

VULVODYNIA

THE ASSOCIATION OF VULVAR PAIN AND UROLOGICAL URGENCY AND FREQUENCY: FINDINGS FROM A COMMUNITY-BASED CASE-CONTROL STUDY.

Sun Y, Harlow BL. Int Urogynecol J. 2019 Aug 2. doi: 10.1007/s00192-019-04052-2. [Epub ahead of print] PMID: 31375872

Vulvodynia is chronic debilitating burning vulvar pain or pain on contact. Although women who suffer from vulvodynia are more likely than others to experience co-morbid interstitial cystitis (IC) and urinary tract infections (UTIs), few studies have explored whether women with vulvodynia experience adverse urinary symptoms (lower urinary tract symptoms [LUTS]) in the absence of urological pain. In this study, 211 participants with and 226 participants without clinically confirmed vulvodynia completed the Pelvic Pain and Urgency/Frequency (PUF) questionnaire and were scored using all questions, and then a subset of questions relating only to their current frequency and bother of urination during day and night, and the frequency, severity and bother of urgency after voiding. Total, symptom, and bother scores were compared in women with and without vulvodynia, and regression models estimated adjusted odds ratios and 95% confidence intervals for the various LUTS symptoms. As expected, 40% of women with vulvodynia met the criteria for IC (PUF > 12) compared with 2% without vulvodynia. After excluding questions related to bladder or vulvovaginal pain, women with vulvodynia, compared with those without, were skewed toward higher PUF scores, including being 2.4 times more likely to report usually or always bothered by night-time voiding, and 18 times more likely to report moderate/severe urgency after urination. It was concluded that women with vulvodynia are substantially more likely to report voiding dysfunction and symptoms of urgency than women with no history of vulvar pain. These findings are independent of comorbid interstitial cystitis or history of UTIs.

STUDY ON THE PREVALENCE AND FACTORS ASSOCIATED TO VULVODYNIA IN SPAIN.

Gómez I, Coronado PJ, Martín CM, Alonso R, Guisasola-Campa FJ. Eur J Obstet Gynecol Reprod Biol. 2019 Jun 21;240:121-124. doi: 10.1016/j.ejogrb.2019.06.005. [Epub ahead of print] PMID: 31260857

The purpose of this study was to study the prevalence and epidemiological characteristics of women with vulvodynia and to assess the risk factors associated to the disease. A cross-sectional study was made in which questionnaires were anonymously and confidentially distributed to Spanish women over 18 years of age between April 2016 and September 2017. The questionnaires were distributed by e-mail and through social networks, women's associations and specific websites. This type of questionnaire has been validated and used in many studies of this kind. The women answered questions referred to epidemiological aspects, demographic parameters, medical history, the presence of vulvodynia, associated factors, and comorbidities. A total of 684 questionnaires were completed. The prevalence of vulvodynia was 6.6% (45 women). Thirteen percent (95 women) had experienced vulvodynia at some point in life. The factors associated to vulvodynia were prior vaginal deliveries, vulvovaginal candidiasis and urinary tract infections. Other pain syndromes such as fibromyalgia, painful bladder syndrome/interstitial syndrome, temporomandibular joint pain, coxofemoral pain or headache have also been associated to vulvodynia. The prevalence of vulvodynia in Spain is similar to that found in other countries. Many factors are involved in its development and persistence, particularly the presence of other pain syndromes and recurrent infections that could trigger complex inflammatory reactions.

REIMBURSEMENT

ALTERNATIVE ACCESS SCHEMES FOR PHARMACEUTICALS IN EUROPE: TOWARDS AN EMERGING TYPOLOGY.

Löblová O, Csanádi M, Ozierański P, Kaló Z, King L, McKee M. Health Policy. 2019 Jul;123(7):630-634. doi: 10.1016/j.healthpol.2019.05.012. Epub 2019 May 20. PMID: 31130319

European governments employ sophisticated health technology assessment and regulatory procedures to identify which pharmaceuticals to fund publicly. However, there are persisting demands from patients for those drugs excluded from positive reimbursement lists, leading to the emergence of what are here termed "alternative access schemes". This paper presents a purposive review of these schemes based on available scholarly and grey literature, illustrated with real-world examples from recent practice. It puts forward an original typology of alternative access schemes based on their marketing authorization (regulation) and reimbursement (redistribution) status. The authors describe the complex, multidimensional policy trade-offs between the principles of patient freedom of choice, clinical autonomy, encouragement of innovation, evidence-informed decisions on safety and quality, access to treatment, and financial sustainability, involved in marketing authorization and reimbursement decisions. They discuss the ways in which alternative access schemes differ and conclude that their typology can illuminate salient policy dilemmas raised by alternative access schemes in national drug reimbursement systems.

PATTERNS OF ALTERNATIVE ACCESS: UNPACKING THE SLOVAK EXTRAORDINARY DRUG REIMBURSEMENT REGIME 2012-2016.

Löblová O, Csanádi M, Ozierański P, Kaló Z, King L, McKee M. Health Policy. 2019 Aug;123(8):713-720. doi: 10.1016/j.healthpol.2019.05.021. Epub 2019 Jun 8. PMID: 31277882

Many countries employ "alternative access schemes" (e.g. compassionate use, early access programs, off-label use) that seek to provide patients with access to drugs not included on a positive drug list. These schemes offer flexibility to policymakers but often lack transparency and clear rules. This ambiguity allows for dynamic responses to weaknesses in the main drug approval and reimbursement systems, but also opportunistic use by the health professionals, industry or patients. Yet, most descriptions of these schemes focus on the de jure rather than the de facto situation, presenting a potentially misleading picture. The authors describe one such scheme in practice: the Slovak "extraordinary reimbursement regime" (ERR), using semi-structured interviews with 18 experts and a new dataset of ERR drugs. The ERR expanded rapidly, doubling between 2012 and 2016. It combined features of four reimbursement schemes: (1) a backdoor market access for expensive drugs; (2) a compassionate use scheme for investigational drugs combined with a "legacy drugs" scheme for older unlicensed drugs; (3) a disease-specific scheme for cancer and orphan drugs; and (4) a scheme for off-label and "off-indication" drugs. These four features reflect broader challenges facing the Slovak reimbursement system. They conclude that detailed study of the type, size and evolution over time of alternative access schemes can serve as indicators of health policy objectives neglected by standard reimbursement systems.

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