

# International Painful Bladder Foundation

*The IPBF is a voluntary non-profit organization for interstitial cystitis/bladder pain syndrome/hypersensitive bladder*  
[www.painful-bladder.org](http://www.painful-bladder.org)

## IPBF e-Newsletter and Research Update

Issue 35, January 2014

*An IPBF update 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, chronic pelvic pain and associated disorders.*

This issue of the IPBF e-Newsletter includes the following topics:

- **Happy New Year!**
- **Meeting Reviews**
- **Upcoming Events**
- **Studies**
- **Books**
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### HAPPY NEW YEAR 2014! ANOTHER YEAR WITH MANY CHALLENGES

First of all, the IPBF would like to wish all its readers a Happy and Healthy New Year. 2014 will undoubtedly present many challenges for the IC/BPS and chronic pelvic pain world, but we are used to challenges and difficulties, we have always faced them, and this year will be no different. The global economic crisis has led to the need for huge cutbacks in healthcare systems, inevitably resulting in prioritizing. In Europe, for example, we are seeing overburdened and financially hard-pressed health services resorting to cutting back on treatments and drugs covered by insurance. It is also a fact of life that governments today, with their huge deficits, are only interested in short-term financial solutions and it does not occur to them that patients who do not receive proper treatment today may need far more expensive treatment or surgery in the future.

The patient organisations around the world which represent the indispensable “rock” for many IC/BPS patients are very active and have themselves developed considerable expertise and knowledge of the full spectrum of IC/BPS. But in many countries, they too are suffering from the global economic crisis and are naturally very concerned about how they can best help their members who may have no affordable access to effective treatment or even to a doctor. These are huge challenges for patients and health professionals and we have to make sure that our IC/BPS patients are not swept under the carpet by health authorities anxious to cut expenses at any cost! While research is becoming increasingly global with multi-centre studies covering several countries, treatment is still a “local” affair. Treatment available in one country is neither available nor affordable in another.

This situation has not been helped by frequent changes in terminology in a healthcare world now dominated by electronic coding systems and multiple authorities with a finger in the healthcare pie. If codes do not match, the result can be lack of reimbursement of treatment, inability to claim social benefits, etc.

A further problem we are now facing, particularly in the Western countries where the IC movement began, is that many of our highly dedicated doctors with their expertise and empathy are now reaching retirement age. This means that we need to do our utmost to attract trainee specialists into this field worldwide.

On the positive side, the good news is that despite financial restraints we are seeing more research from around the globe – and on a large scale from the very active East Asian researchers - into the wide spectrum of

IC/BPS, chronic pelvic pain, the complexities of the nervous system and neuro-urology, comorbidities and their interactions, biomarkers and many new avenues of research and hopefully this will eventually bear fruit in the form of new treatment. Research into phenotyping (= subtyping patients) should eventually lead to less trial and error in treatment and consequently less wastage and a reduction in costs. We are also witnessing a welcome surge of interest by the allied professions, including nurses and physiotherapists, with dedicated pelvic pain physiotherapy centres being set up in many countries.

## MEETING REVIEWS

### KYOTO ICICJ3/ESSIC MEETING REVIEW

The International Journal of Urology (IJU) special supplement on the ICICJ3/ESSIC meeting held in Kyoto in 2013 is expected to be published in March this year. We will keep you updated.

Our own review of the ICICJ3/ESSIC 2013 conference is still available on the IPBF website, [click here](#).

## UPCOMING EVENTS

### ROYAL SOCIETY OF MEDICINE (RSM), ABDOMINAL PAIN MEETING, 24 JANUARY

The RSM is organising a meeting on abdominal pain on Friday 24 January 2014 at the Royal Society of Medicine, 1 Wimpole Street, LONDON. The aim is to inform participants of the basic mechanisms of abdominal pain in health and disease. The audience will learn about the latest advances in the pathophysiology of abdominal pain and learn about psychological and pharmacological treatments. Further information, [click here](#).

### RARE DISEASE DAY: 28 FEBRUARY 2014

### IAPO 6TH GLOBAL PATIENTS CONGRESS 29-31 MARCH 2014, ASCOT UK,

IAPO is the International Alliance of Patients' Organizations ([www.patientsorganizations.org](http://www.patientsorganizations.org)). The theme of the 6th Global Patients Congress is: Better access, better health: A patient-centred approach to universal health coverage. The Congress will be held on 29-31 March 2014 in Ascot, UK. This event is the global event for patient leaders and others working to improve healthcare systems globally. The 6th Global Patients Congress will bring together expertise and experience in how to build patient-centred healthcare globally. The Congress provides a global platform for high level policy debate, knowledge and skills building and opportunities for exchange and networking. Multi-stakeholder plenary and workshop sessions will focus on topics that explore questions such as: What are the barriers to access to healthcare in different world regions? What are the principles that promote equity? What are the indicators of quality healthcare? What is the value of innovation? How should healthcare be financed? The members' day will include capacity-focussed sessions on how patients' organizations can advocate on issues of access to healthcare. The multi-stakeholder programme will explore a patient-centred approach as it relates to three themes: equity, quality and finance in all world regions. For further information, [click here](#).

### EUROPEAN ASSOCIATION OF UROLOGY (EAU) 29TH ANNUAL CONGRESS, 11-15 APRIL, 2014. STOCKHOLM

This congress will include poster session 38 on painful bladder syndrome, hemorrhagic and interstitial cystitis on Sunday 13 April while ESU Course 29 on Monday 14 April concerns chronic pelvic pain in men and women.

For full programme, go to [www.eaustockholm2014.org](http://www.eaustockholm2014.org).

### THE EUROPEAN CONFERENCE ON RARE DISEASES & ORPHAN PRODUCTS (ECRD 2014), 8-10 MAY 2014, ANDEL'S HOTEL, BERLIN, GERMANY

The European Conference on Rare Diseases & Orphan Products (ECRD) is the unique platform/forum across all rare diseases, across all European countries, bringing together all stakeholders: patients' representatives, academics, health care professionals, industry, payers, regulators and policy makers. ECRD covers research, development of new treatments, healthcare, social care, information, public health and support at European, national and regional levels. ECRD provides the state of the art of the rare disease environment, monitoring and benchmarking initiatives. The advanced programme for ECRD Berlin 2014 is now available online in 6 languages: [English](#), [French](#), [Spanish](#), [German](#), [Russian](#) and [Polish](#). For further information, [click here](#).

This conference is organized by **EURORDIS** (<http://www.eurordis.org>), a non-governmental patient-driven alliance of patient organizations representing 606 rare disease patient organizations in 56 countries covering

over 4000 diseases. ECRD 2014 will include the annual EURORDIS membership General Assembly which will be held on Thursday, 8 May at the Andel's Hotel, Berlin. The General Assembly will take place from 9 to 11 am. This is a Member only event. A selection of forums and capacity-building workshops will follow the EURORDIS General Assembly. These sessions are designed to empower patients and patients' advocates and encourage learning from each other's experience. For further information on the membership meeting, [click here](#).

#### **AMERICAN UROLOGICAL ASSOCIATION ANNUAL MEETING (AUA), 16-21 MAY 2014, ORLANDO, FLORIDA, USA A WEALTH OF COURSES ON CHRONIC PELVIC AND UROGENITAL PAIN**

Those planning to attend the AUA in Orlando this year will find a wealth of courses on offer on IC/BPS, chronic pelvic pain and urogenital pain, looked at from every point of view and with a fabulous array of speakers.

##### **002IC: Evaluation and Management of Urogenital Pain, Friday May 16, 1 – 3 p.m.**

This course will cover a detailed overview of the causes and treatment of urogenital pain. The combination of urologists and anesthesiology pain medicine physicians will allow an integrated approach of the urologist and the pain medicine physician working together on diagnosis and treatment of these conditions. Speakers: Michael Sabia, MD (director), Allen D. Seftel, MD, Hossein Sadeghi-Nejad, MD

##### **009IC: Urologic Pelvic Pain Meets Late Night TV, Saturday May 17, 1 – 3 p.m.**

With nearly 100 years of combined experience in the field of male and female urological chronic pelvic pain syndrome (UCPPS), the expert presenters will educate and inspire the audience with memorable case studies, employing a unique, interactive format. Dozens of common case scenarios will be presented, along with practical diagnostic methods and easily applied management strategies.

Speakers: Jeannette M. Potts, MD (director), Christopher K. Payne, MD, Rhonda Kotarinos, PT, DPT.

##### **016PG: Urological Pelvic Pain: The “Nuts and Bolts” of Therapy, Saturday May 17, 3:30 – 6:30 p.m.**

This course is designed for those who wish to enhance their knowledge base and skill set regarding treatment. It will begin with an overview of pain management strategies, and then discuss conservative interventions such as behavioural therapy, dietary changes and physical therapy and then discuss more “aggressive” approaches to urological care, covering topics including medical management, trigger point injections, nerve blocks, neurostimulation techniques, intravesical instillations, endoscopic procedures and conventional surgery.

Speakers: Robert M. Moldwin, MD (director), Kristene E. Whitmore, MD, Robert J. Evans, MD.

##### **060PG: Contemporary Urological Management of Women with Sexual Dysfunction, Monday May 19, 8:30 – 11:30 a.m.**

The goal of this course is to present the basic principles and current management of women with sexual health problems with presentations on a rational, step-care clinical paradigm with hormonal, non-hormonal, surgical and neuromodulation treatments, focusing on basic principles of clinical management of women with urological conditions who also have sexual health concerns. Speakers: Irwin Goldstein, MD (director), Andrew T. Goldstein, MD, FACOG, Noel N. Kim, PhD, Kenneth M. Peters, MD.

##### **084PG: Interstitial Cystitis/Bladder Pain Syndrome: A Primer and a World-View, Tuesday May 20, 8:30 – 11:30 a.m.**

This course will look at IC/BPS from an international viewpoint, including information about the history of the syndrome, nomenclature, definition, epidemiology, associated disorders, confusable diseases, etiology, clinical presentation and treatment. A new section on gynecological manifestations and associated disorders has been added to the presentation. The faculty will discuss why there have been so many problems associated with diagnosis and management over the last century, and the tremendous progress in harmonization around the world that has occurred in the last decade and which is ongoing. Treatment guidelines from Asia, Europe and the USA will be compared and contrasted. Speakers: Philip M. Hanno, MD (director), Arndt Van Ophoven, MD, David A. Burks, MD, Jorgen Nordling, MD, Mauro Cervigni, M.D.

For further information, [click here](#).

#### **1ST GLOBAL CONGRESS ON LOWER URINARY TRACT DYSFUNCTION, 11-13 JUNE 2014, BRUSSELS, BELGIUM**

A new initiative, the 1<sup>st</sup> Global Congress on LUTD, aims to bring together top experts and delegates for an in-depth discussion of the different aspects of lower urinary tract dysfunction, with a focus on difficulties and

dilemmas of clinical decision making. The programme will be divided into three main topics: non-neurogenic male LUTD, non-neurogenic female LUTD, neurogenic LUTD. For further information, [click here](#).

#### **ESSIC ANNUAL MEETING, 14/15 JUNE 2014, PHILADELPHIA, USA**

ESSIC – the International Society for the Study of BPS – will be holding its annual meeting 2014 in Philadelphia. This meeting will be hosted by Philip Hanno, MD and the theme of the meeting will be Hunner lesion. More details will be placed on the ESSIC website ([www.essic.eu](http://www.essic.eu)) in due course.

#### **3<sup>RD</sup> INTERNATIONAL NEURO-UROLOGY MEETING: IN HONOUR OF THE RETIREMENT OF PROFESSOR JEAN-JACQUES WYNDAELE, 28-30 AUGUST, 2014, ZURICH, SWITZERLAND**

This special meeting will be organized by the Swiss Continence Foundation in honour of the retirement of Professor J-J Wyndaele who has made such a valuable contribution and devoted so much energy to IC/BPS and to patient organizations over more than a decade. Further information will be available in due course on the Swiss Continence Foundation [website](#).

#### **15<sup>TH</sup> WORLD CONGRESS ON PAIN, 6-11 OCTOBER 2014, BUENOS AIRES, ARGENTINA**

The International Association for the Study of Pain (IASP) will hold its 15th World Congress on Pain October 6-11, 2014, in Buenos Aires, Argentina! The Congress will attract more than 6,000 pain specialists from all over the world who will converge on Buenos Aires and present the most up-to-date information on the field of pain, from laboratory science to clinical diagnosis, management, and prevention, with a programme covering every aspect of acute and chronic pain from basic science to clinical practice. For further information, [click here](#).

#### **INTERNATIONAL PELVIC PAIN SOCIETY (IPPS) 2014 ANNUAL MEETING, OCTOBER 23-25, 2014, CHICAGO**

A date for your diary. [Click here](#).

#### **INTERNATIONAL CONTINENCE SOCIETY ANNUAL SCIENTIFIC MEETING, 20-24 OCTOBER 2014, RIO DE JANEIRO**

A date for your diary. [Click here](#).

## **STUDIES**

### **Women's Bladder Pain Research Study in USA**

A research study in the USA is still enrolling women between the ages of 18 and 80 who have IC/BPS. The study medicine is being tested to evaluate how effective it can be in treating women with moderate to severe IC/BPS pain. Upon qualifying for the study, you may:

- Have a better understanding of your IC/BPS
- Acquire study-related medical tests, procedures, and medicine at no cost
- Receive reimbursement for study-related time and travel

There is no cost to participating patients and they can take part in the study even if their health insurance network is different from the study doctor or they are not covered by health insurance. If you are interested in learning more about this IC/BPS research study, please visit [www.BladderPainStudy.com/IPBF.htm](http://www.BladderPainStudy.com/IPBF.htm) or call the research study team toll-free (USA) at 866-303-5080. This should be done as soon as possible since enrolment will close soon.

## **BOOKS**

### **IASP Press**

The International Association for the Study of Pain (IASP) has new books on pain which can be accessed on the IASP Press home page. [Click here](#). More IASP publications including the regularly published Clinical Updates on pain can be found [here](#).

### **Acupuncture for Pain Management**

*Editors: Yuan-Chi Lin, Eric Shen-Zen Hsu.*

*Publisher: Springer New York*

*ISBN: 978-1-4614-5274-4 (Print) 978-1-4614-5275-1 (Online)*

There is currently considerable interest in acupuncture for treating pain. A book was recently published on this topic. For more information: [click here](#).

## **WEBSITES**

### **Webcast on stem cells and tissue engineering on International Continence Society (ICS) website**

Many IC/BPS patients ask us about developments in the field of tissue engineering in relation to the bladder. The ICS has a very useful and informative webcast online. This is the State of the Art Lecture by Professor Christopher Chapple on developing tissue-engineered solutions presented at ICS 2013 in Barcelona: <http://www.ics.org/2013/programme/session/1243>.

### **NIDDK information online**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) produces a wide variety of excellent patient information on many topics. To mark Gastroesophageal Reflux Disease (GERD) Awareness Week in November 2013, it drew attention to its web information on gastrointestinal diseases. For example:

<http://digestive.niddk.nih.gov/ddiseases/pubs/yrdd/index.aspx> with an overview of the digestive system and how it works.

<http://digestive.niddk.nih.gov/ddiseases/pubs/gerd/index.aspx> which deals with gastroesophageal reflux (disease).

And not forgetting the useful NIDDK information on IC/PBS at:

<http://kidney.niddk.nih.gov/KUDiseases/pubs/interstitialcystitis/index.aspx>

It may be handy to know that much of the NIDDK information is also available in Spanish.

## **RESEARCH HIGHLIGHTS**

### **A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS AND RELATED DISORDERS**

*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 and Hunner's lesion are synonymous. When reviewing the article, we generally use the terminology used by the authors.

### **STATISTICAL VALIDATION OF THE SHORTER-MOLDWIN FOOD SENSITIVITY QUESTIONNAIRE FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS) PATIENTS.**

Shorter B, Ackerman M, Varvara M, Moldwin RM. J Urol. 2013 Dec 5. pii: S0022-5347(13)06013-8. doi: 10.1016/j.juro.2013.11.055. [Epub ahead of print] PMID: 24316093

The AUA Guideline on IC/BPS suggested dietary change as a first line treatment. Shorter and colleagues from the Smith Institute for Urology previously developed a validated survey instrument to determine which foods, beverages and supplements exacerbate the symptoms of this condition. The purpose of this current study was to develop a shortened questionnaire that would provide an easily self-administered food-symptom history useful for clinical practice and future research investigations. Using data from their previously validated food sensitivity questionnaire, they remodelled the original, lengthy survey to an abbreviated list which included the 35 most problematic comestibles. The instrument was reviewed by a panel of experts for face and content validity, tested for internal consistency, readability and clarity, and for test-retest reliability. Fifty two (42%) of the 124 patients who completed a baseline questionnaire returned the second instrument one week after completing the first. Internal consistency was determined to be high. Forty seven patients (90.4%) indicated they were food sensitive. Test-retest reliability of the questionnaire was assessed using Spearman correlation coefficients, and ranged from moderate to very strong. Discrepancies between survey instruments with regard to individual comestibles occurred only 1% of the time. The authors concluded that their short form diet history questionnaire (based upon a previously validated "long form") is a reliable newly validated instrument that will help identify comestibles associated with IC/BPS symptoms. Its brevity makes it simple to administer and useful in the dietary management of these patients.



**UROLOGIC SYMPTOMS OF A SUBSET OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS) PATIENTS WITH A POLY-SYMPTOMATIC, POLY-SYNDROMIC PATTERN OF PRESENTATION.**

Lai HH, North CS, Andriole GL, Cupps L, Song D, Ness TJ, Hong BA. *J Urol.* 2013 Dec 19. pii: S0022-5347(13)06131-4. doi: 10.1016/j.juro.2013.12.031. [Epub ahead of print] PMID: 24361369

The aim of this MAPP study was to characterize the urologic symptoms of a subset of urologic chronic pelvic pain syndrome (UCPPS) patients who have both a high somatic symptom burden and a wide symptom distribution fitting a "poly-symptomatic, poly-syndromic" (PSPS) pattern of presentation. 81 UCPPS patients enrolled in the NIDDK MAPP Research Network Study at the Washington University in St. Louis and the University of Alabama at Birmingham sites completed a symptom questionnaire to assess their somatic symptom burden and its distribution, the Genitourinary Pain Index (GUPI) to assess their UCPPS symptoms and impact on quality of life, and self-reported treatment-seeking behaviours for their UCPPS symptoms. The PSPS symptom pattern was defined as self-report of numerous painful and non-painful somatic symptoms across many organ systems and symptom categories on the PSPS questionnaire. UCPPS patients with the PSPS pattern reported more severe genitourinary pain on a Likert scale, more frequent pain in the past week, and more widespread distribution of the pain in the genital and pelvic areas compared to UCPPS patients without PSPS. PSPS patients also had significantly higher scores on the pain subscale, quality of life subscale (worse), and the total scores on the GUPI questionnaire than patients without PSPS. Patients with the PSPS pattern reported significantly more treatment-seeking behaviours than other patients. The authors concluded that the PSPS pattern might be an important phenotypic factor to assess in the evaluation of UCPPS with clinical and research implications. This may be a distinct clinical subgroup among UCPPS patients.

**CHANGES IN SYMPTOMS DURING UROLOGIC CHRONIC PELVIC PAIN SYNDROME SYMPTOM FLARES: FINDINGS FROM ONE SITE OF THE MAPP RESEARCH NETWORK.**

Sutcliffe S, Colditz GA, Pakpahan R, Bradley CS, Goodman MS, Andriole GL, Lai HH. *NeuroUrol Urodyn.* 2013 Nov 23. doi: 10.1002/nau.22534. [Epub ahead of print] PMID: 24273163

The aim of this interesting study by Sutcliffe and colleagues from the USA was to provide the first description and quantification of symptom changes during interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome symptom exacerbations ("flares"). Participants at one site of the Trans-Multidisciplinary Approaches to the study of chronic Pelvic Pain Epidemiology and Phenotyping Study completed two 10-day diaries over the 1-year study follow-up period, one at baseline and one during their first flare (if not at baseline). On each day of the diary, participants reported whether they were currently experiencing a flare, defined as "symptoms that are much worse than usual" for at least 1 day, and their levels of urination-related pain, pelvic pain, urgency, and frequency on a scale of 0-10. Linear mixed models were used to calculate mean changes in symptoms between non-flare and flare days from the same participant. Eighteen of 27 women and 9 of 29 men reported at least one flare during follow-up, for a total of 281 non-flare and 210 flare days. Of these participants, 44.4% reported one flare, 29.6% reported two flares, and 25.9% reported  $\geq 3$  flares over the combined 20-day diary observation period, with reported flares ranging in duration from 1 day to  $>2$  weeks. During these flares, each of the main symptoms worsened significantly by a mean of at least two points and total symptoms worsened by a mean of 11 points for both sexes (all  $P \leq 0.01$ ). It was concluded that flares are common and correspond to a global worsening of urologic and pelvic pain symptoms.

**BEFORE THE ONSET OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME, THE PRESENCE OF MULTIPLE NON-BLADDER SYNDROMES IS STRONGLY ASSOCIATED WITH A HISTORY OF MULTIPLE SURGERIES.**

Warren JW, Morozov V, Howard FM, Wesselmann U, Gallicchio L, Langenberg P, Clauw DJ. *J Psychosom Res.* 2014 Jan;76(1):75-9. doi: 10.1016/j.jpsychores.2013.10.013. Epub 2013 Nov 1. PMID: 24360145

Certain functional somatic syndromes (FSSs) such as fibromyalgia and irritable bowel syndrome are accompanied by diffuse pain amplification. Women with interstitial cystitis/bladder pain syndrome (IC/BPS) have numerous FSSs, as well as other non-bladder syndromes (NBSs) that are linked to the FSSs. They also report multiple surgeries. Since pain is a common indication for surgery, they tested the hypothesis that NBSs were associated with surgeries. In this multi-centre study, Warren and colleagues interviewed 312 incident IC/BPS cases and controls on NBSs and number of surgeries before the index date (for cases, IC/BPS onset date). Poisson and logistic regression analyses adjusted for age, race, educational level, and menopause. Among IC/BPS cases, the authors found that the number of NBSs was strongly correlated with the number of surgeries. They suggest that understanding temporal relationships will be necessary to explore causal linkages and may modify surgical practice.

### **ROLE OF URINARY CATIONS IN THE ETIOLOGY OF BLADDER SYMPTOMS AND INTERSTITIAL CYSTITIS.**

*Parsons CL, Shaw T, Berecz Z, Su Y, Zupkas P, Argade S. BJU Int. 2013 Dec 10. doi: 10.1111/bju.12603. [Epub ahead of print] PMID: 24325253*

The aim of this study by Parsons and colleagues from the University of California was to identify and characterize urinary cationic metabolites, defined as toxic factors, in patients with interstitial cystitis (IC) and control subjects and to evaluate the cytotoxicity of the urinary cationic metabolite fraction of patients with IC vs control subjects and of individual metabolites in cultured urothelial cells. Cationic fractions (CFs) were isolated from the urine specimens of 62 patients with IC and 33 control subjects by solid phase extraction using an Oasis® MCX cartridge. CF metabolites were profiled by C18 reverse-phase high performance liquid chromatography (RP-HPLC) with UV detection, quantified by area under the peaks using known standards, and normalized to creatinine. RP-HPLC and liquid chromatography-tandem mass spectrometry (LC-MS and LC-MS/MS) were used to identify major CF peaks. HTB-4 urothelial cells were used to determine the cytotoxicity of CF and of individual metabolites with and without Tamm-Horsfall-Protein (THP). Major urinary cationic metabolites were characterized and found to be present in higher amounts in patients with IC compared to control subjects. The cytotoxicity of cationic metabolites in patients with IC was significantly higher compared to control subjects, and control THP effectively lowered the cytotoxicity of these metabolites. These data provide new insights into toxic factor composition as well as a framework to develop new therapeutic strategies to sequester their harmful activity, which may help relieve bladder symptoms associated with IC.

### **URGENCY AND PAIN IN PATIENTS WITH OVERACTIVE BLADDER AND BLADDER PAIN SYNDROME. WHAT ARE THE DIFFERENCES?**

*Castro-Diaz D, Cardozo L, Chapple CR, Espuña M, Kelleher C, Kirby M, Milsom I, Sievert KD, Tubaro A. Int J Clin Pract. 2013 Dec 22. doi: 10.1111/ijcp.12317. [Epub ahead of print]. PMID: 24373133*

The Overactive Bladder Syndrome (OAB) and the Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) are different urological conditions sharing 'urgency' as a common symptom. The aim of this particularly interesting and welcome review on urgency was to address existing knowledge and establish how these symptoms are interrelated and to determine whether or not there is a common link between both symptoms complexes that help to distinguish one from the other. Whilst in BPS the hallmark symptom is pain on bladder filling, urgency is the defining symptom of OAB. Whilst it is likely that the pain in BPS/IC arises from local inflammation in the bladder wall, the nature of urgency as a symptom, its origin, and the relationship between urgency and pain, as well as the different afferent mechanisms associated with the genesis of these sensory symptoms, remains unknown. Although the aetiology of both OAB and BPS/IC is unclear, the influence of environmental factors has been suggested. Both are chronic conditions with very variable symptom resolution and response to therapy. The relationship with voiding dysfunction, gynaecological causes of chronic pelvic pain or the possible alteration of the hypothalamic-pituitary-adrenal axis and psychological disorders has not been established. Inflammation has been suggested as the common link between OAB and BPS/IC. OAB and BPS/IC are different symptoms complexes that share urgency as a common symptom. None of them have a specific symptom although pain on bladder filling is the hallmark symptom in BPS/IC. Bladder pain with urgency should be a trigger for referral to the provider with appropriate knowledge and expertise in this disease state, whereas the management of OAB should be part of normal routine care in the community.

### **CLINICAL PHENOTYPING OF UROLOGIC PAIN PATIENTS.**

*Kartha GK, Kerr H, Shoskes DA. Curr Opin Urol. 2013 Nov;23(6):560-4. doi: 10.1097/MOU.0b013e3283652a9d. PMID: 24080805*

Urologic pain conditions such as chronic prostatitis/chronic pelvic pain syndrome, interstitial cystitis/bladder pain syndrome and chronic orchialgia are common, yet diagnosis and treatment are challenging. Current therapies often fail to show efficacy in randomized controlled studies. Lack of efficacy may be due to multifactorial causes and heterogeneity of patient presentation. Efforts have been made to map different phenotypes in patients with urologic pain conditions to tailor more effective therapies. This review from the Cleveland Clinic looks at current literature on phenotype classification in urologic pain patients and their use in providing effective therapy. There has been validation of the 'UPOINT' system (urinary symptoms, psychosocial dysfunction, organ specific findings, infection, neurologic/systemic and tenderness of muscle) to better categorize male chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/bladder pain syndrome. Refinement of domain systems and recent cluster analysis has suggested possible central processes involved in urologic pain conditions similar to systemic pain syndromes such as fibromyalgia, chronic fatigue and irritable bowel syndrome. Domain characterization of urologic pain conditions via phenotype mapping can

be used to better understand causes of chronic pain and hopefully provide more effective, targeted and multimodal therapy.

**CAN THE ADRENERGIC SYSTEM BE IMPLICATED IN THE PATHOPHYSIOLOGY OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS? A CLINICAL AND EXPERIMENTAL STUDY.**

*Charrua A, Pinto R, Taylor A, Canelas A, Ribeiro-da-Silva A, Cruz CD, Birder LA, Cruz F. Neurourol Urodyn. 2013 Dec 24. doi: 10.1002/nau.22542. [Epub ahead of print] PMID: 24375689*

The purpose of this Portuguese study was to evaluate sympathetic system activity in bladder pain syndrome/interstitial cystitis (BPS/IC) patients and to investigate if chronic adrenergic stimulation in intact rats induces BPS/IC-like bladder modifications. A TILT test showed an increase of sympathetic activity. Noradrenaline levels in blood at resting conditions and in 24-hr urine samples were higher in BPS/IC patients. Phenylephrine administration increased visceral pain, spinal Fos expression, bladder reflex activity, urinary spotting and the number of expelled fecal pellets. The mucosa showed urothelial thinning and increased immunoreactivity for caspase 3 and bax. Trypan blue staining was only observed in phenylephrine treated animals. Suburothelial nerves co-expressed alpha1 and TRPV1. Mastocytosis was present in the suburothelium. Cystitis increased sympathetic nerve density and urinary noradrenaline levels. The authors concluded that excessive adrenergic stimulation of the bladder may contribute to the pathophysiological mechanisms of BPS/IC.

**URINE ALKALIZATION IMPROVES THE PROBLEMS OF PAIN AND SLEEP IN HYPERSENSITIVE BLADDER SYNDROME.**

*Ueda T, Yoshida T, Tanoue H, Ito M, Tamaki M, Ito Y, Yoshimura N. Int J Urol. 2013 Nov 13. doi: 10.1111/iju.12324. [Epub ahead of print]. PMID: 24224617*

The purpose of this study from Kyoto, Japan by Ueda and colleagues was to investigate the efficacy of urine alkalization therapy using citrates in patients with hypersensitive bladder syndrome. A total of 76 patients with urinary frequency were assessed for their symptoms using a 2-day voiding diary as well as the urine pH at each voiding during the screening period. Their symptoms were also assessed by pain score, King's health questionnaire, and O'Leary-Sant symptom and problem index scores. Finally, 50 patients were evaluated for changes in symptoms after oral treatment with citrates for 2-4 weeks after the screening period. After the treatment, the authors found significant increases in the urine pH, and significant decreases in the number of micturitions per day and the number of episodes of pain/discomfort per day were observed. In the King's health questionnaire, the sleep/energy domain score was significantly improved. In a subgroup analysis based on urine pH (urine pH <6.2 and ≥6.2), significant improvements in the voiding symptoms, the sleep/energy domain score and the O'Leary-Sant problem index were observed in the group with urine pH of ≥6.2. There were statistically significant differences between the subgroups in the volume per voiding, maximum volume per voiding and the problem index. In addition, the subgroup, in which patients had pain in the screening period, showed statistically significant improvements in the number of micturitions per day, episodes of pain/discomfort per day, the sleep/energy domain score and the problem index. It was therefore concluded that urine alkalization therapy is likely to be effective in the treatment for hypersensitive bladder syndrome.

**EVALUATION OF THE IMPACT OF THE URINARY SYMPTOMS ON QUALITY OF LIFE OF PATIENTS WITH PAINFUL BLADDER SYNDROME/CHRONIC PELVIC PAIN AND RADIATION CYSTITIS: EURCIS STUDY.** [Article in English, Spanish]

*Rapariz-González M, Castro-Díaz D, Mejía-Rendón D; en representación del grupo EURCIS. Actas Urol Esp. 2013 Dec 18. pii: S0210-4806(13)00356-2. doi: 10.1016/j.acuro.2013.09.016. [Epub ahead of print] PMID: 24360594*

The purpose of this Spanish study was to evaluate the impact of urinary symptoms of Painful Bladder/Chronic Pelvic Pain Syndrome and Radiation Cystitis (PBCPPS) on the Quality of Life, and self-esteem of the patient. An observational, multicentre, epidemiological and cross-sectional study was carried out on patients with Painful Bladder/Chronic Pelvic Pain Syndrome and Radiation Cystitis. Data was recorded on severity of urinary symptoms and QoL impairment using the PUF Score. The patients evaluated the QoL deterioration grade through the King's Health Questionnaire (KHQ), and the level of their anxiety and self-esteem with the Goldberg's Anxiety Scale (GAS) and Rosenberg's Self-Esteem Scale (RSES), respectively. Post-hoc comparisons were performed between the results of the KHQ of this study and a sample of patients with urinary incontinence (UI). Results on RSES were analyzed with data from the general population and from patients with erectile dysfunction. It was concluded that patients with Painful Bladder Syndrome/Chronic Pelvic Pain Syndrome and Radiation Cystitis present high levels of anxiety, and significant reductions in both quality of life and self-esteem.



### **WHAT IS THE ROLE FOR BIOMARKERS FOR LOWER URINARY TRACT DISORDERS? ICI-RS 2013.**

*Fry CH, Sahai A, Vahabi B, Kanai AJ, Birder LA. NeuroUrol Urodyn. 2014 Jan 16. doi: 10.1002/nau.22558. [Epub ahead of print] PMID: 24436105*

Fry and colleagues from Surrey, London and Bristol UK and Pittsburgh USA explain that a biomarker is an entity that measures a normal or pathological process, or the response to an intervention. A biomarker must measure exclusively and be sufficiently sensitive to the process of interest. Alternatively, a biomarker may give clues regarding the underlying pathology of the condition and be a useful research or specialist tool. If a biomarker is to be of practical benefit then it must also be economical and practical to use. This article considers chemical moieties as biomarkers, although in principle physical markers (e.g., bladder wall thickness) could also be defined as such.

### **OPTIMIZATION OF A PAIN MODEL: EFFECTS OF BODY TEMPERATURE AND ANESTHESIA ON BLADDER NOCICEPTION IN MICE.**

*Sadler KE, Stratton JM, Deberry JJ, Kolber BJ. PLoS One. 2013 Nov 5;8(11):e79617. doi: 10.1371/journal.pone.0079617. PMID: 24223980*

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating urological condition that is resistant to treatment and poorly understood. To determine novel molecular treatment targets and to elucidate the contribution of the nervous system to IC/BPS, many rodent bladder pain models have been developed. In this study from Pittsburgh, Sadler and colleagues evaluated the effects of anesthesia induction and temperature variation in a mouse model of bladder pain known as urinary bladder distension (UBD). Their results highlight the significance of the dynamic effects of anesthesia on pain-like changes and the importance of close monitoring of temperature while performing UBD. For successful interpretation of VMRs and translation to human disease, body temperature should be maintained at 37.5°C and isoflurane induction should gradually decrease over the course of 90 minutes.

### **URINARY BLADDER, CYSTITIS AND NERVE/UROTHELIAL INTERACTIONS.**

*Birder LA. Auton Neurosci. 2013 Dec 25. pii: S1566-0702(13)00775-3. doi: 10.1016/j.autneu.2013.12.005. [Epub ahead of print] PMID: 24412640*

Neuroscientist Dr Lori Birder from Pittsburgh notes that a hallmark of functional pain syndromes, such as bladder pain syndrome/interstitial cystitis (BPS/IC), is pain in the absence of demonstrable infection or pathology of the viscera or associated nerves. There are no clear definitions of this syndrome, no proven etiologies and no effective treatments able to eradicate the symptoms. This condition is characterized by suprapubic pain, associated with bladder filling and can also be accompanied by a persistent strong desire to void, increased frequency of urination and nocturia. Severe cases of this disorder, which affects primarily women, can have considerable impact on the quality of life of patients due to extreme pain and urinary frequency, which are often difficult to treat. In addition, BPS/IC patients may also suffer co-morbid conditions where pain is a common symptom (such as irritable bowel syndrome, fibromyalgia). Theories explaining the pathology of bladder pain syndrome are many and include an altered bladder lining and possible contribution of a bacterial agent.

### **[EFFICIENCY OF O'LEARY-SANT SYMPTOM INDEX AND PROBLEM INDEX IN THE DIAGNOSIS OF INTERSTITIAL CYSTITIS].** [Article in Chinese]

*Xu L, Zhang P, Zhang N, Yang Y, Wu ZJ, Zhang CH, Zhang XD. Zhonghua Yi Xue Za Zhi. 2013 Nov;93(42):3347-50. PMID: 24418029*

The purpose of this article in Chinese from Beijing was to evaluate the efficiency of O'Leary-Sant problem index and symptom index (OPSI) in the diagnosis of interstitial cystitis (IC). A total of 82 patients, initially diagnosed as IC, with urinary frequency, urgency and pain on pubic area during bladder filling phase from January 2008 to March 2013 were enrolled. OPSI was used to evaluate their symptoms. They were eventually divided into IC and non-IC groups according to the clinical diagnosis. The scores of OPSI, interstitial cystitis problem index (ICPI) and interstitial cystitis symptom index (ICSI) were compared between two groups. And the ROC curve was plotted to screen the diagnostic specificity and sensitivity. 58 were diagnosed with IC and the rest with non-IC. The average score of OPSI for groups IC and non-IC were  $24.7 \pm 6.9$  and  $23.2 \pm 7.8$  respectively. And the ICPI score for two groups were  $11.7 \pm 3.2$  and  $10.2 \pm 3.7$  and the ICSI score  $13.0 \pm 4.0$  and  $13.1 \pm 4.3$  respectively. No significant differences existed between two groups. If an OPSI score of 12 or greater for diagnosing IC, the sensitivity was 98% and specificity 8%. Because of a high sensitivity, OPSI was a useful indicator for screening IC

patients from others. In the ROC curve, acreage under curve for OPSI, ICPI, ICSI were  $0.548 \pm 0.071$ ,  $0.622 \pm 0.069$  and  $0.492 \pm 0.070$  respectively. These three indices were not good indicators for diagnosing IC. It was concluded that the O'Leary-Sant symptom index and problem index has a high sensitivity but a low specificity in the diagnosis of IC. Therefore, it should not be used to differentiate interstitial cystitis. A cut-off OPSI value of 12 may be used for differentiation.

#### **GRADING OF EVIDENCE FOR BLADDER PAIN SYNDROME: A COMPARATIVE REVIEW OF STUDY QUALITY ASSESSMENT METHODS.**

*Tirlapur SA, Khan KS. Int Urogynecol J. 2013 Nov 23. [Epub ahead of print] PMID: 24271457*

Clinical guidelines on bladder pain syndrome (BPS) report quality ratings for evidence based on study design. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system takes into account several domains in addition to limitations of study design for assigning quality ratings. Tirlapur and Khan from London compared the quality of evidence described in current BPS literature. They report that all existing systematic reviews and guidelines on BPS management were reviewed, and included evidence was rated according to GRADE on a four-point scale (1-4, from very low to high). These ratings were compared to the two reported quality assessments that assigned levels or strengths to evidence; both had a four-point scale: level of evidence 1-4 from meta-analysis of randomised studies to expert opinion; and strength of evidence 1-4 from very low to high. It was concluded that GRADE, a refined method of assigning quality to evidence, provided a more conservative gauge, giving a realistic assessment of the value of recommendations for consideration in practice.

#### **BLADDER PAIN SYNDROME: VALIDATION OF SIMPLE TESTS FOR DIAGNOSIS IN WOMEN WITH CHRONIC PELVIC PAIN: BRAVADO STUDY PROTOCOL.**

*Tirlapur SA, Priest L, Wojdyla D, Khan KS. Reprod Health. 2013 Dec 4;10(1):61. [Epub ahead of print] PMID: 24304546*

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Bladder pain syndrome (BPS), a condition with no gold standard diagnosis, comprises of a cluster of signs and symptoms. Bladder filling pain and bladder wall tenderness are two basic clinical features, present in a high number of sufferers. This study from London aims to validate the performance of these simple tests for BPS in women with chronic pelvic pain (CPP). They report that they will conduct a prospective test validation study amongst women with unexplained CPP presenting to gynaecology outpatient clinics. Two index tests will be performed: patient reported bladder filling pain and bladder wall tenderness on internal pelvic bimanual examination. A final diagnosis of BPS will be made by expert consensus panel. They will assess the rates of index tests in women with CPP; evaluate the correlation between index tests and Pelvic Pain Urgency/Frequency (PUF) questionnaire results; and determine index test sensitivity and specificity using a range of analytical methods. Assuming a 50% prevalence of BPS and an 80% power approximately 152 subjects will be required exclude sensitivity of < 55% at 70% sensitivity. The results of this test validation study will be used to identify whether a certain combination of signs and symptoms can accurately diagnose BPS.

#### **THE SEVERITY OF EXPERIMENTAL AUTOIMMUNE CYSTITIS CAN BE AMELIORATED BY ANTI-CXCL10 AB TREATMENT.**

*Singh UP, Singh NP, Guan H, Hegde VL, Price RL, Taub DD, Mishra MK, Nagarkatti M, Nagarkatti PS. PLoS One. 2013 Nov 21;8(11):e79751. doi: 10.1371/journal.pone.0079751. PMID: 24278169*

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In the United States, it is estimated that eight million people, mostly women, have IC/PBS. New evidence that autoimmune mechanisms are important in the pathogenesis of IC/PBS triggered interest. SWXJ mice immunized with a homogenate of similar mice's urinary bladders develop an autoimmune phenotype comparable to clinical IC with functional and histological alterations confined to the urinary bladder. Using the murine model of experimental autoimmune cystitis (EAC), Singh and colleagues found that serum levels of CXCR3 ligand and local T helper type 1 (Th1) cytokine are elevated. Also, IFN- $\gamma$ -inducible protein10 (CXCL10) blockade attenuated overall cystitis severity scores; reversed the development of IC; decreased local production of CXCR3 and its ligands, IFN- $\gamma$ , and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ); and lowered systemic levels of CXCR3 ligands. Urinary bladder CD4(+) T cells, mast cells, and neutrophils infiltrates were reduced following anti-CXCL10 antibody (Ab) treatment of mice. Anti-CXCL10 Ab treatment also reversed the upregulated level of CXCR3 ligand mRNA at urinary bladder sites. The decreased number and percentage of systemic CD4(+) T cells in EAC mice returned to normal after anti-CXCL10 Ab treatment. The authors conclude that, taken together, their findings provide important new information about the mechanisms underlying EAC pathogenesis, which

has symptoms similar to those of IC/PBS. CXCL10 has the potential for use in developing new therapy for IC/PBS.

**PREVENTION OF ANTI-MICROBIAL PEPTIDE LL-37-INDUCED APOPTOSIS AND ATP RELEASE IN THE URINARY BLADDER BY A MODIFIED GLYCOSAMINOGLYCAN.**

Lee WY, Savage JR, Zhang J, Jia W, Oottamasathien S, Prestwich GD. *PLoS One*. 2013 Oct 30;8(10):e77854. doi: 10.1371/journal.pone.0077854. PMID: 24204996

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Current therapies for IC/PBS primarily focus on replenishing urothelial glycosaminoglycan (GAG) layer using GAG analogs and managing pain with supportive therapies. However, the elusive etiology of IC and the lack of animal models to study the disease have been major hurdles developing more effective therapeutics. Previously, Lee and colleagues showed an increased urinary concentration of antimicrobial peptide LL-37 in spina bifida patients and used LL-37 to develop a mouse model of cystitis that mimics important clinical findings of IC. Here they investigate (1) the molecular mechanism of LL-37 induced cystitis in cultured human urothelial cells and in mice, (2) the protective effects of GM-0111, a modified GAG, within the context of this mechanism, (3) the physiological and molecular markers that correlate with the severity of the inflammation, and (4) the protective effects of several GAGs using these biomarkers in our LL-37 induced cystitis model. They found that LL-37 quickly induces release of ATP and apoptosis in the urothelium. These changes can be inhibited by a chemically-modified GAG, GM-0111. Furthermore, they also found that GAG analogs provide varying degrees of protection against LL-37 challenge in mice. According to the authors, these findings suggest that GM-0111 and possibly GAG molecules prevent the development of cystitis by blocking the apoptosis and the concurrent release of ATP from the urothelium.

**SEGMENTAL HYPERALGESIA TO MECHANICAL STIMULUS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME - EVIDENCE OF CENTRAL SENSITIZATION.**

Lai HH, Gardner V, Ness TJ, Gereau RW 4th. *J Urol*. 2013 Dec 5. pii: S0022-5347(13)06071-0. doi: 10.1016/j.juro.2013.11.099. [Epub ahead of print] PMID: 24316091

The purpose of this study by Lai and colleagues was to investigate if interstitial cystitis/bladder pain syndrome (IC/BPS) subjects demonstrate mechanical or thermal hyperalgesia, and whether the hyperalgesia is segmental or generalized. 10 female IC/BPS subjects and 10 age-matched female controls without co-morbid fibromyalgia or narcotic use were recruited for quantitative sensory testing. Using the Method of Limits, pressure pain and heat pain thresholds were measured. Using the Method of Fixed Stimulus, the visual analog scale (VAS) pain experienced was recorded when a fixed pressure/temperature was applied. They found that female subjects with IC/BPS showed segmental hyperalgesia to mechanical pressure stimulation in the suprapubic area (T10-T12). This segmental hyperalgesia may be explained in part by spinal central sensitization.

**CHARACTERIZATION OF BLADDER SENSORY NEURONS IN THE CONTEXT OF MYELINATION, RECEPTORS FOR PAIN MODULATORS, AND ACUTE RESPONSES TO BLADDER INFLAMMATION.**

Forrest SL, Osborne PB, Keast JR. *Front Neurosci*. 2013 Nov 7;7:206. doi: 10.3389/fnins.2013.00206. PMID: 24223534

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Forrest and colleagues from Australia note that bladder sensation is mediated by lumbosacral dorsal root ganglion neurons and is essential for normal voiding and nociception. Numerous electrophysiological, structural, and molecular changes occur in these neurons following inflammation. Defining which neurons undergo these changes is critical for understanding the mechanism underlying bladder pain and dysfunction. Their study also identified a sub-population of sacral sensory neurons that are likely to be undergoing structural remodelling during acute inflammation of the bladder. Together these results contribute to increased understanding of the neurons that are known to be involved in pain modulation and hyperreflexia during inflammation.

**PURINERGIC SIGNALLING IN THE URINARY TRACT IN HEALTH AND DISEASE.**

Burnstock G. *Purinergic Signal*. 2013 Nov 22. [Epub ahead of print] PMID: 24265069

Purinergic signalling is involved in a number of physiological and pathophysiological activities in the lower urinary tract. In the bladder of laboratory animals there is parasympathetic excitatory cotransmission with the purinergic and cholinergic components being approximately equal, acting via P2X1 and muscarinic receptors, respectively. Purinergic mechanosensory transduction occurs where ATP, released from urothelial cells during distension of bladder and ureter, acts on P2X3 and P2X2/3 receptors on suburothelial sensory nerves to initiate

the voiding reflex, via low threshold fibres, and nociception, via high threshold fibres. In the human bladder, the purinergic component of parasympathetic cotransmission is less than 3 %, but in pathological conditions, such as interstitial cystitis, obstructed and neuropathic bladder, the purinergic component is increased to 40 %. Other pathological conditions of the bladder have been shown to involve purinoceptor-mediated activities, including multiple sclerosis, ischaemia, diabetes, cancer and bacterial infections. In the ureter, P2X7 receptors have been implicated in inflammation and fibrosis. Purinergic therapeutic strategies are being explored that hopefully will be developed and bring benefit and relief to many patients with urinary tract disorders.

#### **ACTIVATION OF EXTRINSIC APOPTOTIC PATHWAY FROM BLADDER BIOPSY IN PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME**

Lee JD, Lee MH. *Urology*. 2013 Dec;82(6):1451.e7-1451.e11. doi: 10.1016/j.urology.2013.08.042. PMID: 24295264

Lee and Lee from Taiwan investigated the intrinsic or extrinsic pathway of apoptosis from bladder biopsy that was performed in interstitial cystitis/painful bladder syndrome (IC/PBS). Although previous studies have reported observations of the dysfunction, denudation, and thinning of the bladder urothelium in patients associated with an increase of cell apoptosis, the molecular mechanism is unclear. The study group consisted of 32 patients with IC/PBS, and the control group consisted of 12 volunteers without any symptoms of IC. Bladder biopsies were obtained from both the groups. The expression of apoptosis-associated proteins was observed by detecting the Bcl-2/Bax ratio and the levels of cleaved caspase-9, Fas, cleaved caspase-8, and cleaved caspase-3 to differentiate intrinsic or extrinsic pathway. The data were analyzed using Mann-Whitney U test. Increased levels of cleaved caspase-3 were found in the IC/PBS group relative to the control group. The levels of the extrinsic apoptotic pathway proteins, Fas and cleaved caspase-8, were also increased in the study group compared with the control group. There was no significant difference in the levels of the intrinsic apoptotic pathway proteins, including cleaved caspase-9 and the Bcl-2/Bax ratio, between the control and study groups. The authors concluded that their findings demonstrate the activation of extrinsic apoptotic pathway from bladder biopsy in patients with IC/PBS. They are of the opinion that this study might help to clarify the molecular changes and lead to a better understanding of this bladder disease.

#### **INTRAVESICAL HYALURONIDASE CAUSES CHRONIC CYSTITIS IN A RAT MODEL: A POTENTIAL MODEL OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

Lv YS, Yao YS, Rong L, Lin ME, Deng BH, Xie Y, Huang H, Lin TX, Xu KW, Huang J. *Int J Urol*. 2013 Nov 28. doi: 10.1111/iju.12358. [Epub ahead of print] PMID: 24286489

The purpose of this rat study from China was to determine whether a potential rat model of bladder pain syndrome could be developed through long-term intermittent intravesical hyaluronidase. A total of 64 female Sprague-Dawley rats were divided into a control group, a low-dose hyaluronidase (1 mg/mL) group, a high-dose hyaluronidase (4 mg/mL) group and a hyaluronic acid-treated group. Hyaluronidase was given intravesically three times a week for 1 month. Hyaluronic acid (0.5 mL, 0.8 mg/mL) was introduced intravesically to hyaluronidase-treated rat bladders. Histological changes, cystometry, nociceptive behaviours, and messenger ribonucleic acid levels of inflammatory factors were evaluated and compared between groups. All hyaluronidase-treated rats showed chronic inflammation and fibrosis, increased and activated mast cells, thinned bladder epithelium with abnormal expressions of uroplakin III and zonula occluden-1, and increased levels of interleukin-6 and intercellular adhesion molecule-1 messenger ribonucleic acid. However, the inflammatory score and levels of interleukin-6 and intercellular adhesion molecule-1 were more significant in the high-dose hyaluronidase group than in the low-dose hyaluronidase group. Furthermore, hyaluronidase-treated rats showed markedly decreased intercontraction intervals, bladder capacity and increased sensitivity to pain compared with controls. Hyaluronic acid treatment significantly decreased the inflammatory level, number of mast cells, sensitivity to pain, levels of interleukin-6 and intercellular adhesion molecule-1, and increased intercontraction intervals and bladder capacity. It was concluded that long-term intermittent intravesical hyaluronidase could develop a severe chronic cystitis with diffused fibrosis accompanied by altered histology and bladder function. This chronic cystitis rat model can resemble the clinical and histopathological features of human bladder pain syndrome, and might be a potential valuable model for investigation of this troublesome disease.

#### **ROLES OF ADENOSINE A1 AND A2A RECEPTORS IN THE CONTROL OF MICTURITION IN RATS.**

Kitta T, Chancellor MB, de Groat WC, Kuno S, Nonomura K, Yoshimura N. *Neurourol Urodyn*. 2013 Sep 9. doi: 10.1002/nau.22487. [Epub ahead of print]. PMID: 24014261

Kitta and colleagues from Pittsburgh and Hokkaido note that adenosine is a neurotransmitter that exerts numerous physiological effects in many organs. However, few studies have focused on the role of adenosine receptors in the control of micturition. They therefore examined the role of adenosine A1 and A2A receptors in the control of bladder activity in rats with normal or acetic acid (AA) irritated bladders. Cystometrograms during saline or 0.2% AA infusion were recorded under urethane anesthesia in female Sprague-Dawley rats. After a stabilization period, CCPA (A1 receptor agonist) and/or ZM24138 (A2A receptor antagonist) were administered intravenously (i.v.), intrathecally (i.t.), intracerebroventricularly (i.c.v.), or intravesically. Micturition parameters were recorded and compared before and after drug administration. The authors found that i.v., i.t., or i.c.v. administration of CCPA or ZM24138 significantly increased intercontraction intervals (ICIs) in both saline and AA infusion groups. During AA infusion, the inhibitory effects induced by i.c.v. CCPA or i.t. ZM24138 were significantly greater than those by i.t. or i.c.v. administration, respectively. Intravesical administration of CCPA, but not ZM24138, significantly increased ICI. According to the study team, these results indicated that: (1) when nociceptive signals from the bladder increase, adenosine A1 receptor-mediated inhibition of micturition is enhanced in the brain, compared to the normal condition, (2) A1 receptor activation also exerts a peripheral inhibitory effect on micturition, and (3) adenosine A2A receptor-mediated excitatory mechanisms are enhanced in the spinal cord following C-fiber bladder afferent stimulation. They therefore suggest that adenosine A1 receptor agonists and A2A receptor antagonists might be effective for the treatment of overactive bladder and/or bladder hypersensitive disorders, in which C-fiber afferent function is enhanced.

### **INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME (IC/PBS) DILEMMAS IN DIAGNOSIS & TREATMENT**

*Mishra NN. Current Women's Health Reviews, 2013, 9, 122-130*

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Interstitial Cystitis/Painful Bladder Syndrome is a controversial chronic disease characterized by pain, urgency and frequency. Patients with severe symptoms have a very miserable life. There is still no international consensus on its name, definition, investigations and management. American, European and Asian guidelines have been recently framed but differ on many important issues. Presentations of IC/PBS patients are highly individual with the same or similar symptoms expressed differently. However, an important aspect of the symptoms is their relation to micturition. Since no internationally accepted standards exist for diagnosis and treatment, considerable variation is observed in the patient investigations. Investigations are divided between mandatory and optional. Sonography of kidney-ureter-bladder and urine culture are mandatory investigations as they rule out other pathologies. However, there is no consensus on important investigations such as cystoscopy. Some urologists believe painful bladder syndrome to be a clinical disease diagnosed on the basis of history and minimum investigations, while according to others cystoscopy confirms the disease by ruling out other potential causes of the symptoms and also helps in management decision-making. No standard protocol exists for treatment. All the available treatments work on a few patients and it is difficult to decide which treatment is best for a given patient. This dilemma has led to a policy of staged treatment where various treatment modalities are applied to the patient one after other, starting with less invasive and progressing to more invasive. Some treatment modalities like intravesical Botulinum toxin and neuro-modulation are for patients with refractory IC/PBS only.

### **PAINFUL BLADDER SYNDROME: AN UPDATE AND REVIEW OF CURRENT MANAGEMENT STRATEGIES.**

*Dyer AJ, Twiss CO. Curr Urol Rep. 2014 Feb;15(2):384. doi: 10.1007/s11934-013-0384-z. PMID: 24384999*

Interstitial cystitis/painful bladder syndrome (IC/PBS) remains a prevalent, but untreated disease with a poorly understood pathophysiology. Nonetheless, four main processes currently appear to be involved in producing IC/PBS symptoms: (1) disruption of the bladder GAG/proteoglycan layer, (2) upregulated immune/inflammatory response, (3) neural upregulation, and (4) pelvic floor dysfunction. This review focuses on current and emerging therapies aimed at these potential targets together with an update on IC/PBS therapy.

### **INTRAVESICAL RESINIFERATOXIN FOR THE TREATMENT OF STORAGE LOWER URINARY TRACT SYMPTOMS IN PATIENTS WITH EITHER INTERSTITIAL CYSTITIS OR DETRUSOR OVERACTIVITY: A META-ANALYSIS.**

*Guo C, Yang B, Gu W, Peng B, Xia S, Yang F, Wen D, Geng J, Zhang Y, Zheng J. PLoS One. 2013 Dec 20;8(12):e82591. doi: 10.1371/journal.pone.0082591. PMID: 24376550*

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While Resiniferatoxin (RTX) has been widely used for patients with storage lower urinary tract symptoms (LUTS), its clinical efficiency has not yet been well evaluated. In this China/USA study, a meta-analysis was performed to evaluate the exact roles of intravesical RTX for the treatment of storage LUTS in patients with



either interstitial cystitis (IC) or detrusor overactivity (DO). A meta-analysis of RTX treatment was performed through a comprehensive search of the literature. They found that RTX could significantly reduce bladder pain in patients with either IC or DO, and increase MCC in patients with DO. However, no significant improvement was observed in frequency, nocturia, incontinence or FDC. Given the limitations in the small patient size and risk of bias in the included trials, great caution should be taken when intravesical RTX is used before a large, multicentre, well-designed random control trial with a long-term follow-up is carried out to further assess the clinical efficacy of RTX in patients with storage LUTS.

**DOWN REGULATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IS ASSOCIATED WITH DECREASED INFLAMMATION AFTER INTRAVESICAL ONABOTULINUMTOXINA INJECTIONS COMBINED WITH HYDRODISTENTION FOR PATIENTS WITH INTERSTITIAL CYSTITIS - CLINICAL RESULTS AND IMMUNOHISTOCHEMISTRY ANALYSIS.**

*Peng CH, Jhang JF, Shie JH, Kuo HC. Urology. 2013 Dec;82(6):1452.e1-6. doi: 10.1016/j.urology.2013.09.003. PMID: 24295265*

The objective of this study from Taiwan was to measure the expression of vascular endothelial growth factor (VEGF) in bladder tissue and improvement of clinical symptoms and inflammatory biomarkers after repeated onabotulinumtoxin A injections in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Twenty-one patients with IC/BPS received 4 sets of intravesical 100-U onabotulinumtoxin A injections combined with hydrodistention. Assessments at baseline and 6 months after each treatment included O'Leary-Sant Symptom Score, bladder pain visual analog scale, functional bladder capacity (FBC), grade of glomerulations under cystoscopic hydrodistention, and urodynamic parameters. The bladder specimens at baseline and at the fourth treatment were investigated by western blotting for the expression of VEGF, Bcl-2-associated X protein (Bax), and phospho-p38, and immunohistochemistry staining for apoptotic and mast cell activity. Six women with genuine stress urinary incontinence served as controls for comparison. The measured immunohistochemical parameters were significantly higher in patients with IC/BPS than the controls. Statistically significant decrease in the expression of VEGF was noted in patients treated with repeated onabotulinumtoxin A injections compared with baseline. The apoptotic cell count and mast cell activity were also reduced. Significant increases in FBC and global response assessment score were also observed after onabotulinumtoxin A treatment. However, except for mast cell activity, VEGF expression and apoptotic cell count were still significantly higher than the controls. The authors concluded that increased VEGF was associated with bladder inflammation and smaller FBC in patients with IC/BPS and decreased after repeated onabotulinumtoxin A injections and hydrodistention, suggesting VEGF plays an important role in the pathogenesis of IC/BPS.

**AN UPDATED SYSTEMATIC REVIEW AND STATISTICAL COMPARISON OF STANDARDISED MEAN OUTCOMES FOR THE USE OF BOTULINUM TOXIN IN THE MANAGEMENT OF LOWER URINARY TRACT DISORDERS.**

*Mangera A, Apostolidis A, Andersson KE, Dasgupta P, Giannantoni A, Roehrborn C, Novara G, Chapple C. Eur Urol. 2013 Nov 1. pii: S0302-2838(13)01109-3. doi: 10.1016/j.eururo.2013.10.033. [Epub ahead of print] PMID: 24239446*

Botulinum toxin A (BoNTA) has received regulatory approval for use in neurogenic detrusor overactivity (NDO) and overactive bladder (OAB), but it remains unlicensed in other lower urinary tract symptoms (LUTS) indications such as nonneurogenic LUTS in men with benign prostatic enlargement (LUTS/BPE), bladder pain syndrome (BPS), and detrusor sphincter dyssynergia (DSD). The purpose of this study from Sheffield, UK was to compare statistically the outcomes of high level of evidence (LE) studies with placebo using BoNTA for LUTS indications; NDO, OAB, LUTS/BPE, BPS and DSD. The authors conducted a systematic review of the published literature on PubMed, Scopus, and Embase reporting on BoNTA use in LUTS dysfunction. Statistical comparison was made between high LE studies with placebo and low LE studies. Mangera and colleagues concluded that BoNTA significantly improves all symptoms and urodynamic parameters in NDO and OAB. The effect of BoNTA in treating LUTS dysfunction appears to be overestimated in lower as opposed to higher LE studies.

**A MULTICENTRE, PROSPECTIVE, RANDOMISED, DOUBLE-BLIND STUDY TO MEASURE THE TREATMENT EFFECTIVENESS OF ABOBOTULINUM A (ABOBTXA) AMONG WOMEN WITH REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

*Manning J, Dwyer P, Rosamilia A, Colyvas K, Murray C, Fitzgerald E. Int Urogynecol J. 2013 Nov 26. [Epub ahead of print] PMID: 24276074*

The purpose of this Australian study was to determine whether abobotulinumtoxin A (AboBTXA) is an effective treatment for interstitial cystitis/bladder pain syndrome (IC/BPS). Manning and colleagues performed a double-blind study of 54 women with severe, refractory IC from three referral centres whom they randomly allocated

to treatment with hydrodistension + injection of normal saline or to hydrodistension + injection with AboBTXA. The O'Leary-Sant questionnaire consists of problem (OLS-PI) and symptom (OLS-SI) index scores, and bladder diary data were compared between AboBTXA and control patients at baseline and at 3 months of follow-up. Measurements were made beyond 3 months, but no further randomised comparison was possible due to the ability of nonresponsive patients in either group to have AboBTXA treatment. Complete data were available in 50 patients, and in both groups, OLS questionnaires showed improvement at 3 months. It was concluded that for chronic refractory IC/BPS patients, AboBTXA was associated with no overall improvement in total OLS score, although significant benefit was noted in a small number of patients. The absence of post-treatment UTI was associated with a better response to AboBTXA.

#### **SACRAL NEUROMODULATION FOR REFRACTORY OVERACTIVE BLADDER, INTERSTITIAL CYSTITIS, AND PAINFUL BLADDER SYNDROME.**

Laviana A, Jellison F, Kim JH. *Neurosurg Clin N Am.* 2014 Jan;25(1):33-46. doi: 10.1016/j.nec.2013.08.001. PMID: 24262898

Various pelvic floor conditions, including overactive bladder syndrome and chronic pelvic pain, have been successfully managed with neuromodulation of sacral nerves. Sacral neuromodulation is a procedure involving the implantation of a programmable pulse generator that delivers low-amplitude electrical current via quadripolar tined leads through the S3 foramen. Durable efficacy has been demonstrated in retrospective studies, but questions regarding ideal patient candidacy and optimal technical considerations remain unanswered.

#### **ELIMINATION OF HUNNER'S ULCERS BY FULGURATION IN PATIENTS WITH INTERSTITIAL CYSTITIS: IS IT EFFECTIVE AND LONG LASTING?**

Ryu J, Pak S, Song M, Chun JY, Hong S, Choo MS. *Korean J Urol.* 2013 Nov;54(11):767-71. doi: 10.4111/kju.2013.54.11.767. Epub 2013 Nov 6. PMID: 24255759

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The purpose of this study from Korea was to evaluate the outcome of fulguration of Hunner's ulcers (HUs) in painful bladder syndrome/interstitial cystitis (PBS/IC) that is refractory to conservative treatment. Patients diagnosed with refractory PBS/IC and treated with fulguration between 2011 and 2013 were identified through screening of medical records. To evaluate treatment outcomes, voiding diaries, the visual analogue scale (VAS) for pain, and two IC symptom questionnaires (pelvic pain and urgency/frequency scale [PUF] and O'Leary-Sant IC symptom index and IC problem index [OS]) were used. Fulguration was deemed to be successful if the VAS score was <2 or less than half of the preoperative VAS score. 27 patients with PBS/IC in whom conservative treatments had failed were enrolled. Two months after fulguration, decreases were observed in the mean 24-hour urinary frequency, 24-hour urgency episodes, and the VAS, PUF symptom, PUF bother, OS symptom, and OS problem scores. At 5 and 10 months, all variables had worsened. At 2, 5, and 10 months, the success rates were 94.1%, 70.0%, and 33.3%, respectively. Four patients underwent one repeat fulguration on average 11.3 months after the first fulguration. Repeat fulguration was not significantly associated with any clinical characteristics. In PBS/IC that was refractory to medication or other conservative treatments, HU elimination by fulguration effectively improved symptoms. However, this effect decreased gradually over time.

#### **INTRAVESICAL HEPARIN: INTERSTITIAL CYSTITIS (PAINFUL BLADDER SYNDROME).**

Generali JA, Cada DJ. *Hosp Pharm.* 2013 Nov;48(10):822-4. doi: 10.1310/hpj4810-822. PMID: 24421434

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This useful Hospital Pharmacy feature is extracted from Off-Label Drug Facts, a publication available from Wolters Kluwer Health. Off-Label Drug Facts is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made.

#### **DOWN REGULATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IS ASSOCIATED WITH DECREASED INFLAMMATION AFTER INTRAVESICAL ONABOTULINUMTOXINA INJECTIONS COMBINED WITH HYDRODISTENTION FOR PATIENTS WITH INTERSTITIAL CYSTITIS—CLINICAL RESULTS AND IMMUNOHISTOCHEMISTRY ANALYSIS.**

Peng CH, Jhang JF, Shie JH, Kuo HC. *Urology.* 2013 Dec;82(6):1452.e1-6. doi: 10.1016/j.urology.2013.09.003. PMID: 24295265

The purpose of this study from this exceptionally active research team in Taiwan was to measure the expression of vascular endothelial growth factor (VEGF) in bladder tissue and improvement of clinical symptoms and inflammatory biomarkers after repeated onabotulinumtoxin A injections in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Twenty-one patients with IC/BPS received 4 sets of intravesical 100-U onabotulinumtoxin A injections combined with hydrodistention. Assessments at baseline and 6 months after each treatment included O'Leary-Sant Symptom Score, bladder pain visual analog scale, functional bladder capacity (FBC), grade of glomerulations under cystoscopic hydrodistention, and urodynamic parameters. The bladder specimens at baseline and at the fourth treatment were investigated by western blotting for the expression of VEGF, Bcl-2-associated X protein (Bax), and phospho-p38 (p-p38), and immunohistochemistry staining for apoptotic and mast cell activity. Six women with genuine stress urinary incontinence served as controls for comparison. They found that increased VEGF was associated with bladder inflammation and smaller FBC in patients with IC/BPS and decreased after repeated onabotulinumtoxinA injections and hydrodistention, suggesting VEGF plays an important role in the pathogenesis of IC/BPS.

## **KETAMINE CYSTITIS**

### **NERVE HYPERPLASIA: A UNIQUE FEATURE OF KETAMINE CYSTITIS.**

*Baker SC, Stahlschmidt J, Oxley J, Hinley J, Eardley I, Marsh F, Gillatt D, Fulford S, Southgate J. Acta Neuropathol Commun. 2013 Oct 8;1(1):64. doi: 10.1186/2051-5960-1-64. PMID: 24252413*

Baker and colleagues from York, UK report that there is an emerging association between ketamine abuse and the development of urological symptoms including dysuria, frequency and urgency, which have a neurological component. In addition, extreme cases are associated with severe unresolving bladder pain in conjunction with a thickened, contracted bladder and an ulcerated/absent urothelium. In this article they report on unusual neuropathological features seen by immunohistology in ketamine cystitis. Ketamine cystitis afflicts predominantly young patients, with unknown long-term consequences, and requires a strategy to control severe bladder pain in order to remove a dependency on the causative agent. The authors suggest that their study indicates that the development of pain in ketamine cystitis is mediated through a specific neurogenic mechanism that may also implicate the urothelium.

### **TREATMENT OF KETAMINE-ASSOCIATED CYSTITIS WITH CHONDROITIN SULPHATE.**

*Smart C, Kabir M, Pati J. Br J Nurs. 2013 Oct 10-23;22(18):S4, S6, S8-9. PMID: 24121772*

Smart and colleagues from Homerton University Hospital, London note that chronic cystitis associated with ketamine use is a growing problem among a young patient population who use the drug recreationally. Patients may present with symptoms such as urinary frequency, dysuria, urgency and haematuria in accident and emergency departments, GP surgeries, urology outpatient departments, drug rehabilitation or substance misuse units, genitourinary medicine clinics or continence services. The authors emphasize that nurses in these areas therefore need to be aware of the symptoms associated with ketamine-associated bladder damage and be prepared to ask patients about recreational drug use and inform them of possible treatments. This case report illustrates one patient's successful response to treatment with chondroitin sulphate 0.2% (Gepan) over a 1-year period.

## **DRUG HYPERSENSITIVITY**

### **NONALLERGIC DRUG HYPERSENSITIVITY REACTIONS.**

*Farnam K, Chang C, Teuber S, Gershwin ME. Int Arch Allergy Immunol. 2012;159(4):327-45. doi: 10.1159/000339690. Epub 2012 Jul 25. PMID: 22832422*

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**Although this is a slightly older review article, dating from 2012, we thought that it would nevertheless be of interest bearing in mind that there is a group of IC/BPS patients (and also fibromyalgia patients) who suffer from this extremely difficult problem of often multiple (nonallergic) hypersensitivities to drugs and chemicals which make all treatment a massive dilemma. Both the patients and their physicians can become quite desperate about this problem.**

Nonallergic drug hypersensitivities, also referred to as pseudoallergic or anaphylactoid reactions, have clinical manifestations that are often indistinguishable from allergic reactions. Farnam and colleagues from the Division of Rheumatology, Allergy and Clinical Immunology at the University of California at Davis performed a PubMed search using the terms 'drug allergy, drug hypersensitivity, pseudoallergies, anaphylaxis and nonallergic drug reactions' and reviewed 511 publications dated between 1970 and 2012. A total of 160 papers

that were relevant to the most common nonallergic drug hypersensitivity reactions were selected for discussion. Nonallergic drug hypersensitivities do not involve either IgE-mediated (type 1) or delayed (type 4) hypersensitivity. Nonallergic hypersensitivities are commonly referred to as pseudoallergic or idiosyncratic reactions. The common nonallergic drug hypersensitivities are secondary to chemotherapeutic drugs, radiocontrast agents, vancomycin, nonsteroidal anti-inflammatory agents, local anesthetic reactions and opiates. Protocols for skin testing of radiocontrast, nonsteroidal anti-inflammatory agents, local anesthetics and chemotherapeutic agents have been developed, though most have not been validated or standardized. Other diagnostic tests include in vitro-specific IgE tests, and the current 'gold' standard is usually an oral challenge or bronchoprovocation test. In the case of aspirin, even though it is not believed to be IgE-mediated, a 'desensitization' protocol has been developed and utilized successfully, although the mechanism of this desensitization is unclear. It was concluded that diagnostic methods exist to distinguish allergic from nonallergic drug hypersensitivity reactions. The best option in nonallergic drug hypersensitivity is avoidance. If that is not possible, premedication protocols have been developed, although the success of premedication varies amongst drugs and patients.

**Note: if anyone knows of new publications on this relatively understudied topic, please contact us.**

## **CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME**

### **NEW DEVELOPMENTS IN THE DIAGNOSIS AND TREATMENT OF CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME.**

*Pontari M, Giusto L. Curr Opin Urol. 2013 Nov;23(6):565-9. doi: 10.1097/MOU.0b013e3283656a55. PMID: 24080807*

The purpose of this review from Philadelphia was to describe new developments in the diagnosis and treatment of chronic prostatitis/chronic pelvic pain syndrome (CPPS). Symptoms in men with chronic prostatitis/CPPS appear to cluster into a group with primarily pelvic or localized disease, and a group with more systemic symptoms. Several other chronic pain conditions can be associated with chronic prostatitis/CPPS, including irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. Markers of neurologic inflammation and autoimmune disease parallel changes in symptoms after treatment. Treatment options include new alpha-blockers, psychological intervention, and prostate-directed therapy. The areas of acupuncture and pelvic floor physical therapy/myofascial release have received increased recent attention and appear to be good options in these patients. Future therapy may include antibodies to mediators of neurogenic inflammation and even treatment of bacteria in the bowel. The diagnosis of chronic prostatitis/CPPS must include conditions traditionally outside the scope of urologic practice but important for the care of men with chronic pelvic pain. The treatment is best done using multiple simultaneous therapies aimed at the different aspects of the condition.

## **CONFUSABLE CONDITION**

### **SQUAMOUS CELL CARCINOMA OF THE BLADDER MIMICKING INTERSTITIAL CYSTITIS AND VOIDING DYSFUNCTION.**

*Prudnick C, Morley C, Shapiro R, Zaslau S. Case Rep Urol. 2013;2013:924918. doi: 10.1155/2013/924918. Epub 2013 Oct 10. PMID: 24224109*

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Squamous cell carcinoma (SCC) of the bladder is a relatively uncommon cause of bladder cancer accounting for <5% of bladder tumours in the western countries. SCC has a slight male predominance and tends to occur in the seventh decade of life. The main presenting symptom of SCC is haematuria, and development of this tumour in the western world is associated most closely with chronic indwelling catheters and spinal cord injuries. A 39-year-old Caucasian female presented with bladder and lower abdominal pain, urinary frequency, and nocturia which was originally believed to be interstitial cystitis (IC) but was later diagnosed as SCC of the bladder. Presentation of SCC without haematuria is an uncommon presentation, but the absence of this symptom should not lead a practitioner to exclude the diagnosis of SCC. This case is being reported in an attempt to explain the delay and difficulty of diagnosis. Background on the risk factors for SCC of the bladder and the typical presenting symptoms of bladder SCC and IC are also reviewed.

## **CHRONIC PELVIC PAIN**

### **CHRONIC PELVIC PAIN.**

Stein SL. *Gastroenterol Clin North Am.* 2013 Dec;42(4):785-800. doi: 10.1016/j.gtc.2013.08.005. Epub 2013 Oct 23. PMID: 24280400

Chronic pelvic pain is pain lasting longer than 6 months and is estimated to occur in 15% of women. Causes of pelvic pain include disorders of gynecologic, urologic, gastroenterologic, and musculoskeletal systems. The multidisciplinary nature of chronic pelvic pain may complicate diagnosis and treatment. Treatments vary by cause but may include medicinal, neuroablative, and surgical treatments.

#### **PELVIC PAIN: A PATHWAY FOR CARE DEVELOPED FOR BOTH MEN AND WOMEN BY THE BRITISH PAIN SOCIETY.**

Baranowski AP, Lee J, Price C, Hughes J. *Br J Anaesth.* 2014 Jan 6. [Epub ahead of print] PMID: 24394942

This paper by Baranowski and colleagues from the Pain Management Centre, National Hospital for Neurology & Neurosurgery, University College London, explains the key points and highlights some of the controversies in the development of the British Pain Society's pelvic pain patient pathway map. The authors note that many clinicians lack experience and confidence with this group of patients. The difficulties of classification and definitions in this area are also discussed in detail. These are historical causes of disagreement among specialists which can lead to confused clinical care. The authors note that this group of patients has multiple issues that cross many professional boundaries and they are best managed by the coordinated involvement of multiple teams. Patients suffer from significant distress and disability that often needs specialist assessment and intervention (interdisciplinary). This suggests that an integrated approach is required across the historic boundaries of primary and secondary care. A variety of interventions, including opioids and neuromodulation are recommended in the pathway and the controversies surrounding these inclusions are discussed in detail.

Useful link: [http://bps.mapofmedicine.com/evidence/bps/chronic\\_pelvic\\_pain\\_for\\_men\\_and\\_women\\_1.html](http://bps.mapofmedicine.com/evidence/bps/chronic_pelvic_pain_for_men_and_women_1.html)

#### **PREVALENCE AND RISK FACTORS OF PELVIC PAIN.** [Article in English, Spanish]

Díaz-Mohedo E, Hita-Contreras F, Luque-Suárez A, Walker-Chao C, Zarza-Luciáñez D, Salinas-Casado J. *Actas Urol Esp.* 2013 Oct 24. pii: S0210-4806(13)00332-X. doi: 10.1016/j.acuro.2013.09.006. [Epub ahead of print] PMID: 24206627

The aim of this study from Malaga, Spain was to determine the prevalence of Chronic Pelvic Pain (CPP) symptoms in Malaga and province and to identify risk factors associated. A cross-sectional study was carried out in Malaga and its province, 18-65 years-old throughout a non-probability sampling by quotas, stratified by sex, age and counties. All participants completed the QCPP-M, a self-administered questionnaire, validated tool due to its ability to discriminate patients with and without CPP. They found a high prevalence of CPP symptoms in Málaga (22.8%), this is related with significantly several risk factors.

### **VULVOVAGINAL**

#### **CONTACT HYPERSENSITIVITY TO OXAZOLONE PROVOKES VULVAR MECHANICAL HYPERALGESIA IN MICE.**

Martinov T, Glenn-Finer R, Burley S, Tonc E, Balsells E, Ashbaugh A, Swanson L, Daughters RS, Chatterjea D. *PLoS One.* 2013 Oct 25;8(10):e78673. doi: 10.1371/journal.pone.0078673. PMID: 24205293

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The interplay among pain, allergy and dysregulated inflammation promises to yield significant conceptual advances in immunology and chronic pain. Hapten-mediated contact hypersensitivity reactions are used to model skin allergies in rodents but have not been utilized to study associated changes in pain perception in the affected skin. In this study, Martinov and colleagues from St Paul, Minnesota characterized changes in mechanical hyperalgesia in oxazolone-sensitized female mice challenged with single and repeated labiar skin exposure to oxazolone. Hyperalgesia lasted up to 24 hours along with local influx of neutrophils, upregulation of inflammatory cytokine gene expression, and increased density of cutaneous labiar nerve fibers. Three daily oxazolone challenges produced vulvar mechanical hyperalgesic responses and increases in nerve density that were detectable up to 5 days post-challenge even after overt inflammation resolved. This persistent vulvar hyperalgesia is resonant with vulvodinia, an understudied chronic pain condition that is remarkably prevalent in 18-60 year-old women. An elevated risk for vulvodinia has been associated with a history of environmental allergies. They report that their pre-clinical model can be readily adapted to regimens of chronic exposures and long-term assessment of vulvar pain with and without concurrent inflammation to improve our understanding of mechanisms underlying subsets of vulvodinia and to develop new therapeutics for this condition.

#### **VULVOVAGINAL CANDIDIASIS AS A CHRONIC DISEASE: DIAGNOSTIC CRITERIA AND DEFINITION.**



Hong E, Dixit S, Fidel PL, Bradford J, Fischer G. *J Low Genit Tract Dis.* 2014 Jan;18(1):31-8. doi: 10.1097/LGT.0b013e318287aced. PMID: 23760143

Although recurrent vulvovaginal candidiasis is defined as 4 or more discrete attacks of vulvovaginal candidiasis per year, there is no diagnostic nomenclature or definition for the many women who are chronically symptomatic. This Australian study aims to establish and propose a definition and a set of diagnostic criteria, which would enable clinicians to promptly identify and treat women with chronic vulvovaginal candidiasis (CVVC). Data were obtained prospectively from 50 women with presumptive CVVC and 42 controls. Historical and clinical features of CVVC identified by expert consensus were compared between the 2 groups. Diagnostic criteria were then prospectively applied to a further 163 patients to verify their accuracy. The authors propose that CVVC can be confidently diagnosed using the major criteria of a chronic nonspecific and nonerosive vulvovaginitis that includes at least 5 or more properties from the following criteria: soreness, dyspareunia, positive vaginal swab either at presentation or in the past, previous response to antifungal medication, exacerbation with antibiotics, cyclicity, swelling, and discharge. This condition responds reliably to oral antifungal medication.

## **SJÖGREN'S SYNDROME**

### **SJÖGREN'S SYNDROME ACCOMPANIED WITH INTERSTITIAL CYSTITIS: A CASE REPORT AND REVIEW OF THE LITERATURE.**

Liang D, Lu J, Guo A. *Clin Rheumatol.* 2014 Jan 7. [Epub ahead of print] PMID: 24395198

Liang and colleagues from the Department of Rheumatology, Chinese PLA General Hospital in Beijing, China present a case report of a patient with Sjögren's syndrome accompanied with interstitial cystitis. A 64-year-old woman complained of dry mouth for 21 years, recurrent swelling and pain on the right parotid in 2000, and urinary irritation symptoms in the past 2 years. Several courses of different types of antibiotics could not relieve her urinary irritation symptoms. Bladder hydraulic dilatation had only transient effects. Urine sediment contained neither erythrocytes nor leukocytes, and urine cultures yielded no growth. However, increased  $\gamma$ -globulin, positive antinuclear antibodies, and anti-SS-A and anti-SS-B antibodies were detected. Histopathological data of labial salivary glands showed three foci of numerous mononuclear cells. Cystoscopy revealed redness, edema, angiectasis, and extensive ecchymosis of the mucosal surface and several small floating cruor entities in the bladder. Urinary bladder biopsy specimens revealed the absence of urothelium and edematous lamina propria and submucosa, with diffuse or multiple focal chronic inflammatory cell infiltration. Based on these findings, she was diagnosed with Sjögren's syndrome accompanied with interstitial cystitis. Therapy with corticosteroids relieved the symptoms significantly.

### **DISTAL RENAL TUBULAR ACIDOSIS ASSOCIATED WITH SJOGREN SYNDROME.**

Lim AK, Choi MJ. *Intern Med J.* 2013 Dec;43(12):1330-4. doi: 10.1111/imj.12300. PMID: 24330363

Renal tubular acidosis is a common cause of normal anion gap metabolic acidosis but these disorders can be easily missed or misdiagnosed. Lim and Choi from Australia highlight the approach to assessing renal tubular acidosis by discussing a case study with a temporal data set collected over more than 5 weeks. They highlight the principles and the necessary information required for a diagnosis of classic distal renal tubular acidosis (dRTA). They also briefly review several aspects of type 1 renal tubular acidosis related to autoimmune disease, drugs and thyroid disorders.

## **STEM CELL ENGINEERING**

### **ENDOMETRIAL STEM CELL DIFFERENTIATION INTO SMOOTH MUSCLE CELL: A NOVEL APPROACH FOR BLADDER TISSUE ENGINEERING IN WOMEN.**

Shoae-Hassani A, Sharif S, Seifalian AM, Mortazavi-Tabatabaei SA, Rezaie S, Verdi J. *BJU Int.* 2013 Oct;112(6):854-63. doi: 10.1111/bju.12195. PMID: 24028767

The purpose of this study from Iran was to investigate manufacturing smooth muscle cells (SMCs) for regenerative bladder reconstruction from differentiation of endometrial stem cells (EnSCs), as the recent discovery of EnSCs from the lining of women's uteri, opens up the possibility of using these cells for tissue engineering applications, such as building up natural tissue to repair prolapsed pelvic floors as well as building urinary bladder wall. Human EnSCs were successfully differentiated into SMCs, using hydrogels as scaffold. EnSCs may be used for autologous bladder wall regeneration without any immunological complications in

women. Currently work is in progress using bioabsorbable nanocomposite materials as EnSC scaffolds for developing urinary bladder wall tissue.

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