

REVIEW OF THE INTERNATIONAL CONTINENCE SOCIETY 48th ANNUAL SCIENTIFIC MEETING 28-31 AUGUST 2018, PHILADELPHIA, USA

By Jane Meijlink

The International Continence Society (ICS) annual scientific meeting attracts a multidisciplinary group including urologists, gynaecologists, neurologists, nurses, physiotherapists, basic scientists and physiologists as well as patient advocates from around the world. This year's meeting was held in Philadelphia, renowned as the birthplace of the United States of America. Topics this year included pathophysiology, diagnosis and treatment in the fields of urinary incontinence and lower urinary tract and pelvic floor dysfunction (e.g. interstitial cystitis/bladder pain syndrome, prolapse, overactive and underactive bladder). There was also a focus this year on nocturia (urination at night) and tremendous interest in neurological aspects and current research in this field. The fact that the meeting was held in the USA provided the possibility of hearing more about the work of the National Institutes of Health in a Round Table session on Innovation in LUTS Clinical Research Networks.

In recent years we have seen a steady increase in interest in chronic pelvic and bladder pain at ICS. This has been a very welcome development for everyone in the IC/BPS field. The recently established "ICS Institute", which comprises "Schools" to serve the e-learning needs of members and provide training in designated centres of excellence, also includes a School of Pelvic Pain, the Director of which is Professor Kristene Whitmore. This interest is now also reflected in the number of abstracts submitted for the conference related to IC/BPS, in the scientific programme as a whole and in the fact that top doctors and researchers in our field from around the world attended the meeting in Philadelphia. This year's programme included two podium oral abstract sessions dedicated to IC/BPS, a workshop on intravesical treatment, another workshop on chronic pelvic pain and sexual dysfunction and much more besides.

ICS is well-known for its standardisation of terminology and definitions. However, doctors and researchers around the world are still using a variety of different terms/definitions, and this particularly applies in our field of IC/BPS/PBS/HSB! It was stressed that we need common terminology and definitions, using the same terms to mean the same thing. This will also promote better international cooperation, research and data exchange. But at a patient level in today's bureaucratic, electronic healthcare world, it is also vital for the right diagnosis, right treatment and reimbursement of that treatment. A major problem in our IC/BPS field is that medical societies have omitted to address this widespread non-reimbursement issue. For the sake of the patients, action is needed.

Further information on the ICS 2018 programme may be found at <https://www.ics.org/2018>

State-of-the-Art Lecture: "LOWER URINARY TRACT SENSATION – VOIDING WITH FEELING"

Speaker: Professor Jerry Gebhart

"Even if you cannot see anything in the bladder on cystoscopy, this doesn't mean that there isn't something very wrong with the nerves in the bladder wall".

A highlight of the ICS annual meeting was the wonderful state-of-the-art presentation by Professor Jerry Gebhart, the well-known anaesthesiologist and pain expert from Pittsburgh and Director of the Center for Pain Research, who spoke on "Lower Urinary Tract Sensation – Voiding with Feeling".

Professor Gebhart discussed the neurological mechanisms underlying the development of hypersensitivity in organs such as the bladder. He also stressed that there are still many gaps in our current knowledge, including the role of the urothelium, the field of cross-organ sensitisation and what is it exactly that sustains sensitisation. Underlying mechanisms are poorly understood while organ hypersensitivity can often occur in the absence of a current pathobiological explanation for the discomfort and pain. This means that chronic visceral pain is notoriously difficult to manage. Perhaps his most poignant statement for IC/BPS patients was that “even if you cannot see anything in the bladder on cystoscopy, this doesn’t mean that there isn’t something very wrong with the nerves in the bladder wall”. This needs to go on every urology student’s syllabus!

Workshop 2: WHERE ARE WE WITH INTRAVESICAL THERAPEUTICS IN 2018?

Chair: Rufus Cartwright (United Kingdom), Speakers: Mauro Cervigni (Italy), Pradeep Tyagi (United States), Angie Rantell (United Kingdom), Heidi Brown (United States)

This workshop looked at the state-of-the-art in intravesical treatment of the bladder and addressed three functional conditions: interstitial cystitis/bladder pain syndrome, overactive bladder/detrusor overactivity and recurrent urinary tract infection (UTI).

The urothelium is not merely a barrier, it plays an important sensory role. It has a key role in detrusor functioning, and damage to the urothelium or its glycosaminoglycan coating (GAG layer) may be central to bladder pain and recurrent UTI.

While intravesical treatment is widely used in Europe, it has often been recommended for refractory patients who have failed to respond to many other treatments. However, it was suggested that earlier intravesical treatment of the disease in newly diagnosed patients might help prevent further chronic impairment of the urothelium. Intravesical treatment directly treats the bladder itself, while oral treatments alone may have unpleasant systemic side-effects, with little of the active ingredients actually reaching the bladder. Multimodal treatment may be the answer in many patients, particularly those with comorbidities, while those with only bladder symptoms may benefit from intravesical treatment alone. According to the speakers, disadvantages of intravesical treatment include the fact that it may have a short duration of action and therefore need to be frequently repeated and there is a risk of infection due to catheterisation. Finally, and perhaps most importantly from a practical point of view, there is the cost factor and lack of reimbursement in many countries. This means that even if the intravesical treatments are available, patients may have no access to them due to the cost. It is high time that this non-reimbursement issue is addressed!

A big problem is the lack of well-conducted large-scale randomised controlled trials. Some of the instillations are still unlicensed, while others are licensed as medical devices.

Professor Mauro Cervigni from Rome (also Vice-President of ESSIC) addressed the evidence for instillations for IC/BPS, giving an overview of currently licensed intravesical options. He discussed the role of the GAG layer in IC/BPS and the problem of the defective urothelial barrier. We still do not know the pathophysiological mechanism by which the GAG layer loses its protective barrier function, causing increased permeability into deep bladder layers, irritated nerves and inflammation, he said.

There are 6 major classes of GAGs:

- Chondroitin sulphate
- Dermatan sulphate
- Keratan sulphate
- Heparin sulphate
- Heparin
- Hyaluronan

A defective urothelium allows toxic substances to diffuse into the bladder wall, thereby causing sensory urgency, increased urinary frequency and pain. GAGs also protect the bladder urothelium from bacterial adherence and serve as blood-urine barriers.

Bladders instillations may include GAG replenishment (Hyaluronic Acid (also known as Hyaluronan) and Chondroitin Sulphate - individually or combined), Cocktails (which may include for example lidocaine, triamcinolone, gentamicin, heparin, PPS, prednisone), and Dimethylsulfoxide (DMSO). Tacrolimus was also mentioned by Dr Pradeep Tyagi. Botox was reviewed and it was concluded that this treatment is currently moving from injection to instillation. It was noted that Botox needs volume help for effective delivery. Dr Tyagi also looked at polymeric devices and thermosensitive hydrogel – used in drug delivery systems - to extend exposure through sustained drug delivery. Liposomes rely on endocytosis and have been tested in controlled clinical studies. Future options are necessary for the delivery of large molecular weight drugs, he said.

Angie Rantell looked at the practical aspects of giving instillations to patients, emphasizing that manufacturers' instructions should always be followed, patients should be fully informed prior to starting a course of therapy.

It was concluded that there is a lack of research and best practice guidelines for instillations. Furthermore, larger-scale studies with long-term follow-up are urgently needed and researchers need to take a close look at the placebo response which undermines so many clinical trials.

Workshop 8: APPROACH TO CHRONIC PELVIC PAIN AND SEXUAL DYSFUNCTION

Chair: Kristene Whitmore (United States), Speakers: Karolynn Echols (United States), Erica Fletcher (United States), Neha Rana (United States), Jane Meijlink (Netherlands).

This workshop provided an overview of chronic pelvic pain syndromes, their potentially multifactorial etiologies, and a stepwise approach to the patient. As Professor Whitmore noted, bearing in mind that Chronic Pelvic Pain (CPP) may be multifactorial, a systematic approach is necessary in the evaluation of the patient. Important aspects include a detailed history including any relevant medical comorbidities, laboratory results, imaging, and any previous surgical procedures. The evaluation should rule out any identifiable pathology which could contribute to the pain. A thorough investigation should look into the factors that may alleviate and/or worsen the symptoms. The physical examination plays a crucial role and should include the abdomen, back, and pelvis in standing, supine, and lithotomy positions to evaluate the skin, muscles, neurologic response, and internal organs. Given the association of CPP with depression and anxiety, providers should also assess potential psychosocial factors.

Integrative Medicine (IM) sees the patient as a whole: mind, body and way of life. It utilizes all appropriate evidence-based resources and therapeutic options: conventional and complimentary alternative medicine (CAM). Diet and lifestyle modifications in addition to physical therapy, biofeedback, medications, surgery and integrative medicine modalities such as manual medicine, nutraceuticals, yoga, acupuncture, aromatherapy and energy medicine can be used alone or in combination to relieve symptoms.

Physical Therapy evaluation and treatment is an essential component in the care of CPP patients. 70-90 percent of CPP patients have associated diagnoses of spinal and/or other musculoskeletal dysfunction. Pelvic musculoskeletal imbalance can cause or augment urological and gynaecological symptoms.

From the patient perspective, Jane Meijlink (IPBF) looked at the impact of chronic pelvic pain syndromes on sexual relationships. Even today, talking to others about your own intimate sexual experiences – particularly problematic, negative aspects – is still extremely difficult, embarrassing and enveloped in an aura of stigma and taboo. CPP conditions such as bladder pain in IC/BPS/HSB, urethral

pain and vulvodynia, can have a disruptive and distressing impact on sexual relationships. Support group helplines are intensively used by patients who are stressed and even suicidal about failing sexual relationships. While it is important for patients to be able to discuss this problem with their partner to try to find solutions together, expert help may be needed in the form of counselling or sex therapy. An important problem is that many patients find it difficult or impossible to raise this intimate and very private topic with their doctor. It is therefore important for the clinician treating the patient to take the initiative in raising this issue and helping the patient and partner to find expert help and advice for painful sex.

Many of the patient support groups now provide excellent information on sexual intimacy issues for patients both online and in the form of leaflets.

ROUND TABLE DISCUSSION 9: ROLE OF THE NERVOUS SYSTEM

Speakers: E. Chartier-Kastler, J. Mogil, T. Chelimsky, F. Cruz

In a round table discussion on the role of the nervous system, we heard more about the problematic placebo effect in clinical trials from Dr Jeffrey Mogil who informed us that the placebo response is on the increase in clinical trials with drug response on the decrease! Another interesting piece of information was that pain drugs may work quite differently in men and women.

SESSION 6 (PODIUM SHORT ORAL) - INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME 1

Chairs: Prof Philip Hanno (United States), J. Quentin Clemens (United States)

In this IC/BPS session I, new research abstracts were presented.

#56 MRI IMAGING OF HUMAN BLADDER WALL USING INTRAVESICAL NOVEL CONTRAST MIXTURE: APPLICATIONS IN PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS (PBS/IC)

Chermansky C, Janicki J, Moon C, Kaufman J, Tyagi P.

PRIZE AWARD: Best in Category Prize - Pelvic Pain Syndromes / Sexual Dysfunction

There is an unmet need for an imaging technique which will differentiate ulcerative [lesion] IC from non-ulcerative [non-lesion] IC. MRI is a radiation-free imaging technique that demonstrates excellent contrast of pelvic tissues in 3D-anatomy. Intravesical novel contrast mixture (NCM) has been recently shown to improve the CNR of rat bladder wall injured with protamine sulfate. In this clinical study, the safety and feasibility of MRI enhanced with intravesical NCM in evaluating patients with PBS/IC was tested. NCM instillation in subjects did not evoke pain or discomfort. MRI enhanced with intravesical NCM allowed differentiation of the bladder wall into different tissue layers with an increased depth of gadolinium diffusion in the ulcerative-type PBS/IC patients. It was concluded that NCM instillation achieves artifact-free differential contrast and spatial resolution of human bladder wall, which is not possible with instillation or injection of single contrast agents. These findings demonstrate the safety and feasibility of NCM enhanced MRI to characterize changes within the bladder wall for phenotyping PBS/IC. This pilot study was limited by the small size and was not powered to demonstrate the group-wise differences in bladder wall thickness. Future prospective studies are needed to determine the utility of MRI in helping further the understand of PBS/IC phenotypes.

#57 TITLE: EVALUATION OF URINARY CULTURES IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: ARE THERE DIFFERENCES IN COLONY COUNTS?

Rinko R, Munoz J, Dawson M, Rana N, Whitmore K.

Little is understood about the flora in patients with IC/BPS. Recent work suggests that the urinary microbiome plays an important role in IC/BPS. This biological data could have implications in the diagnosis and treatment of IC/BPS. During evaluation of urinary symptoms, a urine culture is collected to rule out a urinary tract infection. Rinko and colleagues propose that there may be a correlation between low level bacterial counts in urine cultures in IC/BPS in the absence of a clinical urinary tract infection, defined as >100,000 colony-forming units (CFU) of bacteria. The most common culture result was no growth, 561 (67.9%), the most common urinary bacteria cultured from patients with IC/BPS were Enterococcus, E. coli, group B Streptococcus (GBS), and Klebsiella. In patients with IC/BPS these bacteria tend to culture out at lower CFU than 100,000 CFU. This study emphasizes the need for making the DNA sequencing tests more available and more research into the microbiome of healthy bladders compared to those with IC/BPS. This area is poorly understood and may cause

unnecessary use of antibiotics in patients with IC/BPS symptoms and re-addresses the role of infection in IC/BPS.

#58 STOOL AND VAGINAL MICROBIOTA TESTS AS A DIAGNOSTIC TOOL IN WOMEN WITH PAINFUL BLADDER SYNDROME / INTERSTITIAL CYSTITIS

Hessdoerfer E.

Histamine seems to play a major role in IC as neurogenic inflammation is one of the hypothesis of IC. Antihistamines are part of the guideline recommendations, foods high in histamine (e.g. Shorter-Moldwin Food Sensitivity Questionnaire) aggravate IC symptoms. Vaginal microbiome tests recently assume changes in IC patients. Within this retrospective case collection, the role of histamine overload in the gut is highlighted along with a gut and vaginal microbiota analysis. The author concluded that testing for histamine in stool and vaginal dysbiosis could be new diagnostic tools in Painful Bladder Syndrome / Interstitial Cystitis patients. Treatment with pre- and probiotics and colon cleansing already known in alternative medicine could be a new therapeutic option for IC patients.

#59 A SYSTEMATIC REVIEW OF SURGICAL TECHNIQUES FOR THE TREATMENT OF BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS

Bratt D, Downey A P, Osman N I, Mangera A, Reid S V R, Inman R I, Chapple C R.

Surgical intervention is reserved for the most severe refractory cases, and includes subtotal cystectomy, orthotopic neobladder formation, total cystectomy and urinary diversion. However, to date, there is no consensus on patient selection for surgery or the optimal surgical approach. Bratt and colleagues systematically reviewed the available literature, and evaluated the evidence relating to safety and efficacy of surgical interventions for treating BPS/IC. Overall rates of success following any surgery were 77.2%. They concluded that the choice of operation for patients within this group remains a topic of debate and one which they feel they cannot categorically recommend in this review. There is a clear need for prospective studies and randomisation of patients to fully differentiate between total cystectomy and bladder conserving procedures. However, the data suggest that in all instances, total removal of the bladder may yield more favourable long-term results in patients who do not have typical end-stage disease and reduces the risk of requiring a secondary procedure. Interpretation of this data should be guarded given the relatively low patient numbers, risk of selection bias and lack of a consensus on diagnostic criteria.

#60 EVALUATION OF SELF INSTILLATION OF CHONDROITINE SULFATE VERSUS INSTILLATIONS GIVEN BY A DEDICATED NURSE IN THE TREATMENT OF PATIENTS SUFFERING FROM BLADDER PAIN SYNDROME

Hjuler A, Rasmussen S A, Jensen B T, Ryhammer A M.

Instillation of chondroitin sulphate (CS) in the bladder is one of the cornerstones in treatment of Bladder Pain Syndrome (BPS). CS is instilled into the bladder via a catheter and contributes to the repair of a defective GAG layer. Treatment is administered in weekly sessions over a course of 6 weeks. Many hospitals let patients come to the institution and have a nurse do the catheterization and instillation (nurse provided instillation, NPI). The authors have for several years taught patients to perform clean intermittent self-catheterization (CISC) and let them do self-instillations (SI) in their own home. They have, however, never evaluated the treatment systematically. The purpose of this study was to find out if treatment results depend on whether patients do SI or NPI and to evaluate whether patients had any preference at the end of treatment. Furthermore, they wished to estimate possible differences in resources spent for both patients and nurses. It appeared that NPI gives better treatment results than SI when looking at self-reported bladder symptoms like pain, urgency and frequency. The better treatment results are, however, not reflected in results regarding treatment satisfaction and patients' preferences regarding treatment modality. All patients in this study preferred to do SI as opposed to NPI despite the better treatment results and the possibility of having a consultation with a health care professional when given the NPI. UTI is a complication related to SI, probably indicating a learning curve for the patients performing CISC. SI offers a substantial reduction in resources and time spent for both patients and nurses. There is, however, a difference in treatment results in favour of NPI.

#61 USEFULNESS OF LONG-TERM DIETARY MANIPULATION FOR FEMALE PATIENTS WITH PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS.

Oh-Oka H.

Given that there is currently no established treatment for PBS/IC, complementary and alternative medicine (CAM) therapies such as behavioural therapy, physical therapy, stress reduction, and dietary manipulation (DM) can be potential treatment options. This study investigated the effect of a 1.5-year intensive systematic

DM (ISDM) in women with stable PBS/IC. The study included 40 female patients with PBS/IC in stable condition. In cooperation with the nutrition control team, the developed an original PBS/IC diet (1,500 kcal, 65 g protein, 40 g fat, 220 g carbohydrate, 1,000 ml water, 7 g salt). Data regarding daily food intake and food-related symptoms were collected by conducting a detailed interview of each patient, and they set meal menu to control PBS/IC symptoms and advised the patients to reduce the intake of specific food items to the maximum possible extent. The following food items were removed from or restricted in the diet of patients: tomatoes, tomato products, soybean, tofu product, spices, excessive potassium, citrus, high-acidity-inducing substances, etc. They found that intensive systematic dietary manipulation relieves various symptoms of PBS/IC and improves QOL over the long term and may also reduce the need for other treatments.

#63 DOES REPEATED HYDRODISTENSION WITH TRANSURETHRAL COAGULATION FOR INTERSTITIAL CYSTITIS WITH HUNNER LESIONS CAUSE BLADDER CONTRACTION?

Tomoe H.

Transurethral resection or coagulation (TUR/TUC) is recommended in the AUA IC/BPS Guideline. While it is effective, recurrence is highly possible. As bladder contraction is one of the troublesome problems after repeated TUR and TUC, even experts believe that repeated surgeries should not to be done to avoid bladder contraction. However, Professor Hikaru Tomoe found that repeated hydrodistension with TUC did not cause bladder contraction. She and her colleagues in Tokyo evaluated the effects and the side effects of repeated hydrodistension with TUC for IC with Hunner lesions. Repeated surgery contributed to improvement of symptoms and bladder capacity. It did not cause worsening of symptoms and did not reduce bladder capacity. Repeated hydrodistension with TUC for recurrence IC with Hunner lesions improves symptoms. It was not a direct cause of bladder contractility and in fact tended to result in increased bladder capacity. However, coagulation that is too deep may cause damage to the muscle layer and lead to contraction of the muscle.

#64 THERAPEUTIC EFFECT OF REPEAT PLATELET-RICH-PLASMA INTRAVESICAL INJECTIONS FOR IC/BPS REFRACTORY TO CONVENTIONAL TREATMENT

Jhang J, Wu S, Lin T, Kuo H.

Although IC/BPS has been known for more than 100 years, current treatments are usually unsuccessful in achieving long-term bladder pain relief and irritable symptom improvement. Several intravesical or oral medications have been tried, but the long-term therapeutic efficacy of these agents has not been proven. This study investigated the clinical efficacy of platelet-rich plasma (PRP) intravesical injection on 40 patients (3 men) with IC/BPS. Platelets can act as modulators of inflammation and tissue regeneration through the release of growth factors, cytokines and extracellular matrix modulators. The study results demonstrated that repeated intravesical injections of autologous PRP could increase bladder capacity and provide IC symptom improvement in patients with IC/BPS refractory to conventional therapy. Autologous PRP injection is safe and effective in selected patients. Although this pilot study lacked a placebo control, the improvements in IC/BPS symptoms and FBC after PRP treatment indicate the feasibility of such treatment for IC/BPS. It was concluded that repeated intravesical PRP injection is well tolerated, appears to be a safe and effective in medically refractory IC/BPS and provides significant symptom improvement.

#65 WHAT ARE THE MOST EFFECTIVE INTERVENTIONS FOR TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS? A NETWORK META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

Imamura M, Scott N, Wallace S, Ogah J, Ford A, Brazzelli M.

There is currently no definitive cure for BPS, but a large number of treatments which aim to alleviate symptoms are employed with limited evidence. Previous research is hampered by its focus on numerous pairwise comparisons, which makes it difficult to identify the most effective treatments. This study aimed to bring together evidence for all available treatments that have been assessed in randomised controlled trials (RCT) by means of a network meta-analysis (NMA), which allow simultaneous comparisons of multiple interventions. Some interventions appear to be more effective than others. However, there is considerable uncertainty around the estimates of effect and longevity of treatment is unclear. Adverse events were very inconsistently reported. Although a large number of participants experienced one or more adverse events in most trials, these were described as 'primarily mild to moderate in severity' by the trialists. It was concluded that some treatments may be more effective. However, how much more effective is uncertain as there was substantial heterogeneity within treatment types and categories. Few data were available for each comparison. Follow-up was typically short. Better understanding of the disease mechanism would help develop better treatments. Large, well-conducted RCTs are needed.

#66 ANXIETY SCORE DOES NOT INFLUENCE TREATMENT OUTCOME IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yu W, Yeh H, Kuo H.

This study investigated the impact of anxiety severity on therapeutic results of 75 IC/BPS patients (68 female and 7 male) patients. The primary endpoint was changes of Beck's Anxiety Inventory (BAI) for anxiety mood before and 3 months after treatment. Secondary endpoints included the changes of Global Response Assessment (GRA), O'Leary-Sant score (OSS), and Visual Analog Scale (VAS). The clinical symptom scores were also compared with cystometric bladder capacity (CBC) under the urodynamic study. All patients completed the study. The results of this study suggest baseline BAI does not influence treatment outcome of IC/BPS. Regardless of the level of anxiety, IC/BPS patients had significant improvement in ICSI, ICPI, VAS, and GRA. The change in BAI was significantly greater in patients with a GRA ≥ 2 . The improvement of GRA was mainly due to decrease of symptoms and problems of the bladder. It was therefore concluded that the improvement in physical and visceral distress symptoms of BAI is significantly associated with an increase in GRA after treatment, indicating that IC/BPS patients should be advised to receive regular and persistent treatment to achieve a better therapeutic outcome.

SESSION 24 (PODIUM SHORT ORAL) – BASIC SCIENCE: OVERACTIVE BLADDER AND PAIN

Chairs: Dr Robert M Levin (United States), Dr Kristene E Whitmore (United States), Dr Rita Valentino

MOLECULAR DETERMINANTS OF AFFERENT SENSITIZATION IN THE FACE OF UROTHELIAL BARRIER DYSFUNCTION

Carattino M, Rued A, Rooney J, Montalbetti N

The internal surface of the urinary bladder is lined by the urothelium, a barrier-forming epithelium that restricts the passage of ions and metabolic products from the urine into the bladder interstitium. Urothelial abnormalities, which range from mucosal ulcerations, urothelial ruptures and widening of the space between urothelial cells to denuded epithelium, have been reported in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Although aberrant bladder afferent signalling is considered to play an important role in symptoms generation in IC/BPS, little is known about the sensory pathways that are involved in this process and the mechanisms that promote afferent sensitization. The authors previously showed that the over-expression of *Cldn2* in the rat urothelium reproduces the cardinal features of IC/BPS by a mechanism that involves A delta fiber afferents. The data presented in this report suggest that the functional changes seen in rats transduced with *AdCldn2* reflect in part changes in ion channels that control neuronal excitability. These findings provide novel potential targets to treat hypersensitive bladder disorders.

#458 THE UROTHELIAL FIBROGENESIS AND INFLAMMATION CYTOKINES IN PATIENTS OF IC/BPS WITH DIFFERENT CLINICAL PHENOTYPES AND SYMPTOM SEVERITY

Jhang J, Birder L, Jiang Y, Hsu Y, Ho H, Kuo H

Previous studies showed unhealthy urothelium inflammation in IC/BPS. Bladder wall fibrosis was also noted in IC/BPS, especially in the patients with Hunner lesion. The aim of this study was to investigate the urothelial fibrogenesis and inflammatory cytokines in patients with IC/BPS. This study revealed increased fibrogenic cytokine TGF- β in human IC/BPS urothelium. The FGFR, which was associated with tissue healing, was significantly decreased in IC/BPS bladder. Their data suggest abnormal fibrogenic activity, impaired tissue healing and increased inflammatory cytokines may involve in the pathogenesis of IC/BPS.

#461 CHRONIC STRESS INCREASES PLASMATIC AND URINARY LEVELS OF NGF LEADING TO INCREASED BLADDER PAIN AND BLADDER HYPERACTIVITY. EXPERIMENTAL STUDY IN THE RAT.

Dias B, Charrua A, Cruz F

A relationship between chronic stress and BPS/IC is well established. In this study, Dias and colleagues hypothesized that in animals subjected to chronic stress there is an increase in NGF expression and that the high affinity TrkA blockade will prevent alterations in the bladder function. It was found that stress conditions induce a marked increase in the systemic NGF levels, as seen by the massive increase in the plasmatic levels. The levels in the urine were more modest. Although also increased during stress, the authors are of the opinion that this increase reflects the systemic increase rather than the local production. Chronic stress conditions induced a massive production in systemic NGF that may influence the response of somatic and visceral sensory fibers. These findings open the opportunity to use NGF levels in the plasma and the blockade

of TrkA receptors for the diagnosis and treatment of chronic visceral painful conditions, such as BPS/IC, respectively.

SESSION 29 (PODIUM SHORT ORAL) - INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME 2

Chairs: Dr Christopher K Payne (United States), David Klumpp (United States)

#610 POSSIBLE USEFULNESS OF BLOOD INFLAMMATORY MARKER C-REACTIVE PROTEIN AS A BIOMARKER FOR HUNNER LESIONS IN INTERSTITIAL CYSTITIS

Miyata Y, Matsuo T, Araki K, Nakamura Y, Sagara Y, Ohba K, Sakai H

Recently, there have been a few reports on correlation between blood inflammatory markers and disease prognosis in chronic inflammation and malignant tumors. Therefore, the authors assessed usefulness of presurgical serum C-reactive protein (CRP) level as a biomarker for Hunner lesions in IC prior to performing bladder hydrodistension. Unfortunately, from the results of this study, they could not differentiate between interstitial cystitis and non-IC hypersensitive bladder or normal bladder with CRP values. However, although serum CRP levels alone were insufficient for differential diagnosis between N-type IC and hypersensitive bladder, preoperative CRP levels were high in H-type IC patients. The results suggest the potential usefulness of CRP levels as a presurgical marker in the differential diagnosis of Hunner lesions. Additionally, CRP levels correlated with the severity of IC symptoms. They therefore concluded that serum CRP levels might be a marker for the presence of Hunner lesion in patients with interstitial cystitis.

#611 THE ROLE OF VIRAL INFECTION IN THE PATHOGENESIS OF IC/BPS –A STUDY OF URINARY VIRUS IN PATIENTS WITH IC/BPS AND THEIR CLINICAL CORRELATIONS

Jhang J, Birder L, Jiang Y, Hsu Y, Ho H, Kuo H

Although the diagnosis of interstitial cystitis and bladder pain syndrome (IC/BPS) should be made after ruling out bacterial cystitis, microorganism infection in the bladder is still considered as a possible etiology of IC/BPS. Early viral studies of IC/BPS revealed conflicting results due to small case numbers. The aim of this study was to use polymerase chain reaction (PCR) to investigate different kinds of virus load in the urine of patients with IC/BPS. The authors' data revealed using PCR could detect urinary bocavirus and adenovirus DNA in IC/BPS patients and control subjects. However, HSV and BK virus could not be detected in their PCR study. Virus infection as a possible etiology of IC/BPS had been a long-standing debatable issue. This study does not show any significant association between urinary virus load and IC/BPS. Further investigations using different PCR primers or in situ hybridization to detect virus presence in IC/BPS bladders are necessary to explore the role of virus in the pathogenesis of IC/BPS.

#612 CONTEMPORARY OUTCOMES OF SURGERY FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Downey A P, Osman N I, Park J, Mangera A, Inman R I, Reid S V R, Chapple C R

The role of surgery for BPS/IC is uncertain and currently reserved for patients who are considered refractory to treatment. European Association of Urology guidelines for BPS suggest patients should only undergo surgery as a "last resort" and should be managed in a specialist centre. While no particular surgical technique is recommended, total cystectomy with ileal conduit is the most common. Other techniques described are supratrigonal or subtrigonal cystectomy with augmentation or total cystectomy and orthotopic neobladder formation. Downey and colleagues reported their experience and outcomes of surgical intervention for bladder pain syndrome in a tertiary referral centre. They concluded that surgery for patients with BPS/IC is reserved for patients with severe symptoms who are considered refractory to other treatment options. In their experience, patients have lower rates of persistent pain following total cystectomy and ileal conduit formation compared to subtotal cystectomy and augmentation and total cystectomy with neobladder formation. It is important that all patients with refractory BPS are fully counselled pre-operatively in order to manage expectations and consider the risks of any procedure fully before embarking on surgical intervention.

#613 COMPARISON OF CLINICAL CHARACTERISTICS BETWEEN INTERSTITIAL CYSTITIS AND HYPERSENSITIVE BLADDER

Watanabe D, Akiyama Y, Nomiya A, Niimi A, Aizawa N, Kume H, Igawa Y, Homma Y

Interstitial cystitis (IC) and hypersensitive bladder (HSB) have a common lower urinary tract symptom profile in the form of hypersensitive bladder symptoms, such as bladder pain/discomfort, sensory urinary urgency, or high frequency. IC and HSB are to be classified by the endoscopic presence of Hunner lesions (Hunner type IC, HIC),

presence of mucosal bleeding after distension (MBAD) and absence of Hunner lesions (non-Hunner type IC, NHIC) or absence of both the Hunner lesions and MBAD (HSB), respectively. However, it has been reported that clinical phenotyping cannot distinguish HIC, NHIC, and HSB due to the similar symptomatic profiles. The aim of this study was to compare the clinical manifestations of patients with HIC, NHIC and HSB in 134 female patients with HIC (87), NHIC (33) and HSB (14). Patients with HIC were older and more symptomatic, and showed better responses to hydrodistension compared to those with NHIC or HSB. Almost no clinical parameters were different between NHIC and HSB. It was concluded that clinical characteristics were distinct in HIC, while indistinguishable between NHIC and HSB.

#614 EVALUATION OF THE INCIDENCE AND RISK FACTORS ASSOCIATED WITH VESICoureTERAL REFLUX IN PATIENTS WITH ULCERATIVE BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Oh C Y, Lee S H, Cho S T, Kim Y H, Lee K W, Kim J H, Yoon H, Shin D G, Bae J H.

This study investigated the incidence and risk factors associated with vesicoureteral reflux (VUR) in patients with ulcerative bladder pain syndrome/Interstitial Cystitis (BPS/IC). 211 patients with BPS/IC who underwent cystoscopy and confirmed the presence of Hunner's ulcer from May 2011 to July 2017 were investigated retrospectively. Among these patients, 113 patients whose functional bladder capacity was 300cc or less according to the voiding diary were included in this study. In patients with severe IC, serious bladder contraction may develop, resulting in a decreased bladder capacity and possible VUR. However, in clinical practice, not all patients with IC and a decreased bladder capacity have VUR. Moreover, the severity of the decreased bladder capacity does not necessarily correlate with the severity of VUR. Thus, we speculated that the development of VUR in patients with IC must be due to a variety of interrelated factors. In our study, the peri-ureteral location of Hunner's ulcer played an important role in the presence of VUR. The incidence of VUR in patients with ulcerative BPS/IC is relatively high and the urologist has to consider the presence of VUR in the management of the patients with ulcerative BPS/IC especially in the case of peri-ureterally located Hunner's ulcer.

#615 THE ASSOCIATION OF VULVODYNIA AND UROLOGICAL URGENCY AND FREQUENCY: FINDINGS FROM A COMMUNITY-BASED STUDY

Harlow B L, Sun Y

A recent study suggested that by age 40, 8% of women will experience vulvar pain on contact for a period of at least 3 months that limits or prevents sexual intercourse. When clinically confirmed, it is defined as debilitating vulvar discomfort due to burning pain or pain on contact that occurs in the absence of clinically visible pathological findings or identifiable disorders. It has been shown that women who suffer from vulvodynia are more likely than others to experience co-morbid interstitial cystitis and urinary tract infections.

bothersome nocturnal voiding was 32%. Women with any history of interstitial cystitis were excluded from this analysis. The findings from this community-based study suggests that lower urinary tract symptoms (LUTS) are much more prevalent among women with vulvodynia compared to comparable population controls. This suggests further research is needed to better understand why vulvar pain elicits benign urological symptoms and whether women with vulvodynia should be managed by clinicians with experience in both gynecology and urology.

#616 EFFICACY, COMPLICATIONS AND TOLERABILITY OF REPEATED INTRAVESICAL ONABOTULINUMTOXINA INJECTIONS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Almoussa R, Alsowayan Y, Alfadagh A, Almuhrif A

IC/BPS symptoms result in poor quality of life with sleep dysfunction, depression, anxiety and stress. Repeated intravesical OnabotulinumtoxinA injections was studied and found to decrease the expression of vascular endothelial growth factor which play an important role in the pathogenesis of IC/BPS. The aim was to evaluate the outcome, safety, complications and patient's tolerability of repeated intravesical OnabotulinumtoxinA (BOTOX) injection for interstitial cystitis/bladder pain syndrome in one centre in Saudi Arabia. The authors found that repeated intravesical BOTOX injection is an effective, well tolerated and safe treatment modality for patients with IC/PBS. It has a very good outcome in controlling the disease pain symptom and treating bladder wall ulcers.

OPEN DISCUSSION e-Posters

#336 ARE BLADDER PAIN SYNDROME AND OVERACTIVE BLADDER PART OF ONE DISEASE?

Asfour V, Viet-Rubin N, Ford A, Digesu A, Fernando R, Tailor V, Gibbs K, Verdon L, Khullar V.

The purpose of this study from London was to determine whether there is an overlap between overactive bladder with nocturia and bladder pain syndrome. 3428 women were recruited. Overall 1781 women were classified as having an overactive bladder. A Likert scale questionnaire asked about bladder pain. Overall 2452 women felt they had a degree of bladder pain. However, when comparing the bladder pain with the overactive bladder symptoms, the authors found that only 3% of women with an overactive bladder had no bladder pain. The fact that bladder pain appeared to play a key role in overactive bladder symptomatology may suggest a role in the development of OAB symptoms or possibly that OAB and bladder pain are on a spectrum of disease. This would seem reasonable as both are C nerve fibre-based syndromes and they both result in frequency and urgency. They also found that bladder pain plays a fundamental role in women having nocturia and overactive bladder such that 95% of women with OAB and nocturia also had bladder pain. This could suggest a new subcategory of nocturia due to bladder pain. It was concluded that overactive bladder symptoms appear to be related to bladder pain and this could suggest a joint aetiology or a spectrum ranging from pure OAB to pure bladder pain. This may indicate the reasons why some patients with OAB do not respond to treatment.

#514 INTERSTITIAL CYSTITIS INTRAVESICAL THERAPY: COCKTAIL THERAPY VERSUS COMBINED SODIUM HYALURONATE AND CHONDROITIN SULFATE (IALURIL): WHICH ONE TO USE?

Banakhar M

This study compared intravesical combined Sodium Hyaluronate and Chondroitin Sulfate (Ialuril) with cocktail therapy in interstitial cystitis patients and recurrent urinary tract infection regarding therapy outcome, compliance, and risk of infection in a total of 28 patients (4 males, 24 females). It was found that combined Sodium Hyaluronate and Chondroitin Sulfate (Ialuril) is comparable to intravesical cocktail therapy in interstitial cystitis and recurrent UTI patients. However, patients prefer protocol of combined Sodium Hyaluronate and Chondroitin Sulfate over cocktail therapy .

#517 ANGIOGENESIS IN BLADDER TISSUES ARE STRONGLY CORRELATED WITH URINARY FREQUENCY AND BLADDER PAIN IN PATIENTS WITH INTERSTITIAL CYSTITIS

Furuta A, Igarashi T, Suzuki Y, Yamamoto T, Egawa S, Yoshimura N.

In order to clarify the pathophysiology of urinary frequency and bladder pain usually seen in interstitial cystitis (IC) patients with or without Hunner lesions (HIC or NHIC), the authors examined the correlation between bladder inflammation, angiogenesis, fibrosis and denudation of urothelium in bladder biopsied tissues using immunohistochemistry, and O'Leary-Sant scores including symptom indexes (OSSI) and problem indexes (OSPI) and visual analog scale (VAS) pain scores. Bladder biopsied tissues were collected from 12 HIC female patients, 12 NHIC female patients and 12 age-matched female patients (controls) with stress urinary incontinence and pelvic organ prolapse. Their results suggest that angiogenesis in IC bladder tissues is strongly correlated with urinary frequency and bladder pain in patients with NHIC and HIC. Therefore, angiogenesis would be a potential therapeutic target for controlling these urinary symptoms in IC patients.

#518 ARTEMIN: A NOVEL TARGET FOR TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Kullmann F A, McDonnell B, Wolf-Johnston A S, Lynn A, Rodriguez L, Birder LA.

Chronic stress plays a substantial role in the development, maintenance and enhancement of functional bladder disorders including painful bladder syndrome/interstitial cystitis (PBS/IC). Studies have shown that more than half of patients with PBS/IC report daily or constant pain and urinary frequency exacerbated by stressful circumstances. In fact, patients tell their physicians that stress plays a major role in their symptom flares. However, the mechanisms underlying the relationship between stress and hypersensitivity of the urinary bladder are not well understood. Altered levels of neurotrophins have been correlated with bladder hyperexcitability and pain. Artemin is a glia derived neurotrophic factor that supports the survival and development of a group of primary sensory neurons. In this animal model study, the authors examined the influence of psychological stress on artemin levels, bladder hyperalgesia and properties of the primary afferent neurons. Their findings indicate that chronic stress triggers a number of changes that ultimately can exacerbate or predispose to disease such as PBS/IC. Furthermore, they support the concept that stress can alter levels of the neurotrophic factor artemin, which can impact the expression and/or function of nociceptive TRPA1 channels and contribute to visceral sensitivity and pain. Thus, fluctuations in artemin levels with progression of stress-induced cystitis may correlate with neuronal sensitization and aberrant signalling in the periphery and spinal cord. From a clinical perspective, these experiments provide important insights regarding an appropriate window for treatment. For example, intervening with anti-artemin treatment during the initial 'acute' state may prevent neuronal changes, but if this treatment is administered at a later stage it may be deleterious. At later chronic stages, increasing artemin levels and/or activating artemin intracellular pathways may be beneficial.

Manipulation of artemin expression and/or signalling pathways may therefore offer a new pain treatment strategy for PBS/IC patients.

#592 A COMPARISON OF THE OUTPATIENT REIMBURSEMENT FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND IRRITABLE BOWEL SYNDROME TREATMENT IN TAIWAN: A NATIONWIDE POPULATION BASED STUDY

Chang K, Lin H, Wu H, Lee M

Interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS) are chronic pelvic pain disorders. They often coexist which might be due to “neural cross-talk”. Due to elusive etiology, the diagnosis and treatment outcome are disappointed. These patients often have physical, psychological, social and work influences, and consequently need lots of medical care. Clemens (2008) reported IC/BPS mean yearly medical expense 2.4 times higher than the age and gender controlled non- IC/BPS. The cost differences were mainly due to pharmacy and outpatient expense. In this study, we compared public health insurance reimbursement between IC/BPS and IBS in outpatient perspective to evaluate whether IC/BPS had more reimbursement than IBS. The authors found that IC/BPS has significantly different higher proportion of female and lower income. The outpatient reimbursement for IC/BPS was significantly higher than IBS, mainly on the non-pharmacy expenditure. It might be due to the fact that IC/BPS patients need more urodynamic survey and cystoscopic interventions. The etiology of IC/BPS and IBS has been considered multifactorial, and it makes diagnosis and efficient treatment difficult. Because of disease chronicity, expenditure for IC/PBS patient care will increase as time go on. Paying more attention to the disease research and treatment development is encouraged.

#593 A COMPARISON OF THE OUTPATIENT REIMBURSEMENT FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND FIBROMYALGIA TREATMENT IN TAIWAN: A NATIONWIDE POPULATION-BASED STUDY

Lin H, Chang K, Lee M, Wu H

Interstitial cystitis/bladder pain syndrome (IC/BPS) and fibromyalgia (FM) are two non-cancer chronic pain diseases with autonomic dysfunction. They also are one of the comorbidities for each other. They both take long time to get definite diagnosis because of no biomarkers or clear criteria (average: IC/BPS 7 years and FM 5 years). In this study, the authors compared public health insurance reimbursement between IC/BPS and FM in outpatient perspective to evaluate whether IC/BPS had more reimbursement than FM. They found that IC/BPS outpatient expenses were significantly higher than FM in both models. The annual total pharmacy, total non-pharmacy, total claim, and per-visit pharmacy, per-visit non-pharmacy claim and per-visit total claim, all showed significant differences. Though IC/BPS patients were in lower income status, reimbursement was higher than FM. In Taiwan, Elmiron® and Cystistat® have been approved for management of IC/BPS and are likely to make the reimbursement even higher. They concluded that IC/BPS has significantly different gender and income distribution. The outpatient reimbursement for IC/BPS was significantly higher than FM in both pharmacy and non-pharmacy expenditure. Due to IC/BPS patients experiencing more complex health conditions, more pharmacy and non-pharmacy treatment were needed. Because of the chronicity of IC/BPS, the expenditure will increase as time goes by. Paying more attention to disease research and providing more efficient treatment are encouraged.

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