

REVIEW OF THE ANNUAL MEETING OF ESSIC (INTERNATIONAL SOCIETY FOR THE STUDY OF BPS) ROME, ITALY, 17-19 SEPTEMBER 2015

Jane Meijlink

It was tropically hot weather in Rome for the annual meeting of ESSIC (International Society for the Study of BPS, founded 2004) held at the Gemelli Hospital Catholic University of Rome where over 200 delegates received a “warm” welcome in every sense from Professor Mauro Cervigni who organized and chaired this year’s meeting, Professor Jean-Jacques Wyndaele, president of ESSIC, Professor Giovanni Scambia, head of gynaecology at Gemelli Hospital and via Skype from Professor Adrian Wagg, General Secretary of the International Continence Society (ICS). It was good to see so many younger healthcare professionals attending. With many experts now around retirement age, it is important to encourage younger doctors to continue the crusade. Patients were not forgotten either, with a patient speaker session forming part of the programme, and a number of patient representatives, particularly from Italy, in the audience. Simultaneous translation was provided for Italian delegates and vice versa where necessary. The meeting was divided into themed sessions and each session was followed by a question and answer session.

Particularly interesting at this meeting was a new device from Hungary, presented by Dr Sandor Lovasz as an option to replace catheters for instillations and also a study for a promising new drug.

AICI 20th Anniversary

The Associazione Italiana Cistite Interstiziale (AICI) (Italian Interstitial Cystitis Association) is celebrating its 20th anniversary this year and organized a celebratory dinner at the end of the ESSIC meeting. Many congratulations to AICI, and especially to Loredana Nasta, for the support group’s hard work over two decades during which they have greatly raised awareness at all levels in Italy.

1st Session – Preliminary remarks and assessment 1

2015 STATUS UPDATE: NOMENCLATURE, DEFINITION, DIAGNOSIS, TREATMENT

The first day included presentations by Professors Jorgen Nordling and Philip Hanno on the current situation regarding terminology and definitions from different societies around the world, with still no sign of global consensus. Where nomenclature (name of disease or disorder) is concerned, currently in use are interstitial cystitis, bladder pain syndrome (with IC/BPS from the AUA in the USA to ensure access to social benefits etc.), hypersensitive bladder from East Asia, with painful bladder syndrome commonly used in many countries. In other words, still very much a nomenclature *pot pourri*. However, it is important to remember that in practice we have seen that if BPS alone is used it can lead to problems for the patient such as non-reimbursement of treatment developed for IC. And it is particularly for this reason that patient preference is for IC/BPS rather than BPS/IC.

In definitions, the symptom duration varies with 6 months featuring in some definitions, but 6 weeks incorporated in the AUA guideline (to avoid delay in diagnosis and treatment). The East Asian (Japan, Korea, Taiwan) hypersensitive bladder (HSB) (a revival of an old ICS term) forms part of the East Asian frequency/urgency syndrome (FUS) [frequency: frequent voiding, urgency: a compelling desire to void]. This is an inclusive term incorporating overactive bladder (OAB), hypersensitive bladder (HSB), and other conditions associated with frequency and urgency, including PBS and IC.

Hypersensitive bladder (with or without pain) is FUS with urgency due to pain or other unpleasant sensation; painful bladder syndrome is HSB with pain; IC is frequency, hypersensitivity, and/or bladder pain plus abnormal cystoscopy and no confusable disease. It allows for diagnosis in the absence of pain when patients have pressure, discomfort or other unpleasant sensation in the bladder, but do not have what the patient identifies as pain. In the West, these patients may still be getting either no diagnosis or the wrong diagnosis. Urgency and frequency – key symptoms for some 200 years - are no longer mentioned in some definitions, which in the eyes of the patients could lead to a distorted perception of the disease.

Are we in fact talking about many different bladder diseases and disorders with similar symptoms that have been bundled under one name? This is considered possible by many experts including Professor Nordling and was mentioned several times during the conference, although Dr JP van de Merwe from the Netherlands

reminded us that autoimmune diseases, systemic lupus erythematosus for example, can manifest themselves in many very different ways but are still considered to be the same disease. However, there is as yet inadequate scientific evidence to be able to say anything definite one way or the other with regard to IC/BPS. More research is needed, including in the field of phenotyping (subtyping) in both lesion and non-lesion types. As was the case last year, there was once again some discussion arising from several presentations regarding the possibility of splitting off Hunner lesion from non-lesion disease and calling it IC, but scientific evidence is first needed to ensure a transparent, evidence-based decision. However, this is indeed in progress to a certain extent in several centres with abstracts presented at the ICS annual scientific meeting in Montreal. And, as commented by the IPBF chair during this meeting, before any further changes are made to lesion/non-lesion nomenclature, a thorough investigation should be carried out into the potential impact on the patient in practical terms worldwide, since the patients are still suffering from the practical impact of previous rounds of changes in the past 15 years.

Diagnosis is still largely based on history, physical examination, urinalysis and exclusion of confusable diseases (remembering, however, that it is possible to have IC/BPS plus confusable diseases), with cystoscopy still widely performed in many parts of the world, but not a mandatory diagnostic procedure in countries such as the USA. Since it was emphasized at this meeting that cystoscopy is essential for the diagnosis of Hunner lesions, it seems likely that many lesions are not getting diagnosed in some countries. This is a great pity bearing in mind that Hunner lesions respond far better to treatment than non-lesion disease, as noted by several speakers. A sword of Damocles currently hanging over cystoscopy is the issue of glomerulations and whether these in fact have any diagnostic value at all. Wennevik et al recently reviewed the literature to examine the value of glomerulations as diagnostic markers and concluded that there are no convincing data to show that the presence of glomerulations is specifically related to IC/BPS.

[Wennevik GE, Meijlink JM, Hanno P, Nordling J. [The role of glomerulations in Bladder Pain Syndrome - A review](#). *J Urol*. 2015 Aug 26. pii: S0022-5347(15)04683-2. doi: 10.1016/j.juro.2015.06.112. [Epub ahead of print] PMID: 26318984]

Management is generally empiric, starting with conservative measures and progressing to more invasive. It is hoped that long-term phenotyping trials will lead to better and more effective treatment per phenotype and avoid the current trial and error situation, which is also very costly. Many speakers during this conference looked at different types of therapy.

THE COMPLEXITY OF CHRONIC PELVIC PAIN (CPP)

Professor Magnus Fall from Sweden first reminded us of the definition of pain by the International Association for the Study of Pain (IASP): *“Pain is an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage”*

He then looked at causes of CPP symptoms, noting that CPP can be caused by a wide range of conditions, ranging from defined inflammatory processes to centralized pain. Studies have indicated that alteration of central nervous system (CNS) mechanisms can magnify perception with involvement of skeletal muscles and visceral organs. Looking at the example of BPS, one sees associations with irritable bowel syndrome, fibromyalgia, sensitive skin, panic disorders etc., in other words multisystem problems.

Until now, he said, the approach to CPP has been to exclude and treat confusable diseases (definable diseases); otherwise use treatment algorithms with their trial and error problems. Professor Fall stressed that in the past there has been overconfidence in and overuse of surgery and various local treatments for CPP. He noted that the EAU CPP guidelines committee saw chronic pain as a disease in its own right and that today there is a growing awareness that broader expertise is often needed, not only organ specialists. While multidisciplinary teams are ideally needed to investigate and treat CPP, the problem is how to organize this in normal clinical practice where cost factors play a role.

He recommended using a 4-step system as published by Quaghebeur & Wyndaele:

Step 1

Medical history including questioning about complaints in other systems:

- micturition patterns
- bowel habits
- sexual complaints

- detailed pain description

Step 2

Collection of previous assessments

- careful review of previous medical reports
- review of imaging examinations
- review of previous technical examinations

Step 3

A thorough clinical assessment

- clinical neurological assessment
- manual neurodynamic testing
- electrodiagnostic evaluation
- hernia examination
- palpation of the external sex organs
- pelvic examination(rectal/vaginal palpation)

Step 4

- extensive clinical assessment of the musculoskeletal system
- posture
- movement limitations
- asymmetry

Quaghebeur J, Wyndaele JJ. Chronic pelvic pain syndrome: role of a thorough clinical assessment. Scand J Urol. 2015 Apr;49(2):81-9. doi: 10.3109/21681805.2014.961546. Epub 2014 Sep 25.

With the addition of a Step 5

- Psychological assessment

See also: Fall et al. [EAU guidelines on chronic pelvic pain](#). Eur Urol. 2010;57(1):35-48.

“Without relevant phenotyping, we will continue to grope in the dark when we try to help sufferers of CPP”

Looking at what has happened to functional urology in the last ten years, Professor Fall said that the idea was that large symptom syndromes would be useful. However, while OAB is a good term for communication with patients, it is not a diagnosis and includes a large diversity of conditions; phenotyping is essential, without relevant phenotyping, we will continue to grope in the dark when we try to help sufferers of CPP.

While IC was initially a well-defined chronic inflammatory bladder disorder, it later became the designation of a wide symptom complex with not one but a variety of conditions, most of them without signs of inflammation of the bladder interstitium.

BPS includes diverse phenotypes which need identification and unequivocal definitions.

There needs to be international networking on definitions, diagnostics and therapy, consensus on basic and advanced assessment in CPP patients, multidisciplinary team work must be more available, improved research funding is needed, efforts are needed to explore scientifically ignored conditions like urethral pain syndrome, scrotal pain syndrome etc. to better cover the CPP spectrum of conditions, an increase of public awareness is needed. Activities by patient interest groups and exposure in media play a significant role here.

WHY ESSIC USES THE NAME BPS.

Dr JP van de Merwe (Netherlands) briefly looked at the reasons why ESSIC uses the name BPS, noting that they considered it essential for there to be no conflict between nomenclature and knowledge of pathophysiological mechanisms. The name interstitial cystitis excluded patients with typical IC symptoms, but normal cystoscopic and histologic findings from disease classification in many countries around the world. The name BPS is in line with other chronic pelvic pain syndromes. He noted, however, that ESSIC realizes that changing the name IC to BPD could have emotional implications for both patients and patient organizations, with additional implication for insurance and reimbursement in the different health systems. He also noted that a subgroup of BPS patients with Hunner lesions (= ESSIC's BPS type 3C) have interstitial inflammation, thereby complying with the original requirements of the term interstitial cystitis.

2nd Session – Preliminary remarks and assessment 2

THE MAPP RESEARCH NETWORK PROGRAMME: A NOVEL STUDY OF UROLOGIC CHRONIC PELVIC PAIN SYNDROMES.

Professor Robert Moldwin was allocated the challenging task of explaining the entire NIDDK-sponsored MAPP (Multidisciplinary Approach to the Study of Chronic Pelvic Pain) programme in just 10 minutes.

MAPP is a multi-institutional, multidisciplinary, collaborative network dedicated to the study of IC/BPS and CP/CPSPS which together are known as the “urological chronic pelvic pain syndromes” (UCPPS) and is funded by the NIDDK. The MAPP I Trans-MAPP Epidemiology Phenotyping Study was conducted from 2009 to 2012.

The MAPP Network was originally set up due to a lack of clinical advancement in the field of UCPPS; there was little interdisciplinary work; new literature and clinical experience was suggesting that UCPPS probably represents a heterogeneous group of patients, many of whom suffer from pain extending beyond the urogenital system.

In broad terms, the aims of the MAPP Network are:

- to better understand the treated natural history of UCPPS
- to identify clinical factors and research measurements that will define clinically relevant sub-groups of these patients for future clinical trials
- to address underlying disease pathophysiology and natural history using patient cohorts, biospecimens and animal models.

Some of the recent studies suggest that, similar to other forms of chronic pain, central nervous system changes may play a significant role in UCPPS pathophysiology in some patients.

MAPP II is currently underway; its primary protocol is the Trans-MAPP Symptom Patterns Study (SPS) which will follow participants for 3 years. One of its highlight sub-studies is the Analysis of Therapies during the Longitudinal Assessment of Symptoms (ATLAS) protocol during which efforts will be focused on identifying correlations that may exist between specific UCPPS phenotypes and responses to an array of predefined therapies.

PHENOTYPING: HOW CAN WE PROVE THE VALUE?

Professor Daniel Shoskes from Cleveland USA is a well-known expert in the field of phenotyping and co-developer of the UPOINT phenotype system which classifies patients according to 6 clinical domains (urinary, psychosocial, organ specific, infection, neurologic/systemic, tenderness of pelvic muscles). Multimodal therapy is then directed only at the positive domains.

What is the clinical value of phenotyping? He first explained that:

- Some conditions have standard therapy regardless of etiology or symptoms (e.g. renal failure/kidney transplant);
- Some conditions are symptom based with multiple etiologies and treatment depends on etiology (e.g. headache);
- Some conditions have common aetiology but treatment highly influenced by type and extent (e.g. prostate cancer).

So where does IC/BPS and UCPPS fit into this?

- The underlying aetiology is unclear
- They form a spectrum of pelvic and systemic symptoms
- Response rates to immunotherapy, even when superior to placebo/sham, are low and may only help a subset of symptoms [Giannantoni et al, Eur Urol 61:29, 2012]
- Only specific predictor of success for some therapies is Hunner lesion (e.g. fulguration, CyA).

UPOINT and IC/BPS: a weakness in the case of IC/BPS is that there is limited heterogeneity since by definition all patients fulfil the “U” (urinary symptoms) and “O” (bladder involvement) domain criteria. Nevertheless, clinical phenotyping is important in IC/BPS because it is a syndrome with heterogeneity of symptoms, etiology and treatment response. UPOINT is a start but so far has found greater use in CP/CPSPS than female IC/BPS. New phenotypes schemes must be discriminative, clinically relevant and must make a difference guide therapy, otherwise it would be purely an academic exercise, he concluded.

Abstract Session 1**1. Bladder Pain Syndrome as a peripheral sensory disorder***Offiah, E. Dilloughery, S. McMahon, B. O'Reilly*

The purpose of this study was to look at the effect of alkalinized lidocaine on pain perception using Urodynamics in BPS patients. Precise pain perception in this disease is not understood. The authors from Ireland and UK ask whether this is a peripheral pathology with pain of peripheral origin or has the pain become centralized? They hypothesized pain centralization with severe and chronic cases. They found that ¼ patients did not respond to lidocaine. Does this mean central sensitization with chronicity? Does this explain poor treatment response? They recommend a combination of peripheral and systemic treatments.

2. Bladder instillations with a combination of hyaluronic acid and chondroitin sulfate in Bladder Pain Syndrome patients: preliminary results of a 12 weeks administration schedule.*L. Marzullo, L. Lorenzo Soriano, M. A. Bonillo Garcia, E. Martinez Cuenca, S. Arlandis Guzman, E. Broseta Rico, F. Boronat Tormo.*

A retrospective study from Spain to evaluate the efficacy and safety of a 12-week bladder replenishment instillation schedule using a combination of hyaluronic acid and chondroitin sulphate in BPS patients. It reduced symptoms most clearly in patients not previously treated with intravesical therapy.

3. Intravesical instillation therapy in IC/BPS patients: a challenging new way with remarkable advantages.*S. Lovasz*

Dr Sandor Lovasz from Budapest, Hungary presented an ingenious new invention to replace catheterisation in IC/BPS patients. Noting that while catheterisation of female patients is usually a simple, quick procedure with a low complication rate, he explained that IC/BPS on the other hand very often affects the urethra as well as the bladder, causing tenderness or pain. Catheterisation of IC/BPS patients always causes microscopic mucosal lesions, he said, and sometimes even more serious lesions resulting in macroscopic urethrorrhagia and long-lasting, severe pain in the urethra. In Hungary, they have invented and patented a special adapter for Luer-lock syringes which allow direct injection of bladder cocktails into the bladder through the urethral orifice in a retrograde way. Its special conical tip and isolating collar permit drip-free instillation without catheterisation of the bladder. In 7 of 62 patients, the instillation failed due to deep located urethral orifice or urethral kinking. Conventional catheterisation is needed in these patients. All treatable patients preferred the catheter free method over conventional catheterisation. No pain, long-lasting burning sensation or any complications were observed. The new non-invasive instillation method prevents superficial lesions of the urethra and treats its mucosa with highly concentrated non-diluted drug solution. Repeated instillations in 6 male patients suggest that this method can be applied in both male and female patients. This method also reduces time and costs.

4. Hydrodistension plus botulinum toxin in bladder pain syndrome refractory to conservative treatments*L. Lorenzo Soriano, L. Marzullo Zucchet, M. A. Bonillo Garcia, S. Arlandis Guzmán, E. Martínez Cuenca, F. Boronat Tormo*

The aim of this retrospective study was to assess experience with hydrodistension plus botulinum toxin in 25 patients with refractory BPS. The authors found that hydrodistension under general anaesthesia plus botulinum toxin injections is a suitable treatment in refractory BPS and can be performed every 6 months, showing similar effectiveness in primary treatments and relapses.

5. BPS and histamine intolerance - a link?*E. Heßdörfer*

Dr Elke Heßdörfer from Berlin noted that histamine seems to play a major role in IC. The role of histamine overload in the gut and vagina was highlighted in this retrospective case collection. She suggested that neural-mediated crosstalk between pelvic organs could be the answer to the histamine overload in the gut and vagina.

6. Repetitive Transcranial Magnetic Stimulation as Treatment of Neuropathic Pain in Bladder Pain Syndrome: Preliminary Data*E. Onesti, M. Inghilleri, MC. Gori, A. Morciano, G. Tartaglia, L. Nasta, G. Scambia, M. Cervigni*

Although neuropathic pain responds to antidepressants, anticonvulsants and opioid agonists, these drugs are often ineffective or can cause severe side effects. In this pilot study, Onesti and colleagues from Italy

investigated whether modulation of excitability of the motor cortex with repetitive transcranial magnetic stimulation (rTMS) in patients with BPS could result in modification of neuropathic pain and urinary disorders in so far 8 patients with BPS. The authors found that deep H-coil rTMS applied to the motor cortex could provide relief for pain and urinary disorders in IC/BPS patients. The study was limited by small sample size and more data are needed.

For background information: https://en.wikipedia.org/wiki/Transcranial_magnetic_stimulation

3rd Session Diagnosis 1

THE “COATING”: A PASSIVE OR AN ACTIVE ELEMENT?

Dr Claus Riedl from Austria looked at the glycosaminoglycan (GAG) layer or “coating” of the bladder and whether this is a passive or active element. The GAG layer serves as a permeability barrier between the bladder wall tissue (urothelium) and the urine and includes chondroitin sulfate, hyaluronate sodium, glycoproteins, and mucins. It is believed that in IC/BPS patients there may be damage to this GAG layer, allowing urinary cations such as potassium to permeate the tissue and cause pain. Dr Riedl looked at the role of the extracellular matrix (ECM) which is essential for wound healing and regeneration and at the biological effects of GAGs and particularly hyaluronic acid (HA) in wound healing. He emphasized that while GAGs are useful for passive coating, they are also essential active compounds in the wound/epithelialisation process.

Instillation therapy includes the following:

- Hyaluronan (HA) /Cystistat®
- Chondroitin sulfate (ChS)
- A combination of HA/ChS
- Pentosan polysulfate
- Heparin
- DMSO

Further reading:

https://en.wikipedia.org/wiki/Extracellular_matrix

Ghatak S, Maytin EV, Mack JA, Hascall VC, Atanelishvili I, Moreno Rodriguez R, Markwald RR, Misra S. [Roles of Proteoglycans and Glycosaminoglycans in Wound Healing and Fibrosis](#). Int J Cell Biol. 2015;2015:834893. doi: 10.1155/2015/834893. Epub 2015 Sep 10. Open access article.

THE NEUROGENIC COMPONENT OF BPS/CPPS.

Professor JJ Wyndaele from Antwerp, Belgium, looked at the role of sensation in BPS/CPPS which is a syndrome based on symptoms, the most important of which is pain.

He explained that physical sensation is a perception of an individual related to a stimulus in the body. Sensation is by definition subjective, interpreted from input of the sensory nerves.

As shown by the speaker, the bladder lining plays an active role, not a passive one and this is where the symptoms start.

It is important to distinguish between

- Nociceptive pain (through direct stimulation of nociceptor sites. IASP definition: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.)
- Neuropathic pain (caused by direct lesion of the peripheral or central nervous system, as in pudendal neuralgia)

Both nociceptive and neuropathic pain can be present in chronic pelvic pain.

(see <http://www.iasp-pain.org/Taxonomy> for further explanation of these two terms).

Further useful definitions mentioned by Professor Wyndaele were:

Chronic allodynia: pain resulting from a stimulus that ordinarily does not elicit a painful response (e.g. light touch)

Hyperalgesia: an increased sensitivity to a normally painful stimulus: primary hyperalgesia, caused by sensitization of C-fibers, occurs immediately within the area of the injury; secondary hyperalgesia, caused by sensitization of dorsal horn neurons, occurs in the undamaged area surrounding the injury.

Urothelial cells are likely to play a role in pain processes/sensory function. Professor Wyndaele reported that recent evidence has demonstrated that urothelial cells exhibit plasticity. Inflammation/injury can alter the “sensor function” (expression & sensitivity) of urothelial targets.

At a bladder wall level: urothelial cells respond to physical and chemical stimuli via activation of intracellular pathways and release of a number of signalling molecules. Increased release of neurotransmitters/inflammatory mediators (from urothelial, inflammatory and/or neural cells) can influence sensory input. Looking at the role of mast cells, he explained that cytokines from damaged urothelial cells can lead to mast cell proliferation, a phenomenon that has been demonstrated in IC/BPS.

Changes in the brain

Influences of chronic visceral pain include modulation and altered brain chemistry, more frequently prefrontal cortex, decreased thalamus activity, serotonin involvement (IBS), pain modulation.

In BPS/CPPS neurogenic components are very widely present at the levels of

- bladder wall
- peripheral nerves
- spinal cord
- brain.

Professor Wyndaele concluded this part by saying that IC/BPS has a lot to do with nerves and that neurophysiological mechanisms play an important role in IC/BPS, both peripherally and centrally.

Pudendal Neuropathy

Professor Wyndaele now looked at what happens if you have a direct lesion of the nerve, taking as example pudendal neuralgia, a painful neuropathic condition that involves the pudendal nerve, Professor Wyndaele emphasized that it should be seen as separate from IC/BPS. Causes of pudendal neuropathy include:

- Direct trauma to the pudendal nerve: urological, gynaecological, colorectal surgery, orthopaedic or lumbo-sacral neurosurgery;
- Sacral fractures and pelvic injuries, physical stress;
- Compression within the Alcock's canal;
- Protrusion or herniated LS disc.

Symptoms of pudendal neuropathy

- The level, severity and type of fibers involved are reflected in the symptoms:

- Rectal pain
- Anal leakage
- Perineal pain/numbness, genital pain/numbness, frequency, urgency and incontinence
- Difficulty in voiding due to urinary retention
- Erectile dysfunction, ejaculatory dysfunction, or even loss of orgasmic sensation.

- The pain tends to be positional, relieved by standing or lying down, and provoked by sitting.

Diagnosis is mainly clinical

- Pain in vagina/vulva, or posterior in anorectal region (entrapment in ischioanal fossa);
- More likely if unilateral and increasing with transrectal palpation of ischiadic spine;
- Neurologic investigation of perineum is normal, sacral reflexes and tone anal sphincter normal.

Treatment of pudendal neuropathy

- Behavioural modification
- Physical therapy, osteopathy
- Analgesics and other medications (gabapentin, amitriptyline)
- Pudendal nerve block
- Neuromodulation, pulsed radiofrequency
- Surgical nerve decompression.

However, he does not recommend surgical nerve decompression, although this is indeed performed in specialised clinics as in France for PN entrapment as explained later in the meeting by Dr Bautrant.

THE GASTROINTESTINAL APPARATUS AND ITS INTERFERENTIAL ROLE ON THE ASSOCIATED SYMPTOMS.

Professor Antonio Gasbarrini from Italy noted that there are many overlapping (functional) syndromes including for example IC/bladder pain syndrome, irritable bowel syndrome, vulvodynia, chronic constipation, headache, GERD, TMA syndrome, dyspepsia, fibromyalgia.

Taking a look at irritable bowel syndrome (IBS), the definition is given as: “a chronic illness defined by abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months.” *Brandt et al. An evidence-based systematic review on the management of irritable bowel disease. Am J Gastroenterol. 2009;104(S1):S1-35.*

He reported that there is a high percentage of patients with both IC/BPS and IBS and several studies have found a strong association between these two syndromes. In 2009, Rodriguez et al found that up to 48% of IC/BPS patients have IBS.

Evidence for overlap between urological and nonurological unexplained clinical conditions.

Professor Gasbarrini underlined that irritable bowel syndrome (IBS) is no longer considered as a functional disease originating exclusively from psychological stress. Several peripheral mechanisms may be involved in disturbing motor and sensory functions and consequently in producing symptoms. He discussed the role of gut barrier alterations in the pathogenesis of IBS and the role of gut microbiota in IBS, looking particularly at three main landmarks:

1. cause-effect relationship in post-infectious IBS
2. Gut microbiota altered in IBS patients
3. IBS symptoms improved by treatments targeting the microbiota (antibiotics, probiotics, prebiotics).

He discussed the role of infections including for example bacterial, yeast/fungal, viral and parasitic.

Gut microbiota have many effects on the health of the host, including:

- Barrier effect
- Immunocompetence/tolerance
- Synthesis
- Metabolism
- Drug metabolism
- Behaviour conditioning.

However, the gut microbiota have to be kept under control.

He underlined the importance of the mucus layer. The inner mucus layer is dense and does not allow bacteria to penetrate, thereby keeping the epithelial surface free from bacteria, while the outer mucus layer is the habitat of the commensal flora. If the barrier dysfunctions, this can lead to intestinal permeability or leaky gut. He suggested that a leaky gut may be caused for example by sport, stress, food and a whole range of human diseases, including IC/BPS and chronic pelvic pain. Several studies have indicated that intestinal permeability is increased in IBS.

Looking at the role of mast cells, he said that it is possible that the presence of an allergic background correlates with a more severe disease and diarrhoea prominence, possibly by enhancing mucosal mast cell activation and paracellular permeability.

ASSOCIATED RHEUMATIC CONDITIONS (FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, SJÖGREN'S SYNDROME)

Dr JP van de Merwe from the Netherlands then looked at associated rheumatic conditions. He first explained that associated diseases are diseases with a higher prevalence among IC/BPS patients than in those without IC/BPS. An association neither implies nor excludes a causal relationship between the associated disease and IC/BPS. The relevance of this is that an associated disease may provide information about the pathogenesis of IC/BPS.

He stressed that it is particularly important for doctors to know about the associations and to have a high index of suspicion for associated diseases in patients with IC/BPS.

Combined data from the literature indicate that diseases associated with IC/BPS can be grouped into three main groups: allergies, chronic pain syndromes and systemic autoimmune diseases.

Emphasizing that the term “rheumatic” is a very general term, he noted that rheumatic diseases associated with IC/BPS are: fibromyalgia, systemic lupus erythematoses (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS) and chronic fatigue syndrome. However, in fibromyalgia and chronic fatigue syndrome there is

no clinical inflammation or tissue damage, whereas this is present in the other diseases. Chronic fatigue syndrome has a considerable overlap with fibromyalgia.

Study results are problematic due to lack of control subjects, and terminology confusion in studies with self-reported diagnoses by patients using many different terms. Confirmation by studies from other centres is rare.

SLE, RA and Sjögren's syndrome are well-defined diseases with generally accepted diagnostic criteria but also significant overlap. One third of SLE and RA patients also have Sjögren's syndrome.

The speaker noted that where Sjögren's syndrome is concerned a correlation has been shown with IC/BPS. Data on SLE and RA patients suggest that their association with IC/BPS may actually be due to concomitant Sjögren's syndrome. A pathogenic role of autoantibodies to muscarinic M3-receptors is well documented in Sjögren's syndrome. The M3-receptor also plays an important role in the physiology of detrusor muscles. Antibodies to the M3-receptor can have stimulating or blocking effects on the function and number of receptors and could initiate inflammation near nerve endings (M3-receptor).

See also: *Van de Merwe JP. Clin Pract Urol 2007;4:484-491.*

Recognition is important

Dr van de Merwe concluded by underlining that recognition - and consequently treatment - of disorders associated with IC/BPS is very important for the patients.

Further information

For further detailed information on Sjögren's syndrome and other associated conditions, [click here](#).

PELVIC FLOOR: THE POSTURE AND ASSOCIATED DISORDERS

Professors Kristene Whitmore from Philadelphia and Kenneth Peters from Michigan looked at the role of the pelvic floor, how to evaluate it and treat it.

Professor Peters suggested that IC may not necessarily be a disease of the bladder but that the bladder may be an innocent bystander in a larger pelvic/systemic process. To improve symptoms of IC, he said, you must be an astute clinician and think outside the bladder.

They noted that up to 85% of patients diagnosed with IC/BPS suffer from pelvic floor spasm which causes pelvic pain, dyspareunia, urinary frequency and urinary hesitancy. If the pelvic floor is a source of pain and the muscles are in spasm, treating the pelvic floor first before other invasive testing would be appropriate.

Treatment options

Multiple modalities used to manage pelvic floor dysfunction include Pelvic floor physical therapy

- Local medications – vaginal/rectal suppositories
 - relaxants
 - neuropathic pain agents
- Pelvic floor trigger point injections
- Pudendal blocks
 - long-acting anaesthetic +/- steroids
- Intramuscular Botox – 100 to 300 units
- Integrative medicine, psychological support

They stressed the importance of the pudendal nerve, noting the Nantes Criteria as follows:

1. Pain in the anatomical territory of the pudendal nerve
2. Worsened by sitting
3. The patient is not woken at night by the pain
4. No objective sensory loss on clinical examination
5. Positive anaesthetic pudendal nerve block.

It was emphasized that a multidisciplinary approach is absolutely necessary and that it is essential to have the right physiotherapist who has been specifically trained to do this kind of work with these patients.

4th Session: Diagnosis 2

PELVIC ENDOMETRIOSIS: A CONFUSABLE DISEASE

Professor Riccardo Marana, gynaecologist from Rome then addressed endometriosis, an estrogen-dependent chronic inflammatory disease affecting 7-10% of women of reproductive age, 60% of women with pelvic pain

and up to 50% of women with infertility. It is characterized by the implantation of endometrial glands and stroma outside the uterine cavity in ectopic locations, that include the pelvic peritoneum, ovaries, bowel and urinary tract, causing symptoms of dysmenorrhoea, chronic pelvic pain, dyspareunia, dischezia, dysuria and infertility.

Women with endometriosis suffer from fundamental differences as follows:

- GENETIC: the risk of endometriosis is six times higher when the women have a first degree relative with a severe form of endometriosis.
- IMMUNE SYSTEM: impaired immune surveillance.
- BIOCHEMICAL FACTORS: increased E2 production and progesterone resistance in endometriosis.

Diagnosis

Laparoscopic diagnosis remains the gold standard approach, providing its risk are understood and accepted by the patients.

The diagnosis of endometriosis is a histological one.

Medical therapies for endometriosis:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Combined hormonal contraceptive
- Progestogens
- Danazol
- GnRH agonists
- Aromatase inhibitors

Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.

For further information on endometriosis and IC/BPS, see:

The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. Int J Surg. 2013;11(3):233-7. doi: 10.1016/j.ijso.2013.02.003. Epub 2013 Feb 15. Review. PMID: 23419614. Free full article.

VULVODYNIA: AN ISOLATED GYNAECOLOGIC CONDITION OR A POSSIBLE CONSEQUENCE OF BPS?

The topic of vulvodynia was addressed by Professor Leonardo Micheletti from Torino, Italy who began by looking at the definition according to the 2003 Terminology and Classification of the International Society for the Study of Vulvar Disease (ISSVD). Vulvar Disease (VD) is a vulval pain described as a burning sensation, occurring in the absence of relevant visible vulval findings, or a specific, clinically identifiable, neurologic disorder. VD is categorized as a generalized (involvement of the whole vulva) or localized (involvement of a portion of the vulva: vestibulodynia, cliterodynia, hemivulvodynia, etc). Both generalized and localized VD are further subdivided into provoked pain (pain triggered by physical contact), unprovoked (spontaneous pain), or mixed.

See also: Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. Journal of Reproductive Medicine. 2004;49:772-777.

Professor Micheletti also looked at the pathogenesis of vulvodynia, recent neurobiological classification of pain, chronic comorbid pain conditions (particularly fibromyalgia, IC/BPS, CFS, TMD and irritable bowel syndrome) and the relationship between vulvodynia and bladder pain syndrome. He said that Vulvodynia/Provoked Vestibulodynia is a real clinical entity and not a consequence of IC/BPS and in some women it can precede, be synchronous with or follow IC/BPS.

The presence of provoked vestibulodynia or any of the above comorbid pain conditions increases the likelihood that a woman will have one or more of the other chronic pain conditions.

Management of these women, he said, must be multidisciplinary and, because dysfunctional pain syndromes result mainly from abnormal central sensitization, the target for treatment must be the central nervous system and not only the periphery.

PUDENDAL NEURALGIA AND BLADDER PAIN SYNDROME

Pelvic surgeon Dr Eric Bautrant from Aix-en-Provence, France defined pudendal neuralgia as neuropathic pain in the territory of the three branches of the pudendal nerve (inferior rectal nerve, perineal nerve, and dorsal nerve of the clitoris/penis), in accordance with the Aix-en-Provence criteria. He explained that pudendal neuralgia is very frequently associated with visceral pain such as IC/BPS in the pelvi-perineal hypersensitization syndrome.

Pudendal neuralgia may be associated with: bladder pain, urinary frequency, dysuria, other visceral pain, provoked vulvodynia, myo-fascial syndrome.

He concluded that bladder pain syndrome is associated with pudendal neuralgia in pelvi-perineal hypersensitization, that pudendal nerve entrapment is a different entity which can give rise to some urinary symptoms and that knowledge of the PNE and hypersensitization criteria is crucial.

FEMALE SEXUAL DYSFUNCTION AND SEXUAL PAIN: AN INTRODUCTION.

Professor Kristene Whitmore questioned whether physician showed (sufficient) concern for sexual health in women since female patients in studies had reported that few physicians inquired about their sexual health, physicians didn't want to even hear about their sexual problems and that there was frequently no follow-up at subsequent visits. Sexual problems may include hypoactive sexual desire disorder, sexual aversion disorder, sexual arousal disorder, orgasmic disorder, dyspareunia.

Important points about sexual pain: the pain is real, it impacts quality of life, history taking and an accurate diagnosis are key, expectations must be realistic, and a multidisciplinary approach is necessary.

THE EMERGING ROLE OF BPS IN THE MALE POPULATION.

Professor Dan Shoskes from Cleveland reported that the subset of men with IC/BPS has been understudied both for specific diagnostic criteria and response to therapy. Treatment efficacy data for men with IC/BPS is very limited. He emphasized that CPPS and IC/BPS are not the same. Many men with CPPS have no lower urinary tract symptoms. Furthermore, the prostate can be inflamed and a pain generator independent of the bladder. However, men with IC/BPS are often first diagnosed with CPPS.

Key findings in men with IC/BPS are significant lower urinary tract symptoms, suprapubic tenderness and pain that increases with bladder filling and is relieved by emptying. However, CP/CPPS and IC/BPS are syndromes with overlapping symptoms. A diagnosis of IC/BPS in men modestly changes the evaluation pathway and opens choices of bladder based therapies not used in CP/CPPS, including intravesical therapies, botulinum toxin, pentosan polysulfate, cyclosporine and fulguration of Hunner lesion. In his experience, men are less likely to respond to intravesical DMSO based cocktails or PPS, but are more likely to respond to amitriptyline and cyclosporine. Professor Shoskes has found best results with clinical phenotyping and multimodal therapy.

Abstract Session 2 | Oral Communications

7. Failings in Standardisation and Guidelines

Meijlink JM

The aim of standardisation and guidelines is not only to further scientific research and international multi-centre collaboration, but also to improve clinical diagnosis, treatment and ultimately all aspects of the quality of life of the patient. This includes facilitating eligibility for reimbursement of treatment, claiming social security, unemployment and disability benefits and entitlement to all kinds of social services and care, many of which may have an impact on the entire family not just the patient. However, in recent decades, guideline and classification committees have tended to exclude patients and their organisations from any meaningful discussion, at most consulting them at the very end of the decision-making process in order to rubber stamp their document as "patient-approved". This has also been the case in the field of interstitial cystitis/bladder pain syndrome/hypersensitive bladder where a plethora of terms and definitions has led to a breakdown in international communication and has even been to the detriment of the patient in practical terms.

Patient organisations are experts on the challenges and issues facing patients in their daily lives and through their contacts with hundreds and even thousands of patients have a wide view of the whole spectrum of symptoms and chain of developments. This means that they can provide standardisation and guideline health professionals with supplementary information, thereby helping to create a comprehensive picture of each disease and disorder and everything it involves in the widest sense.

Official recognition of a condition is vital, so coding must be correct and uniform across all authorities. Potential problems must be anticipated. However, this cannot be achieved if different societies with their different guidelines, taxonomy and standards committees produce different terminology and definitions, while the International Classification of Diseases (ICD) produces its own variations on terminology and definitions which directly affect the patient.

Furthermore, living in a world rapidly becoming entirely dependent on electronic systems, we need to ask ourselves whether health professionals engaged in standardisation and guidelines have sufficient knowledge of coding, electronic systems and ICD to avoid pitfalls which may ultimately cause harm to the patients. Is sufficient thought being paid by standardisation and guideline groups to this aspect? Should guideline and standardisation committees ensure that they have the possibility to consult experts in the field of coding and electronic systems? And should the World Health Organisation (WHO) be doing more with its ICD to capture a comprehensive global view rather than the limited viewpoint of just a few participants? A study is needed to take a worldwide view and see how differences can be reconciled so as to create a workable system for the benefit of both the patient and meaningful global research and databanks.

[See also *Meijlink JM. [Patient-centred standardization in interstitial cystitis/bladder pain syndrome—a PLEA. Transl Androl Urol 2015. doi: 10.3978/j.issn.2223-4683.2015.08.02](#)*]

8. The Effect of Apical Prolapse Repair on Bladder Pain

S. Shower, A. Fisher, A. Khunda, G. Afridi, R. Nicholson, P. Ballard

The aim of this study was to explore the relationship between uterovaginal prolapsed operations and bladder pain. The authors found that around half the patients will have no change in bladder pain following prolapsed surgery. However, in the other half, two thirds seemed to experience improvement while one third experienced deterioration in their bladder pain. There was no control to assess the natural progression of pain in this cohort. The authors concluded that bladder pain seems to be common in patients with prolapsed and surgical treatment on the prolapsed may have a mild positive effect on it.

9. Gastrointestinal symptoms, quality of life, and impact of nutritional therapy in women with Bladder Pain Syndrome/Interstitial Cystitis: similarities and differences with Irritable Bowel Syndrome

E. Gaetani, T. Musca, G. Camardese, D. Ferrarese, L. Nasta, G. Miggiano, A. Gasbarrini

In this study, the authors carried out a comprehensive analysis of symptoms and quality of life of female subjects with IC/BPS + gastrointestinal symptoms and female subjects with IBS. They found that subjects with IC/BPS and gastrointestinal symptoms have a quality of life that is even more compromised than subjects with IBS and may benefit from an individualized nutritional therapy. They concluded that subjects with IC/BPS merit a multidisciplinary approach that includes the gastroenterologist and the nutritionist.

10. Central Sensitization in Bladder Pain Syndrome

E. Onesti, M.C. Gori, M. Rossi, E. Gaetani, L. Nasta, G. Campagna, G. Scambia, M. Cervigni, M. Inghilleri

Central sensitization (CS) has been proposed as a pathological mechanism to explain the chronic pain related to fibromyalgia, chronic fatigue, irritable bowel syndrome, and IC/BPS, representing an abnormal state of responsiveness or increased activation of the nociceptive system. CS is characterized by allodynia (painful response from normally non-painful stimulus), hyperalgesia (increased sensitivity to pain), expansion of the receptive fields of neurons, and unusually prolonged pain sensation persisting after the stimulus has been removed. Several studies have demonstrated that CS is associated with several changes in the properties of neurons in the central nervous system including alterations in membrane excitability, reduction in inhibitory transmission, and increase in synaptic efficacy. The aim of this study was to analyze the impact of CS in IC/BPS in relation to the disease duration. The authors found that CS appears to be a pathological mechanism detectable at the start of the disease in IC/BPSA patients, with a greater level at onset of symptoms in comparison with the normal population. This result could be a predisposing factor to other diseases related to CS. The delay in diagnosis and the absence of early treatment could facilitate the onset of other diseases characterized by CS.

11. Who does the patient meet before the diagnosis of bladder pain syndrome?

M.C. Gori, E. Onesti, L. Nasta, A. Gasbarrini, E. Gaetani, G. Scambia, M. Inghilleri, M. Cervigni

The aim of this study was to evaluate the different specialists consulted by patients before they receive the diagnosis of IC/BPS. The patients met different health operators, both practitioners and unprofessional

subjects, before the diagnosis of IC/BPS (general practitioner, gynaecologist, surgeon, nutritionist, urologist, gastroenterologist, physiotherapist, anaesthesiologist, rheumatologist and psychiatrist. The main prescribed treatments were: antiepileptic drugs, homeopathic therapies, natural therapies, psychotherapy, antidepressants, invasive surgery, massage, acupuncture, muscle infiltration, contraceptives, biofeedback, mediation and TENS. It was found that the difficulty and delay in diagnosis can expose the patient to the risk of unnecessary and expensive treatments.

12. Safety and Efficacy of AQX-1125 in Interstitial Cystitis/Bladder Pain Syndrome - Results of the Phase 2 Leadership Trial

J. Curtis Nickel, E. Davis, P. Tam, L. Mackenzie, H. Biagi, S. Shrewsbury

AQX-1125, a novel SH2-containing inositol-5-phosphatase 1 (SHIP1) activator, represents a potential therapy for bladder pain syndrome. This 6 week randomized, double-blind, placebo-controlled Phase 2 trial assessed the safety and efficacy of AQX-1125 on average daily bladder pain and in standardized BPS questionnaires. AQX-1125 was well tolerated. It was concluded that women with moderate to severe BPS treated with AQX-1125 reported greater reduction in bladder pain at 6 weeks compared to placebo. These data support continued development of this drug for BPS.

Further information: http://files.shareholder.com/downloads/AMDA-2K683P/771223945x0x851074/2c0ca862-6a8a-4506-9912-e03468a47aab/Aquinox_Presents_at_2015_ESSIC_Conference.pdf

5th Session Diagnosis 3

FUNCTIONAL EVALUATION: URODYNAMICS.

The role of Urodynamics in the diagnosis of IC/BPS is to distinguish IC/BPS symptoms from overactive bladder. Professor Mauro Cervigni pointed out that since filling cystometry is helpful in overactive bladder, it may be useful in cases where OAB and IC coexist (estimated at 14% of patients) and may have a bearing on treatment. The recommended approach is to perform filling cystometry with a filling rate of 50 ml/s to look for instability, volume at first desire to void and cystometric capacity. In females, flowmetry, post void residual urine volume and pressure flow study are optional. However, in males, a flowmetry should be done in all patients and if the maximum flow rate is less than 20 ml/s, a pressure flow study and measure of residual urine volume should be performed.

ELECTRODIAGNOSTICS IN BPS/CPPS

Professor JJ Wyndaele explained that the purpose of electrodiagnostics is to evaluate the peripheral and central nervous system. Methods used include:

- Electric perception threshold in LUT
- Electromyography (EMG)
- Electroneurography (ENG)
- Sensory evoked potentials (SEP)
- Motor evoked potentials (MEP)
- New cerebral imaging techniques

There are also more specific tests to investigate the pudendal and median nerves.

Much information can be gained with electrodiagnostic tests. However, interpretation is not easy, application is usually painful and patients not enthusiastic. What is the clinical value, he asked? None, except if there is a strong suspicion of pudendal neuropathy as a cause of CPPS or of other neuropathy as a cause of aggravating factor.

BIOMARKERS: NOT YET READY FOR PRIME TIME.

What is the potential benefit of a biomarker in a clinical syndrome such as BPS defined by a symptom complex, asked Professor Philip Hanno? Potential benefits are:

- To confirm the diagnosis in a patient with confusable disorders and possible dual etiologies;
- To predict prognosis;
- To predict the response to a specific therapy;

- To better stratify the treatment algorithm;
- To help to identify subsets of patients who may qualify as having discrete diseases and drop from BPS designation;
- But not necessary to distinguish BPS from asymptomatic patients.

However, the problem is that identification of biomarkers for lower urinary tract disorders is difficult. There are multiple disorders which are often based on subjective symptoms and multifactorial in origin.

The most researched biomarkers are:

- Antiproliferative factor
- Epidermal growth factor
- Heparin-binding epidermal growth factor-like growth factor
- Glycosaminoglycans
- Inflammatory mediators in the urine and serum.

Looking at mast cells he noted that Gamper et al had looked at mast cells as a biomarker. Subepithelial mast cell distribution was characteristic for bladder pain syndrome with Hunner lesions. Detrusor mastocytosis had a poor predictive value for bladder pain syndrome. Mast cells assessment did not distinguish bladder pain syndrome without Hunner lesion from overactive bladder or asymptomatic patients. Professor Hanno stressed that he was not aware of data showing that patients with mastocytosis respond differently to antihistamine treatment.

Regarding the future, Professor Hanno believes that one can predict that based on pathologic findings, endoscopic findings and response to therapy, the patient with Hunner lesions will be categorized as having a specific urologic disease and be dropped from the bladder pain syndrome group. Our goal, he said, should be to discover other markers that would better enable treatment of different patient groups and aid pharmaceutical companies in their quest for new, rational therapies.

He concluded that a biomarker can serve as a surrogate endpoint for results of treatment and may help eliminate the huge placebo effect that makes clinical studies so challenging.

CYSTO-HYDRODISTENSION: THE WAY I DO IT - ESSIC PROPOSAL.

Professor Magnus Fall from Sweden looked at the role of cystoscopy in painful bladder conditions. While cystoscopy with hydrodistension was once considered mandatory, it became an optional investigation, at least in some countries. The attitude has changed recently, he said, and there is almost general agreement that there are separate phenotypes and unquestionable differences between entities in terms of cystoscopic features, age at onset, histopathology, complication patterns and response to different treatments, as well as associated symptoms. Today, cystoscopy combined with bladder distension under anaesthesia has regained its role to distinguish phenotypes of BPS including IC. There is, however, still inadequate knowledge among doctors with regard to being able to identify Hunner lesion in clinical practice and this is also having an impact on research.

This presentation described cystoscopic investigations and findings in detail.

Dr Tomohiro Ueda from Kyoto, Japan, reviewed clinical and treatment implications of other findings such as glomerulations and epithelial cracks and the possible mechanism of glomerulations. He also discussed the use of Narrow Band Imaging (NBI) for IC/BPS. This is a technique that demonstrates neovascularisation following overexpression of angiogenetic factors.

PATHOLOGY OF HUNNER DISEASE – CLASSIC IC/ESSIC CATEGORY 3C

Continuing on the topic of Hunner lesion (categorized by ESSIC as 3C), Dr Christina Kabjorn-Gustafsson from Sweden discussed whether it is possible to histologically diagnose Classic IC and separate this from other forms of cystitis with often similar clinical symptoms such as non-lesion IC/BPS. She concluded that it is possible to do this if there is adequate clinical information and particularly adequate deep biopsies with several fragments of the detrusor muscle. Also, if Mab MastCellTryptase is used, a grid. But above all if the pathologist is aware of this disease.

HOW ARE WE PERFORMING HYDRODISTENSION

Dr Sandor Lovasz from Hungary then also looked at hydrodistension, emphasizing that standardization and optimization of the level of intravesical pressure and time of dilation are absolutely essential.

MEDITERRANEAN INCONTINENCE AND PELVIC FLOOR SOCIETY (MIPS) LECTURE

Dr Diaa Rizk discussed the incidence of IC/BPS in the Mediterranean Area and the possible barriers to healthcare access for women. He looked at different cultures in the Mediterranean region where many women may suffer in silence because it is not acceptable for women to complain about symptoms and/or women do not know that it can be treated. He concluded that the true prevalence is unknown.

6th Session Treatment 1

PAIN CONTROL IS MANDATORY.

Professor Marco Rossi, anaesthesiologist in Rome, looked at pain in BPS which may be suprapubic, vaginal/vulvar, inguinal, rectal, abdominal, back. He noted that poor pain control is relatively common in patients with chronic pain and that pain is often undiagnosed and certainly undertreated. This speaker also emphasized the need for integrated and multidisciplinary management. Furthermore, he said that pain control is not simply treatment of the pain, it is also patient education, self-care practices, behaviour modification, stress management and coping techniques. What we need, he said, is a patient-centred shared-care approach.

THE “COATING” PROBLEM AND ITS MANAGEMENT.

Professor Mauro Cervigni looked at treatment for the bladder coating problems. The coating is made from a deep portion and a surface portion composed of glycosaminoglycans (GAGs). The functional glycoproteins play a co-receptors role for hormones and/or growth factors. The structural glycoproteins establish dynamic interactions with the various components of the coating.

The role of glycosaminoglycans in IC/BPS:

- Defective urothelium allows toxic substances to diffuse into the bladder wall, thus causing sensory urgency, frequency and pelvic pain.
- Low and elevated rates of urinary GAG's excretion have been found in patients with IC/BPS, and changes in GAG expression have been noted.
- GAGs protect the bladder urothelium from bacterial adherence and serve as blood-urine barriers: it is postulated that IC/BPS patients have a defective GAG layer
- Interstitial hydraulic permeability is however also governed by the interplay between proteoglycan, GAG and collagen.

Therapy principles for IC/BPS:

- Correct epithelial dysfunction
- Inhibit neural hyperactivity
- Control allergies
- Modulate symptoms.

Different therapeutic strategies are possible for intravesical treatment. GAG replenishment therapy has shown promise in recent research. On the other hand, he said, BCG and RTX do not seem to have any beneficial effect on symptoms in IC/BPS patients.

MASTOCYTOSIS: SHOULD IT GUIDE TREATMENT?

Dr Edoardo Ostardo from Italy looked at mast cells which have been linked to IC/BPS for some decades. Mast cells play a key role in inflammatory processes. When activated, a mast cell rapidly releases its characteristic granules and various hormonal mediators into the interstitium. These chemical mediators cause the characteristic symptoms of allergy. The cornerstone of treatment is avoidance of identifiable triggers for mast cell degranulation (extremes of temperature, mechanical irritation, alcohol, medications, stress or environmental conditions). Effective treatment often consists simply of antihistamines and MC membrane-stabilising compounds.

7th Session Treatment 2

ROUND TABLE.

FOCUS ON NEURO-STIMULATION: SACRAL/TIBIAL/DEEP MAGNETIC BRAIN

A number of speakers looked at different aspects of neuro-stimulation.

Dr Francesco Cappellano from the department of neurology in Milan spoke on PTNS and CPPS: fact or fiction. Noting that changes in the central nervous system (CNS) may magnify perception in such a manner that non-painful stimuli are perceived as pain (allodynia) and painful stimuli may be perceived stronger than normal (hyperalgesia), he postulated that therapies aimed at modulating the nervous system, such as centrally acting medications, sacral neuromodulation (SNM), pudendal neuromodulation (PNM) and percutaneous tibial nerve stimulation (PTNS) might be effective. However, he concluded that one single therapy probably cannot cure a syndrome.

Professor Maurizio Inghilleri, speaking on deep magnetic brain stimulation, looked at the concept of neuroplasticity. The realization that the central nervous system is not “hard-wired” but is plastic and capable of self-regulation and adaptation after injury was well-known, he said, before the range of underlying mechanism was understood. The term “plasticity” is widely used to refer to this self-regulation, although the term includes various electrophysiological functions of neurons. In neurological disorders where it is the overall functional effect of these mechanisms that is clinically relevant, plasticity refers to any lasting change in the nervous system that restores function or in some instances contributes to dysfunction.

In chronic pelvic pain with central sensitization, the pain becomes the disease.

Referring to the MAPP Research Network study “Brain white matter abnormalities in female interstitial cystitis/bladder pain syndrome: a MAPP Network neuroimaging study” (Farmer et al, 2015), he emphasized that it remains unclear whether the white matter properties referred to in this paper are causes or consequences of IC/BPS. It may reflect a predisposition to develop a disease.

Pudendal neuromodulation was discussed by Professor K. Peters (USA) who explained that stimulation of the 3rd sacral nerve has been shown to be effective in treating voiding dysfunction. The pudendal nerve is a distal branch of S2, S3 and S4. The potential benefit of pudendal nerve stimulation is increased afferent stimulation through the sacral nerve roots.

Professor Antonella Giannantoni from Perugia, Italy then spoke on the role of Botox in modulating pain in IC/BPS patients. In her literature review, she identified few randomized controlled trials. There were 6 RCTS from 2009 to 2015, all of which aimed to assess the efficacy of BoNT/A injections for the treatment of IC/BPS. Unfortunately the protocols for the injections varied. Injection sites varied: the bladder floor including the trigone, or excluding the trigone or the trigone only. While there is some evidence of a beneficial effect of BoNT/A on IC/BPS, relatively few patients were included in the studies and follow ups were too short. However, some tasks remain before BoNT/A is established in the treatment of IC/BPS. Definition criteria are still not uniform worldwide. Subtyping and phenotyping are crucial in defining which groups of patients will respond better to a certain treatment. Furthermore, injection techniques and injection sites need to be better defined. Broad collaboration is needed in the design of large, randomized placebo-controlled studies.

NEW INTRAVESICAL OPTIONS FOR BPS/IC PATIENTS

Professor Andrei Zaitcev from Moscow looked at recent advances in intravesical drug/gene delivery, concluding that future improvements in IDD are likely to gain from developments in the field of nanotechnology. He reviewed the latest developments in the field of botulinum neurotoxin (BoNT/A) hyaluronic acid and chondroitin sulfate, alkalized lidocaine plus heparin, continuous lidocaine-releasing intravesical system (LiRIS) and liposomes either empty or as a delivery platform. He noted that liposomes were earliest prototypes of nanoparticles (particles with one of the dimensions in nanometers) that are described as lipid vesicles composed of concentric phospholipid bilayers enclosing an aqueous interior. He also discussed pentosan polysulfate encapsulated in a liposome and BoNT entrapped inside liposomes. Studies published on BoNT/A in IC/BPS have been mixed and the use of BoNT in IC/BPS remains unlicensed. While it may be effective in the short term, repeated injections are required to maintain relief. It has been shown to be effective in both lesion and non-lesion subtypes.

8th Session Treatment 3

THE MANAGEMENT OF HUNNER LESIONS.

Dr Yr Logadottir from Sweden emphasized the dilemma in the field of IC/BPS:

- The patients are not a homogenous group

- The disease does not present in a uniform fashion
- It may be concluded that IC/BPS is a heterogenous syndrome.

There are at least two forms:

- Classic IC/Hunner's disease/BPS ESSIC type 3C
- Non-ulcer IC/non-Hunner BPS.

Classic interstitial cystitis/BPS ESSIC type 3C is a specific disease and is in fact the disease previously described by Hunner and others and is sometimes also referred to as Hunner's disease.

Non-lesion interstitial cystitis/non-Hunner BPS is "the rest of the syndrome".

Management of Hunner lesions may comprise the following:

- Oral medications: may have a stabilizing effect on the urothelium or GAG layer. May include pentosan polysulfate sodium (PPS), hydroxyzine, amitriptyline, anti-inflammatory drugs, immunosuppressants (e.g. cyclosporine A), NOS-inhibitors.
- Instillations: dimethyl sulfoxide (DMSO), PPS, hyaluronic acid (Cystistat), chondroitin sulphate (Uracyst), lidocaine, bacillus Calmette-Guérin (BCG).
- Medication plus other interventions: bladder hydrodistension, botulinum toxin with or without bladder distension, hyperbaric oxygen treatment.
- Neuromodulation
- Transurethral interventions: conservative surgery with complete transurethral resections or coagulation of Hunner lesions; alternatively, use of the neodymium yttrium aluminum-garnet (Nd:YAG) laser.
- Open/major surgical management: simple urinary diversion; reconstructive surgery with continent urinary diversion; reconstructive surgery with supratrigonal cystectomy and ileocystoplasty.

HYPERBARIC OXYGEN THERAPY.

Professor Arndt van Ophoven, Germany, presented a study on hyperbaric oxygen treatment in IC/BPS patients. A total of 30 treatment sessions appeared to be an effective and safe therapy. Adverse events included accommodation, temporary claustrophobia, eustachian tube dysfunction and temporary disorientation.

THE ROLE OF SURGERY.

Professor Jorgen Nordling (Denmark) reviewed surgical options. Concerning hydrodistension, he said that recent literature reports poor results with only a minority of patients reporting a small improvement in symptoms for a relatively short time.

He stressed that procedures such as cystolysis – peripheral denervation, sympathetic denervation and parasympathetic denervation are not indicated for BPS.

Bladder augmentation/cystoplasty, cystoplasty with supratrigonal resection, cystoplasty with subtrigonal cystectomy:

- No outcome difference among bowel segments except for dysuria associated with gastric tissue substitution;
- Weak evidence that cystoplasty with supratrigonal resection may benefit end stage ESSIC type 3C patients (Hunner lesion);
- Subtrigonal cystectomy with cystoplasty has no outcome advantage over supratrigonal but is associated with more complications;
- Literature suggests: 1. Using detubularized intestinal segment, 2. Performing supratrigonal bladder resection, 3. Selecting patients with low cystoscopic bladder capacity.

Total cystectomy and urethrectomy:

- Urinary diversion with/without cystectomy may be the ultimate option for refractory patients;
- Continent diversion may have better cosmetic and lifestyle outcome but recurrence of BPS in the pouch is a real possibility;
- There is no literature evidence of any advantage of continent surgery.

9th Session PATIENT ORGANIZATIONS

ICA: LESSONS LEARNED OVER THE PAST 30 YEARS

Noting that the Interstitial Cystitis Association of America (ICA) had celebrated its 30th anniversary in 2014, Dr Vicki Ratner, President Emeritus of the ICA, emphasized that it had been a very challenging journey. Back in

1984, IC was generally considered to be a rare psychosomatic disorder in menopausal women. We've come a long way since that time, she said, and great progress has been made. There were seven key reasons why the ICA became so successful: the tremendously dedicated ICA staff, Board of Directors and volunteers; a strong Medical Advisory Board and participation of many other urologists from across the USA and abroad; the media; epidemiology; the ICA's pilot research programme; representation in Congress; and a strong working partnership with the National Institutes of Health. The focus of this presentation was the importance of working with the media.

PATIENTS IN STANDARDIZATION

Jane Meijlink, chairman of the International Painful Bladder Foundation, celebrating its 10th anniversary, spoke on the topic of patient participation in standardization. The aim of standardisation and guidelines, she said, is not only to further scientific research and international multi-centre collaboration, but also to improve clinical diagnosis, treatment and ultimately all aspects of the quality of life of the patient. This includes facilitating eligibility for reimbursement of treatment, claiming social security, unemployment and disability benefits and entitlement to all kinds of social services and care, many of which may have an impact on the entire family not just the patient. However, in recent decades, guideline and classification committees have tended to exclude patients and their organisations from any meaningful discussion, at most consulting them at the very end of the decision-making process in order to rubber stamp their document as "patient-approved". This has also been the case in the field of interstitial cystitis/bladder pain syndrome/hypersensitive bladder where a plethora of terms and definitions has led to a breakdown in international communication and has even been to the detriment of the patient in practical terms. Patient organisations are experts on the challenges and issues facing patients in their daily lives and through their contacts with hundreds and even thousands of patients have a wide view of the whole spectrum of symptoms and chain of developments. This means that they can provide standardisation and guideline health professionals with supplementary information, thereby helping to create a comprehensive picture of each disease and disorder and everything it involves in the widest sense. Official recognition of a condition is vital, so coding must be correct and uniform across all authorities. Potential problems must be anticipated. However, this cannot be achieved if different societies with their different guidelines, taxonomy and standards committees produce different terminology and definitions, while the International Classification of Diseases (ICD) produces its own variations on terminology and definitions which directly affect the patient. Furthermore, living in a world rapidly becoming entirely dependent on electronic systems, we need to ask ourselves whether health professionals engaged in standardisation and guidelines have sufficient knowledge of coding, electronic systems and ICD to avoid pitfalls which may ultimately cause harm to the patients. Is sufficient thought being paid by standardisation and guideline groups to this aspect? Should guideline and standardisation committees ensure that they have the possibility to consult experts in the field of coding and electronic systems? And should the World Health Organisation (WHO) be doing more with its ICD to capture a comprehensive global view rather than the limited viewpoint of just a few participants? A study is needed to take a worldwide view and see how differences can be reconciled so as to create a workable system for the benefit of both the patient and meaningful global research and databanks.

DISABILITY AND WELFARE REIMBURSEMENT

Loredana Nasta, founder of the Italian Interstitial Cystitis Association AICI, celebrating its 20th anniversary this year, described how IC/BPS had been neglected and underestimated for decades. Patient organisations played a crucial role in raising awareness of this disease among both the medical and research community and government authorities on the need to find solutions to this devastating bladder condition. The AICI was also instrumental in achieving patients' rights in the healthcare system. Since Italy has a different national health system to other countries, AICI had to work closely with the government and institutions to achieve rights for IC/BPS patients. One of AICI's most important achievements was having IC/BPS recognised as a Rare Disease in 2001 (diagnostic criteria in Italy are stricter than in some countries and bring the number of patients well below the Rare Disease threshold). This made the patients eligible for access to a number of important facilities and benefits. However, the reality is rather different and the path for the patients difficult and complex.

In order to be accepted as participants in scientific and political round tables, the patient organisations/advocates have to be expert in not only all aspects of IC/BPS, but also in EU, national and regional law and human rights. This presents a huge challenge.

AN INTERNATIONAL REGISTRY FOR BPS: A FUTURE OPTION OR A UTOPIA?

Dr Joop P van de Merwe from the Netherlands discussed the challenges of setting up an international registry for BPS. While this could be a useful tool for the investigation of many aspects of the disease, setting up such a registry would be complex and subject to many requirements, for example legal, safety, technical, scientific, methodological, financial and much more besides.

What is a registry? Dr Van de Merwe explained that it is a systematic collection of a clearly defined set of health and demographic data for patients with specific health characteristics, held in a central database for a predefined purpose. Clear definition of the research questions in advance is absolutely essential.

Clinical and research databases

He then looked at the differences between clinical and research databases. A clinical database is report-oriented with data displayed for clinical decision making (e.g. abdominal X-ray report). The emphasis here is on displaying or reporting individual data rather than accumulating multiple records. Not a lot of variables are recorded.

A research database, on the other hand, is table-oriented with data accumulated for eventual export to a statistical package for data analysis and reporting. There is less emphasis here on individual records. Here you create forms to represent tables that are storing information.

Database Design

Important aspects here are what to collect and what questions are to be answered? The focus should be on the key data elements rather than collecting as much data as possible. A further important aspect is what statistical package will be used.

Designing the questions

Try to collect continuous data, converting to categorical during analysis period (e.g. age). Use validated scales/instruments and do not build your own unless unavoidable. Consider asking in more than one way a question concerning a critical variable under study (allows for validity assessment). Avoid measurements that cluster at one position or one end of a scale, e.g. measuring body temperature on healthy outpatients. Pilot the form for 10-20 patients, then revise.

Examples of medical registry problems:

- lack of well-defined research questions
- subjective patient data
- inconsistent data collection, missing values
- loss of patients or centres from follow-up
- loss of the relevance of research questions
- privacy and protection against unauthorized access
- heterogeneity of the patient population
- incorrect sequence of hypothesis and statistical analysis
- GIGO (garbage in, garbage out paradigm)

Data protection

One of the biggest problems today is data protection: while the stored data has to be accessible by participating researchers, it has to be protected from unauthorised persons.

Setting up a registry would be very valuable, but in practice it is fraught with difficulties.

Further information:

Arts DG, De Keizer NF, Scheffer GJ. Defining and improving data quality in medical registries: literature review, case study, and generic framework. J Am Med Inform Assoc. 2002 Nov-Dec;9(6):600-11. PMID: 12386111

ESSIC MANAGEMENT OF BPS PATIENTS.

Professor Hanno concluded the scientific meeting by taking a look at new challenges for ESSIC which include difficult decisions that directly affect diagnosis and indirectly affect the management of BPS. The organization may have to review and update its diagnostic and management algorithms, simplifying algorithms for the front-

line provider. The ESSIC classification table may also need revision: should glomerulations be removed? (See: *Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in Bladder Pain Syndrome - A review. J Urol. 2015 Aug 26. pii: S0022-5347(15)04683-2. doi: 10.1016/j.juro.2015.06.112. [Epub ahead of print].*

There is then the question as to whether Hunner lesion should be removed from the list and recognized as a separate identity and maybe given its original name of interstitial cystitis. Is Hunner lesion indicative of a different disease process that requires different basic science investigations as well as pharmaceutical trials and treatment trials that reflect that it is a defined and separate pathologic process? A scholarly paper is needed to determine whether the answer is yes or no, according to Professor Hanno.

ICD-11

On the subject of the International Classification of Diseases (ICD) version 11, due to be completed in 2017, two ESSIC members are involved (Professors Baranowski and Nordling). However, the IPBF earnestly believes that the patient organizations should most definitely be involved since it was precisely endeavours to undertake classifications without the patients' input that led to the current non-reimbursement problems.

(see also: *Meijlink JM. [Patient-centred standardization in interstitial cystitis/bladder pain syndrome—a PLEA. Transl Androl Urol 2015. doi: 10.3978/j.issn.2223-4683.2015.08.02](#) Open access article.*

The International Painful Bladder Foundation does not engage in the practice of medicine. It is not a medical authority nor does it claim to have medical knowledge. Information provided in IPBF emails, newsletters and website is not medical advice. The IPBF recommends patients to consult their own physician before undergoing any course of treatment or medication. The IPBF endeavours to ensure that all information it provides is correct and accurate, but does not accept any liability for errors or inaccuracies.

© 2015 International Painful Bladder Foundation