

**REVIEW OF THE ESSIC 2018 ANNUAL MEETING
FLORENCE, ITALY, 29 November – 1 December 2018
“Bladder Pain Syndrome/Interstitial Cystitis: Rare or not rare? That is
the question”**

Jane Meijlink



The Auditorium al Duomo in the historic heart of Florence formed the setting for the ESSIC 2018 annual meeting. ESSIC is the International Society (originally the European Society) for the Study of Bladder Pain Syndrome/Interstitial Cystitis and its associated disorders. Its President is Professor Jean-Jacques Wyndaele from Belgium. The ESSIC annual meeting provides an opportunity for clinicians, researchers, patient representatives and other stakeholders with a special interest in BPS/IC and associated disorders to discuss the current situation, present their research or ideas and make suggestions for the future. This year’s meeting in Florence, Italy, chaired by Professor Giulio Del Popolo with Professor Mauro Cervigni as ESSIC Coordinator, was attended by 180 delegates from 18 countries including Australia! There were no fewer than 17 patient representatives from different countries who played an active part in the meeting with a number of presentations, including on the very concerning issue of non-reimbursement of vital treatment for IC/BPS by health authorities and insurances.

Highlights of the 2018 Kyoto Meeting held by ESSIC’s sister organisation ICICJ/SICJ were presented by Rajesh Taneja MD from India. A detailed review of this ICICJ meeting In Japan can also be found on the IPBF website at:

http://www.painful-bladder.org/pdf/2018_ICICJ4_Kyoto.pdf

Speakers in Florence looked at different aspects of diagnosis, treatment, guidelines and presented new research. There was also time for discussion of current problems faced by the IC/BPS world. This review takes a look at just some of the highlights.

Sexuality

For many years, sexuality in IC/BPS and CPP patients was a taboo topic and clinicians never even raised this issue with patients. In turn, patients found it far too embarrassing to discuss such intimate topics with their doctor. Fortunately, sexuality in urogenital chronic pain disorders has now at least partly come out of the closet and this meeting began with a session on “Gender Medicine: different treatment for same pain or same treatment for different pain?” Robert Moldwin MD from the USA looked at quality of sexual life in men with chronic prostatitis, noting that even questionnaires to assess sexual quality of life in the CPPS patient are very inadequate and new instruments need to be developed to investigate ejaculatory pain with erectile dysfunction. The pain should be treated and an integrative care plan developed that relates to the clinical presentation.

Alessandra Graziottin MD from Italy discussed female pain during intercourse, emphasizing that coital pain is a clinically relevant issue. Comorbidities play a very relevant role here too. The speaker looked at the major biological causes of pain disorders which can differ in the fertile age and the postmenopausal age. An important question to ask the patient is where exactly is the pain felt?

Rare or not?

The 2nd Session focused on the theme of Bladder Pain Syndrome/Interstitial Cystitis : Rare or not rare? The theme of rare disease or not is related to the fact that IC/BPS is considered rare in some countries, including Italy, but not rare at all in others such as the USA. Prevalence studies in the past have produced wildly varying figures as a result of patients being diagnosed in different ways, with different cystoscopic practice, and according to different criteria. An important aspect is that in some countries rare disease status means that it is easier to have treatment reimbursed.

Phenotyping

Speaking on epidemiology and the importance of typology, Philip Hanno MD from the USA raised some important issues concerning phenotyping. The term “phenotype” refers to the observable physical properties of an organism. These include the organism’s appearance, development and behaviour. When referring to a disease, phenotyping could improve diagnosis, prognosis, choice of therapy, prevention, pharmaceutical research, and could suggest new treatment pathways.

However, he stressed that early adoption of unproven phenotypes in a clinical setting does nobody any favours. Proving the utility of a phenotype is a critical step. In the case of a syndrome, a phenotype could ultimately prove to be a disease in itself and consequently be removed from a syndrome, for example Hunner lesion. Indeed, so far, the only proven phenotype is Hunner lesion.

Prevalence

Claus Riedl MD from Austria looked at incidence and prevalence in North America, Asia and Europe. However, there are still no standardized instruments defined to evaluate this in IC/BPS, he said. Prevalence does seem to be similar in different regions of the world as well as among different races and ethnicities. Prevalence is higher in women versus men. No clear conclusion can be drawn about age groups affected. Prevalence estimates range from 300 to 2500 per 100,000, depending on definition and methods of evaluation. International consensus is essential but still not happening.

European Reference Networks (ERN) and European Reference Network for Rare and Complex Urogenital Diseases and Conditions (eUrogen)

Mauro Cervigni MD from Italy explained the background and history of ERNs and eUrogen, originally established to facilitate cross-border healthcare within the European Union. The first 24 ERNs were launched in 2017, involving more than 900 highly specialized healthcare units from over 300 hospitals in 26 Member States.

The purpose of eUrogen is to deliver quicker specialist evaluation, more equitable access to diagnosis, treatment and follow-up, for patients with rare urogenital diseases and complex condition who need highly specialized assessment and surgery. Its objectives include: improving care for patients with rare or low prevalence complex diseases or conditions, concentrating expertise where capacity and knowledge are rare, provide access to the most appropriate diagnosis and treatment of certain conditions, allow expertise to travel across borders – not the patient - and to act as a focal point for medical training and research.

Dick Janssen MD from Radboud University Medical Centre in the Netherlands, one of the expert research centres for eUrogen, then gave a presentation on behalf of Margit Fisch MD from Hamburg who leads the eUrogen advisory board for Workstream 2 which includes chronic pelvic pain/interstitial cystitis. Serena Bartezzati from Italy is the patient ePAG member for this advisory board.

The speaker underlined that it makes sense to combine expertise and resources for rare and complex conditions, similar to the situation in the USA with the MAPP Network.

Research planned includes epidemiology/phenotyping study, pain testing study, neuroimaging study, evaluation of promising candidate biomarkers and clinical outcome. An important first step is connecting expertise centres in research & clinical activities. This represents a great potential to obtain future funding for research. (There is currently a digital form available to sign in and make your interest and research activities known). According to the speaker, they are looking for clinics within the ERN eUrogen network that are willing to participate in:

- Knowledge and ideas exchange to increase the impact of improving healthcare for IC/BPS
- Gathering and sharing data
- Tissue/biobank sharing.

Serena Bartezzati, patient advocate, then discussed the role of the ePAG patient advocates on behalf of Loredana Nasta who was unfortunately unable to attend due to a car accident. Serena emphasized that support is needed from ESSIC in creating a European network on IC that will work on a hub & spoke model in each country in terms of research, diagnostic approach and best treatments. Here too it was stressed that we are greatly in need of Consensus in terms of terminology, diagnosis and treatment.

Non-reimbursement of treatment

Non-reimbursement of essential treatment for our patients has now reached serious levels and action is urgently needed, according to patient advocate Jane Meijlink (IPBF). Drugs and medical devices designed for IC/BPS are either not being authorized for marketing at all, or not being approved for reimbursement. The best treatment in the world is of no use if patients cannot afford it, because their healthcare system refuses to pay for it.

We urgently need real international cooperation to achieve consensus, meaningful phenotyping and high quality studies in order to produce Level 1 evidence. Without this, health authorities will neither approve nor reimburse treatments.

The impact of non-reimbursement of treatment on both the clinician and the patient was raised time and time again in presentations during this meeting. Furthermore, the patients and their support groups are often being left to sort out the legal problems in court, even though they themselves did not create the problems.

This cannot be considered a happy state of affairs and action is urgently needed.

Real-life challenges in treating IC/BPS patients: the Dutch case

Treating these challenging patients is of course what it is all about and Erik Arendsen MD, urologist and IC/BPS expert from the Netherlands, gave us an in-depth view of treatment at the specialised Andros/Gynos clinics in the Netherlands.

With a Dutch population of just over 17 million, there are 2000-3000 known IC/BPS patients, although this is likely to be an underestimation of the real number of patients. Of the 400 urologists in the country, 70 are functional urologists and of those only 20 are known to be IC/BPS experts. This means that the workload is enormous.

Like many other European countries, a big problem in the Netherlands is non-reimbursement of many treatments for IC/BPS. Bladder instillation compounds are not registered as medicines but as medical devices. Basic documentation for medical devices is not required for registration at a pharmaceutical level. Unfortunately, 4 years ago, the Dutch HealthCare Institute (Zorg Instituut Nederland) removed compounds from the reimbursement list. Since then the ICP (patient organisation) has been in and out of court with little success. This has presented a major challenge when treating patients who really need intravesical treatment.

The approach taken by the clinic is to ensure that patients receive the right diagnosis and treatment in a one-stop-shopping appointment with a multi-disciplinary team. Before the appointment, an experienced consultant nurse handles intake by phone and also asks the patient to send in the standard questionnaires, and she will help with filling in these forms if required. At the appointment, the urologist takes a history, performs a cystoscopy and finally gives a diagnosis. This includes subtyping (HL or non-HL).

The clinic can offer many different treatment modalities and care is individualised per patient. Other members of the team include a pelvic floor therapist, a gynaecologist makes an analysis of the hormonal situation in the case of female patients, a dietician checks for allergies, bowel problems, and gives dietary advice, while the final part of the appointment is again undertaken by the nurse who can perform PTNS, do an instillation, teach the patient how to do self-instillation at home and provide lifestyle advice.

If necessary other disciplines could be consulted (e.g. sexologist, psychologist, specialist in bowel diseases, neurologist, pain centre or rheumatologist/immunologist), while the patient remains under the supervision of Andros/Gynos as lead practitioner. Patients are regularly monitored. The speaker also explained how the new Ialadapter© (or MID-ii) syringe adapter device, invented by Dr Sandor Lovász, can be used to instil GAG solutions in the bladder, without the need for catheters.

Guidelines

A session was devoted to discussing the guideline situation. This debilitating condition can be difficult to diagnose and treat due to lack of consensus on aetiology, definition and management. JJ Wyndaele MD from Belgium summarized the findings from major national and international guidelines on IC/BPS, looking at eight different guidelines and highlighting areas of disagreement and uncertainty. All have differences in nomenclature, definitions and recommended diagnostic tests. The overall evidence base for the majority of treatments for IC/BPS is of low quality. Larger randomized trials are required to more accurately inform guideline recommendations and clinical management of this complex group of patients. Philip Hanno MD from the USA suggested that there should be a separate guideline for Hunner disease and felt that there is a need for an evidence-based simplified ESSIC guideline on diagnosis. Cystoscopy should be mandatory, at least under local anaesthesia with a flexible endoscope. There is, he said, a need to revise the ESSIC classification. Hunner lesion should be separated off from non-lesion disease. Glomerulation should be used for research purposes only. The most promising phenotypes based on proliferation of data in the literature should be included.

BPS/IC and infection – Microbiota: the bladder and gut

Marco Soligo MD and Antonio Gasbarrini of Italy looked at microbiota in the bladder and gut, explaining how this is a revolutionary development and may change the rules of medicine in the future. Classical infection theories are no longer reliable. Microbes are fundamental for our health. Microbes can be used to fight microbes. It is the proportions of various bacteria in any disease state which are important rather than the appearance of a single microorganism. Daniele Porru MD looked at urinary tract infections (UTIs) which are a major issue for many women. UTIs can coexist in IC/BPS patients, causing an increase in symptoms and pain. Patients should be properly investigated, he said, to exclude complicated causes or gynaecological problems.

The IC/BPS bladder and its neighbours

This session looked at comorbidity aspects. Bladder and bowel are anatomical neighbours with joint innervation. Consequently, bladder and bowel problems are often found together, said JJ Wyndaele. Eleanora Gaetani MD noted that while the acute phase of IBD with inflamed gut and often ulcerated mucosa is clearly different from the apparently normal mucosa characteristic of IBS, more detailed assessment has detected immune activation, increased gut permeability, increased mucosal serotonin availability, abnormalities of enteric nerve structure and function, and dysbiosis in gut microbiota in IBS – all features seen in IBD. An unhealthy gut could lead to an unhealthy bladder through cross-organ sensitisation, inflammation and dysbiosis.

Diagnosis & Assessment

Jörgen Quaghebeur PhD from Belgium first looked at questionnaires which in recent years have been springing up everywhere in every shape and form, none of them the same. Developing an adequate questionnaire is particularly difficult because of the variety of

symptoms, the many systems involved, emotional factors and consequences and especially the impact on the patient's quality of life. This is another area where consensus is needed.

Andrey Zaitcev MD from Russia discussed the limits and advantages of simple cystoscopy (using local anaesthesia), showing us some spectacular pictures and videos of the bladder wall and lesions. (And this reminded us of the urgent need for an Atlas!!).

He emphasized that it is essential to perform cystoscopy in patients with bladder pain in order to diagnose Hunner lesions since treatment for lesions is very different from that for non-lesion disease.

Simple cystoscopy without hydrodistension (office cystoscopy) can play a supplementary role in diagnosing and treating IC/BPS. However, it has limitations since the patient can only accept filling with a very limited volume, irrespective of the true bladder capacity during anaesthesia, there is no anatomical bladder volume measurement, no confirmation of Hunner lesion and no biopsy and histopathology. However, it can detect primary objective changes in the bladder and help to define future initial treatment.

Magnus Fall MD from Sweden noted that cystoscopy with local anaesthesia is not always sufficient to diagnose IC/BPS adequately. On the subject of Hunner lesion, he said that Hunner lesion is not a persistent chronic ulcer but a distinctive inflammatory lesion with characteristic central fragility, resulting in a deep rupture through the mucosa and submucosa when provoked by bladder distension. Multiple superficial cracks sometimes appear during distension. He gave 10 tips for clinicians:

1. Always start with screening for confusable diseases; this will require cystoscopy under local anaesthesia.
2. Use this occasion to examine for vulvar pain syndrome.
3. Explore the pelvic floor systemically for tender points and other anomalies.
4. Always verify or exclude Hunner lesion (HL) before contemplating any treatment; this requires cystoscopy, preferably with bladder distension under anaesthesia.
5. If lesions are cystoscopically identified with suspicion of HL, CIS or suspect metaplasia of importance, perform deep biopsy, including bladder muscle with large forceps or TUR. Cooperate with dedicated pathologist.
6. Any suspicion of CIS: obtain cytology of bladder washing before other measures.
7. HL: resect or fulgurate lesions (completely).
8. Pelvic floor related pain: use appropriate manipulative techniques.
9. No abnormality found at cystoscopy, external and pelvic examination: use Quaghebeur & Wyndaele 4-step plan (Scand J Urol 2015;49:81-9)
10. No clear diagnosis and no result from standard symptomatic treatment: involve the multidisciplinary team without too much delay.

Pathologist Yr Logadottir also stressed that to assess the bladder it is crucial to take adequate biopsies including both the mucous membrane and the underlying muscle.

Looking at mast cells: these are white granulated blood cells with a round nucleus and are found in most tissues. Mast cells are multifunctional immune cells. There is an overexpression

of mast cells in Hunner lesion, but their precise role is still unclear. There has been some controversy as to whether mast cell density has any value in IC phenotyping and there are many conflicting views.

Endometriosis

A session was dedicated to endometriosis and its impact on the patient, with a suggestion that it is time to redefine endometriosis. Like IC/BPS, individualised treatment is key, with integration of medical and surgical treatments and a multidisciplinary approach.

Pain

A session on pain looked at acute versus chronic pain, central sensitization and the role of botox, including in the form of intratrigoal injections. Central sensitization appears to be a pathological mechanism detectable at the beginning of the symptoms in IC/BPS patients. This suggests a predisposing factor to abnormal central sensitization. This is consistent with recent fMRI studies that have shown an alteration in brain connectivity in patients with IC/BPS or fibromyalgia.

Free communications session

Each presentation lasted 5 minutes and covered very diverse topics. Just a few highlights below:

Dick Janssen MD from the Netherlands gave a fascinating presentation on a proposal to obtain Level 1 clinical evidence for IC/BPS using a combined N-of-1 trial design since it is very difficult to obtain Level 1 evidence for IC/BPS using traditional RCT format.

We also heard from patient advocate Balaka Basu who discussed the situation regarding IC/BPS in India where until the late 90s it was generally believed that IC did not exist in India. Even today, the level of ignorance about IC among doctors is still very high. In addition to a lack of awareness and knowledge, there is also a lack of medical facilities. Rural areas are worst affected. Misdiagnosis is common. And patients have to travel long distances to get treatment. IC treatment is expensive in India and many patients are forced to discontinue it due to the cost. Patients have to deal with taboo, social stigma and in many cases even domestic abuse, Balaka told us. There is now a great need for a patient support group.

Sandor Lovasz MD from Budapest explained about his novel device for self-instillation and self-catheterisation for female patients with IC and/or urinary retention and the latest developments with this device.

Rajesh Taneja MD from India presented the outcome of clinical phenotyping linked treatment strategies in patients with Bladder Pain Syndrome in a tertiary care centre. He concluded that phenotyping of IC/BPS patients appears to be the future.

Clinical insight into etiology can help segregate patients to be treated with different agents and phenotyping may predict the outcome in a given patient. The take home message here

was that clinical phenotyping along with ‘group specific medication strategies’ can enhance the results of treatment of IC/BPS patients.

Interactive session

The final session was an interactive one with presentations and discussions on phenotyping, diet, psychology and sex and new treatments.

Diet

Robert Moldwin MD from the USA discussed the role of diet and dietary modification. He explained that there have been few studies because they are very difficult to run. Therefore, most studies have been based on questionnaires with their biases and multiple variables. He emphasized that not every patient is food sensitive. He recommended trying an elimination diet. This is a bland diet using foods from the list of ‘safe items’. After 1 week you add a “challenge item” and after 3 days either keep it or discard it, and continue in this way, all the time keeping a pain diary. Patients with comorbidities may have other dietary restrictions and these need to be taken into consideration. The elimination diet is recommended as the best way to establish true sensitivities. He suggested that increases in water intake may also be helpful. This was followed by a personal patient perspective on diet from Jane Meijlink.

ESSIC 2019 in Amsterdam

The ESSIC 2019 annual meeting will be held in Amsterdam. We will keep you updated in IPBF e-newsletters and details will be available on the ESSIC website www.essic.org.

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