

**REVIEW OF THE ESSIC ANNUAL MEETING,
HUNGARIAN ACADEMY OF SCIENCES
21-23 SEPTEMBER 2017, BUDAPEST, HUNGARY**

The 2017 annual meeting of ESSIC (International Society for the Study of BPS) held at the Hungarian Academy of Sciences in Budapest and chaired by Dr Sándor Lovász attracted over a hundred IC/BPS experts from around the world. However, it was not only a meeting of medical experts in the field, but also an opportunity for IC/BPS patient advocates from as far afield as Israel and India to meet and exchange experiences as well as learn about the latest developments and provide input on the patient point of view. This highlighted the need for all of us - the first generation of IC patient advocates - to find better ways of passing on our knowledge and know-how to the younger, upcoming generation, and perhaps most important of all to give them encouragement and support in their challenging and often daunting and overwhelming task.

A particularly welcome aspect of this year's meeting was the increased time allowed for discussion and questions after each session, thereby facilitating greater interaction and participation by attendees, including patient representatives. In general terms, every presentation and every discussion session highlighted just how complex this bladder disease (or diseases) is and how relatively little we know. It is in fact a question of "the more we learn, the less we know"! Multi-centre studies are needed since there is a lack of reliable data in many areas.

MAIN TOPICS: GAG LAYER, TREATMENT, HUNNER LESION, REVISION OF ESSIC GUIDELINE

Main topics this year included the GAG layer, intravesical treatment, Hunner lesion, revision of the ESSIC guideline and the question as to whether Hunner lesion should be made a separate disease and if so what to call it.

GAG Layer

As explained by Professor J.J. Wyndaele from Belgium and President of ESSIC, the bladder lining (urothelium) is covered by a glycosaminoglycan layer, known for short as the GAG layer. The natural constituents of the GAG layer include hyaluronic acid (HA) - also called either sodium hyaluronate or hyaluronan and which is a nonsulfated glycosaminoglycan -, chondroitin sulfate and heparin sulfate/heparin. In healthy people, the GAG layer serves as a barrier to protect the underlying tissue (submucosa) from toxic elements in the urine. When the GAG layer is damaged, it can allow toxic elements such as potassium to penetrate the tissue and cause pain and inflammation.

Based on the belief that damage to this GAG layer is a cause of symptoms in IC/BPS, GAG layer replenishment therapy (intravesical treatment) is a widely used treatment for patients whose bladder symptoms do not respond to conservative or oral therapy.

Why can the urothelial coating become disrupted in IC/BPS? According to Professor Wyndaele, this may be genetic, or altered function of urothelium basic activities or exogenous factors such as cytotoxic factors in urine not being sufficiently neutralized.

*(For more detailed information, see: Cervigni M. [Interstitial cystitis/bladder pain syndrome and glycosaminoglycans replacement therapy](#). *Transl Androl Urol*. 2015 Dec;4(6):638-42. Review. Free full article, click on title.)*

Mast Cells

Mast cells in the bladder have long been an area of interest in the field of IC/BPS and in the past were in some countries a basis for the diagnosis of IC/BPS, according to Professor J. Nordling from Denmark. Today they may play a supporting role in diagnosis. While best known for their role in allergic reactions, mast cells are believed to play an important role in inflammatory responses. Since they may play a prominent role in a sub-group of patients, they could be of importance in phenotyping. Gamper *et al* 2015 concluded that “subepithelial mast cell distribution was characteristic of bladder pain syndrome/interstitial cystitis with Hunner lesions. Detrusor mastocytosis had poor predictive value for BPS/IC. Mast cell assessment did not distinguish BPS/IC without Hunner lesion from overactive bladder syndrome.”

(See: Gamper M, Regauer S, Welter J, Eberhard J, Viereck V. [Are mast cells still good biomarkers for bladder pain syndrome/interstitial cystitis?](#) J Urol. 2015 Jun;193(6):1994-2000.)

The urothelium and pain

The urothelium, according to Professor Lori Birder from Pittsburgh, is a “transitional” type of epithelium which allows the bladder to expand and contract. Lining the bladder, ureters and renal pelvis, it not only has a barrier function but also has a sensory function. As we see in the systemic autoimmune diseases, chronic syndromes can be exacerbated by stress and this also applies to IC/BPS. Bladder pain is likely to develop by multiple mechanisms either alone or in combination.

Is it possible to improve the barrier function of the urothelium, she asked, ultimately affecting sensation? Intravesical therapies, including liposomes, can be used to improve treatment of bladder symptoms. An advantage is that they have less systemic toxicity.

The urothelium has sensor and transducer functions and can respond to its environment, thereby contributing to bladder instability, hyperactivity and altered sensations.

Questions which remain to be answered are:

- Are there differences in biomarkers that vary over the course of the disease?
- What are the major players in urothelium signalling factors in health versus disease?

While animal models provide insights into lower urinary tract functions in health and disease, the speaker concluded that given the complexities of the human condition, there is a need to better integrate human studies and basic research, the effects of stress, environmental and genetic factors.

Treatment

The treatment algorithm is similar around the world, with relatively minor differences between guidelines, but often depends on what is available locally, what is reimbursed or what patients can afford. And this can vary greatly from country to country. However, it is still trial and error, highly individual, and will remain so until a) a more effective and realistic form of phenotyping is available and b) better research, studies and trials produce a better evidence base. The advice here was: do whatever works. Since there is as yet no cure, treatment is going to be focused on alleviation of symptoms.

Current therapy involves behavioural modification, oral therapy, various kinds of intravesical therapy and surgery.

Initial treatment tends to be conservative and comprises patient education, dietary manipulation, non-prescription analgesics, stress reduction, pelvic floor relaxation techniques, oral medication or intravesical treatment.

Diet management can play a particularly important role. This is again very individual but the main items that may cause bladder irritation are: food/drink containing caffeine, citrus fruit and juices, other acidic food such as tomatoes, vinegar etc., artificial sweeteners, alcoholic drinks, carbonated drinks/soda, highly spiced food especially containing hot pepper.

(See: Effects of Comestibles on Symptoms of Interstitial Cystitis, Barbara Shorter, Martin Lesser, Robert M. Moldwin, Leslie Kushner. Journal of Urology, July 2007, vol. 178, 145-152.

Dr Rajesh Taneja noted that it is a particularly difficult problem for his patients in India where the food is very spicy.

IC/BPS patients with comorbidities, and especially multiple comorbidities, require a multidisciplinary team approach to ensure that treatment is coordinated and prevent treatment for one disease worsening another.

Treatment is always going to be individual since not only are IC patients all different, but patients with systemic autoimmune diseases, chronic pain syndromes, chronic fatigue syndromes and allergies are also all different. However, some kind of phenotypic approach might reduce the hit and miss aspect.

It was emphasized that Hunner lesion patients require a different approach to non-lesion. Hence the importance of lesion diagnosis. However, with regard to symptoms, there may be no significant difference in pain between the two types.

Intravesical Treatment

Phenotyping is recommended to identify patients with a high probability of success for intravesical treatment. Tests for this purpose discussed were the anaesthetic lidocaine test and the modified potassium sensitivity test.

Non-reimbursement of intravesical therapy may be a big obstacle to optimum treatment of patients.

Treatments used entirely depend on a) cost and b) what is available in a given country. While easy, ready-prepared “pre-fill” treatments are available in some countries, in other countries doctors and patients have to mix often multiple ingredients themselves.

The advantage of intravesical treatment is that it is concentrated in the bladder itself, bypassing the rest of the body. This means greatly lowering the risk of systemic side effects. There is also the potential for fast symptom relief.

Intravesical treatments available include hyaluronic acid (HA) also called hyaluronan and sodium hyalurate, chondroitin sulfate (CHS), combinations of HA and CHS, pentosan polysulfate sodium (PPS), heparin, DMSO and cocktails which may include triamcinolone, hydrocortisone, an antibiotic, with/without lidocaine or other anaesthetic such as marcaine, with/without sodium bicarbonate.

Cocktail therapy: A number of intravesical cocktail recipes were presented at the meeting. These can also be found on the IPBF website at

<http://www.painful-bladder.org/pdf/IPBF.intravesicalcocktails.pdf>

Intravesical Lidocaine

Intravesical lidocaine is recommended in many guidelines. While alkalinization increases urothelial penetration of lidocaine and therefore can be expected to improve efficacy, it can also increase systemic absorption and potential toxicity. No studies have directly compared different lidocaine concentrations. Adverse events are typically not serious but may include dysuria, urethral irritation and bladder pain and also the relief is relatively short-term. However, it definitely helps some patients.

Self-administration of intravesical treatment

Self-administration by the patient is a useful option when patients are willing (and able) to undertake this themselves. An advantage is that it gives patients more control over their bladder symptoms and they can have treatment at the moment they need it most.

Why are results with GAG therapy not always successful?

IC/BPS is heterogenous, we may be talking about multiple bladder disorders with multiple causes and therefore some patients may have a “leaky” bladder and other not. Furthermore, the disorder can sometimes be progressive and non-responders may have reached a state where adequate response is no longer possible. Alternatively, the dosing may not be correct: it may not be sufficiently frequent or it may be too frequent giving rise to side effects.

Dr Lovász looked at the side effects of instillation and how to prevent them. The main disadvantage of intravesical treatment is the need for catheterization since side effects are most likely to be caused by the catheter, he said.

Side effects may comprise mucosal lesions, infection, irritation and pain following the instillation since some components of the bladder cocktail may be irritative in some patients. However, there are ways of counteracting this by diluting the solution with isotonic NaCl solution or by adding buffering sodium bicarbonate solution.

With regard to the catheterization problem, Dr Lovász and his team in Budapest have invented a syringe adaptor device. This fits on Luer-lock and Luer-slip syringes and can be used in both men and women. According to Dr Lovász, based on the more than 1000 instillations performed in 110 patients of both genders, it is now possible to state that more than 97% of the patients can be successfully treated by using the catheter-free instillation method. There was certainly great interest in this device in Budapest.

Standardizing terms

It was suggested that the term “responder” in relation to intravesical treatment should be defined and standardized.

Phenotyping

It was also suggested that the different types of GAG layer deficiency should be defined, standardised and phenotyped.

Hunner Lesions

There are huge variations regarding prevalence with some urologists saying they have never ever seen a Hunner lesion and others seeing lesions in over 50% of their patients. The question is then: do all urologists know what they are supposed to be looking for? Many still believe they are looking for true

ulcers. More training and better images of all types of lesion and inflammation is really the only answer.

While each urologist has an own preference for treatment of lesions, pain from lesions can be greatly improved by fulguration/electrocoagulation, laser or resection (surgical removal of the lesion). This treatment needs to be periodically repeated as and when the pain returns. This approach can be combined with other treatments. The corticosteroid triamcinolone has also been shown to be effective for lesions.

Urethral Pain

Urethral pain can vary from a slight burning sensation to severe, intolerable pain, according to Dr Lovász. It can be present independently of urination, making sitting, exercising and sexual intercourse painful or even impossible.

He presented his hypothesis that there is a GAG layer also in the urethra, at least partially. This is based on the fact that:

- Urethral epithelium is histologically similar to the vesical epithelium
- 70% of IC/BPS patients have urethral pain
- GAG replenishment therapy is effective for urethral pain
- The endoscopic view looks similar to the bladder
- Urine can similarly irritate the urethra.

Catheter-free instillation is ideal for GAG layer replenishment in the urethra.

Dr Lovász suggested that a prospective, multi-centre clinical trial should be set up to prove the hypothesis of a compromised GAG layer of the urethra in syndromes presenting with urethral pain.

IC/BPS in men

Professor Robert Moldwin led a session dedicated to taking care of the male IC/BPS patient. Very little has been written about men and IC/BPS in comparison with women. There is a perception that male IC/BPS is rare and male patients tend to be diagnosed with CP/CPPS.

Dilemmas for the male patient include:

- Poor epidemiology
- Lack of awareness
- Confusion (or co-existence) with other pathologies
 - CP/CPPS III
 - BPH
 - UCPPS (IC/BPS OR CP/CPPS)
 - OAB

Males with IC/BPS have been marginalized in terms of epidemiological and clinical studies. As with UTI, every male IC/BPS patient is complicated. There is a significant crossover with other urological conditions. Unique problems are encountered with the male patient, for example with catheter-based therapy. The phenotypic approach is the most practical and patient-friendly.

The Work of the Pathologist: Bladder Biopsies and Clinical Information

Pathologist Dr Christina Kåbjörn Gustafsson from Sweden explained that clinical information and deep bladder biopsies are essential to diagnose classic IC (Hunner lesion) histologically, to separate this condition from other bladder conditions such as non-lesion IC/BPS and also to distinguish it from confusable diseases such as chronic follicular cystitis, eosinophilic cystitis, tuberculous cystitis, metaplastic conditions and carcinoma in situ. This can be done if there is adequate clinical information,

adequate biopsies, several fragments of the detrusor muscle, use of Mab MastCell Tryptase, use of a grid, and of course if the pathologist is aware of the disease!

Dr Kåbjörn Gustafsson gave an example of a pathology report with findings consistent with Hunner lesion:

Microscopically mostly denuded bladder tissue but within saved urothelial no signs of dysplasia. There are areas of ulceration [lesions] with fibrin and inflammatory cells such as neutrophils, and granulation tissue. In the lamina propria, there is edema and severe chronic inflammation. There is both inter- and intrafascicular fibrosis and the number of tryptase positive mast cells in detrusor muscle approximately 65/mm².

Patient Presentations

There were a number of presentations in Budapest from the patient world. Serena Bartezzati, representing both the AICI (Italian Association for Interstitial Cystitis) and UNIAMO (Italian Federation for Rare Diseases), presented a paper by Loredana Nasta on the Prevalence of IC/BPS in Italy. Both of these Italian organizations have been very successful at lobbying authorities and have achieved much, for which we as patients are all very grateful.

The Italian National Institute of Health (ISS) was given the task of setting up a National Registry of Rare Diseases and this includes IC/BPS. In many countries of Europe, IC/BPS is considered a rare disease, while in others and the USA it is not considered rare. However, it is very useful to have it among the rare diseases since drugs for rare diseases receive special priority.

This paper notes that IC epidemiology data are highly inconsistent due to the lack of a shared consensus definition, standard consensus criteria and any valid diagnostic marker. The prevalence of IC/BPS varies from a minimum of 1.8: 10,000 inhabitants up to an estimated 45-50 cases per 10,000 inhabitants. Most studies end with hypothetical estimates.

In 2013-2014, the NRRD collected 1192 patients in a population of almost 61 million. This results in an Italian prevalence of 1.9:100,000 which means that IC/BPS is not a common condition in the Italian population. It is widely agreed that a disease registry is a valuable source of information for epidemiology, to estimate the diagnostic delay and for public health. In the coming years, it will be interesting to evaluate the prevalence pattern of IC/BPS in Italy, in view of a comparison between Italian data and other European Registries.

Jane Meijlink, chair International Painful Bladder Foundation, described how she has seen great changes in the field of patient support, advocacy, empowerment and patient involvement in the field of healthcare in the widest sense since she began in the IC patient movement in 1993. While the basic tasks of a support group for a specific condition have traditionally included:

- raising awareness,
- providing information,
- offering emotional and practical support to patients and their families
- and giving patients the opportunity to have contact with each other.

these have not changed, but the methods used have. Today, the picture has been greatly changed by the rise of the internet which in a relatively short time has given support groups far more possibilities, and provided patients with all kinds of online forums for contact. It has also given patients everywhere access to the websites of groups worldwide, leading to a huge sharing of information. But one of the biggest changes is that the internet has also provided patients with access to medical knowledge and to the latest scientific research into their disorder. Add to this the fact that today many more patients and their advocates are very well educated, and you have the emerging phenomenon of the “expert patient” and the “expert advocate” who are fully up to date with scientific research, and attend medical conferences in their field. This rise of the expert patient is already changing the face of the healthcare world and will likely do so far more in the future. These developments mean that advocacy at all levels is today an important aspect of the work of support groups and their umbrella organizations.

Perhaps the greatest problem and challenge faced by IC support groups is continuity. We have seen a number of support groups started in different parts of the world, she said, only to collapse a few years later because no-one is willing to take over as president when the previous one retires, usually completely stressed out. Perhaps we need a different kind of multi-language, web-based alliance structure to cope with this, she suggested.

Jane Meijlink put in a special plea for ESSIC to take up the new challenges of today, and involve the patient organizations in meaningful, concrete cooperation. This would allow us all to maximize our resources and consequently our impact on the patient, medical and political worlds.

Gail Benshabat from Canada told the very moving story of her daughter Lisa's journey with IC, ending with her death aged only 27 in 2016. A version of this story can be read online at: <https://www.thedialogueprojects.com/blogs/voices/gail-benshabat-in-honor-of-lisa-benshabat> and <https://this.org/2017/04/11/thousands-of-canadian-women-are-dismissed-by-their-doctors-because-of-their-gender/>

SESSION ON ESSIC GUIDELINES: WHAT'S OUT THERE IN 2017 AND WHERE DO WE GO FROM HERE?

A problem today is the difference between Europe, Asia and the USA with regard to nomenclature, definitions and diagnosis and the impact of different diagnostic criteria on studies. The use of different terms can lead to major discrepancies when comparing findings.

How can they be harmonized, is the question? In Europe the name is bladder pain syndrome, or painful bladder syndrome with the EAU reserving the term IC for a subset of patients with verified signs of chronic inflammation extending submucosally. East Asia has an umbrella term: frequency/urgency syndrome which encompasses overactive bladder on the one hand and hypersensitive bladder, painful bladder syndrome and interstitial cystitis on the other, all of which are different, not synonymous. In the USA, the AUA guideline uses interstitial cystitis/bladder pain syndrome (IC/BPS) with no distinction between the two.

However, we ourselves could perhaps add a comment to this that anyone looking at scientific literature will see every terminology variation being used and in conference presentations you will hear the same, plus a tendency for non-Europeans to use IC. While the active global patient support network largely uses IC.

Definitions are also divergent with the East Asians preferring to subtype patients rather than bundle them all together, with hypersensitive bladder as an umbrella term covering patients with or without what the patient considers to be pain but may include pressure, discomfort etc, painful bladder syndrome for patients with hypersensitive bladder with pain and IC reserved for the above plus an abnormal cystoscopy and no confusable disease.

The AUA guideline combines all patients under one heading with a definition referring to an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable cause.

The current ESSIC (and ICI) definition is chronic (6 months or more) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.

We would like to comment here that patients have always had some difficulty with this definition since it makes no mention of a key symptom of IC for well over a hundred years which is “urgency”: an urgent and overwhelming need to urinate. The definition also fails to mention that increased urinary frequency is both day and night which is considered a distinguishing feature.

While diagnostic tests are in the main standard, the use of cystoscopy and biopsy greatly varies, with it being mandatory in some countries and optional in others or only contemplated when conservative treatment has failed. This means that some patients with Hunner lesion may not be receiving appropriate treatment at the earliest possible stage. The cost of the procedure also plays an undoubted role in some countries. An important aspect of cystoscopy is the fact that many urologists still have difficulty in recognising Hunner lesion or even knowing exactly what they are looking for in all its variations. Professor Hanno raised the issue of the inflammatory bladder without lesions: where does this fit into the picture? Glomerulation is now not considered diagnostic, but its cause and significance is still a complete mystery.

(See: Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in Bladder Pain Syndrome - A review. J Urol. J Urol. 2016 Jan;195(1):19-25.)

Where biopsy is concerned, an experienced pathologist with expertise in this field is crucial.

Key issues for discussion by ESSIC with regard to revision of its guideline include:

ESSIC classification system

- Should the classification algorithm eliminate glomerulation?
- Should the classification eliminate Hunner lesion?
- - how do you classify patients with pan-inflammation without isolated Hunner lesion?
- Should ESSIC add other potential phenotypic criteria that are unproven with regard to relevance?
 - o Bladder capacity under anaesthesia
 - o Associated pain syndromes
 - o Pain locations
 - o Response to specific therapies

ESSIC diagnostic algorithm

- Mandate endoscopic evaluation
 - o Local or general
 - o With or without distension

Develop an ESSIC treatment algorithm was one of the suggestions.

An open discussion gave all attendees the chance to express their views. ESSIC plans to set up a working group to look at this.

New: ELMIRON® now authorized for Europe

New is that distribution of Elmiron oral treatment (pentosan polysulfate sodium) on prescription is now authorized in Europe and this will be welcomed by many patients. However, a closer look at the European Medicines Agency (EMA) documentation reveals that the European indication is rather restrictive. The EMA document states: “Elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner’s lesions in adults with moderate to severe pain, urgency and frequency of micturition”. A complicating factor is that glomerulations are

no longer considered to be a reliable diagnostic criterium, so this will only leave Hunner lesion as an indication.

The EMA assessment reports can be found at

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004246/human_med_002103.jsp&mid=WC0b01ac058001d124.

The FDA indication in the USA, on the other hand, states that “ELMIRON® (pentosan polysulfate sodium) is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis.” In other words, a wider indication.

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