

**REVIEW OF THE 4TH INTERNATIONAL CONSULTATION ON
INTERSTITIAL CYSTITIS JAPAN (ICICJ) AND THE ANNUAL MEETING
OF THE SOCIETY OF INTERSTITIAL CYSTITIS OF JAPAN (SICJ),
17-18 APRIL 2018, KYOTO, JAPAN**



This 4th ICICJ conference marked 15 years of the International Consultation on Interstitial Cystitis Japan (ICICJ) and 17 years of the Society of Interstitial Cystitis of Japan (SICJ). The 1st ICICJ was held in Kyoto in 2003, followed by 2007 and 2013. This 4th edition was likewise held in Kyoto. The driving force behind these successful international meetings in Japan is Dr Tomohiro Ueda and we would like to thank him and his organizing team for their tremendous efforts in getting this conference off the ground.

The conference was attended by experts from some 14 countries, as well as many eminent urologists from the host country Japan. Participants also included patient representatives (including 3 from Europe who were among the speakers), representatives from the Pharmaceutical industry, and from the United States Food and Drug Administration (FDA). A truly multi-stakeholder meeting. Although the theme this year was “Hunner Lesion”, the conference took a critical look at the current situation in the whole field of IC/BPS/HSB and the problems we face today in the widest sense, not least of all the very concerning financial situation.

Please note: the proceedings of this meeting will be published in a special open access supplement of the International Journal of Urology (IJU) either at the end of this year or the beginning of next. This review is therefore just a brief look at some of the main points.

MONDAY 16 APRIL: CLOSED BRAINSTORMING CONSULTATIONS

The 2-day conference on 17 and 18 April was preceded on 16 April by an afternoon of special closed “brainstorming” consultations held at the traditional Japanese Yoshida-Sanso venue. Over 30 invited participants were split into 4 workshops:

- A. Pathophysiology
- B. Phenotyping
- C. Hypersensitive bladder and IC/BPS
- D. Hunner lesion and non-Hunner lesion

TUESDAY 17 APRIL – KYOTO INTERNATIONAL CONFERENCE CENTRE

In his opening presentation on the first day of the meeting on 17 April held at Kyoto International Conference Centre, attended by some 90 enthusiastic delegates, Dr Ueda noted that there are probably still many patients around the world with IC/BPS/HSB but no diagnosis. He pointed out that there are still few placebo-controlled studies demonstrating the efficacy of drugs and also stressed that our mission is to develop an accurate diagnostic method and an effective method of treating IC in all its shapes and forms.

The workshop chairs from the previous day's expert consultations then reported back with their workshop summaries, each of which was followed by a lively interactive discussion.

WORKSHOP A. PATHOPHYSIOLOGY

Professor Lori Birder from Pittsburgh was the first speaker, presenting the findings of Workshop A on the pathophysiology of IC, noting that IC/BPS – a chronic disorder involving symptoms of urgency/frequency and pain – is sometimes described as two separate disorders: IC which is a chronic inflammatory disorder and BPS which may often lack an inflammatory component. Peripheral as well as central abnormalities have been reported which may suggest either a top down or a bottom up hypothesis, although in reality it is probably a mixture of the two, she said. The speaker outlined the pros and cons of the many different animal models. When inducing disease in otherwise healthy animals, it is limited to demonstrating a bladder and nervous system response to chemicals. Healthy animals appear to return to normal when the stimulus is removed. Experimental models have shown that stress induces and maintains hyperalgesia by enhancing effects of pain producing substances. A problem is that the diagnosis of most bladder disorders is symptom-based, while their pathophysiology remains controversial and incompletely understood.

Findings from animal models have revealed defects in the urothelial layer. When the barrier is compromised beyond repair, it allows toxic substances to permeate the underlying tissues. Noting that the urothelium is the first line of defence against pathogens and irritative substances, she said that the urothelium is more than simply a barrier and that sensory functions may be a target for multiple therapies.

New evidence reveals that the human urinary tract has a diverse microbiome and that alterations in the urinary microbiota have been linked to urologic diseases.

Chronic stress can certainly exacerbate painful symptoms.

Asking whether we can improve the barrier function of the urothelium, ultimately affecting sensation, Professor Birder noted that intravesical therapies have less systemic toxicity and can be used to improve treatment of a dysfunctional bladder. However, multimodal treatment targeting both peripheral and central levels may be needed for maximum efficacy in chronic pain.

In the lively interactive discussion following this, Dr Lovasz from Budapest pointed out that many guidelines do not even mention the urethra, whereas many patients suffer greatly from urethral pain. Professor Birder noted that the protective cells in the urethra can easily be damaged by catheterization. Professor Homma added that urethral pain is also a big problem in male patients and particularly frustrating for the patient. This underlines, he said, that we should not simply focus on the bladder but the whole lower urinary tract, while Professor Hanno then noted that in male patients pain at the tip of the penis could sometimes be referred pain from the neck of the bladder.

WORKSHOP B. PHENOTYPING

The findings of this group were presented by Professor Philip Hanno who began by looking at the definition of the term phenotype. The term phenotype refers to the observable physical properties of an organism, including the organism's appearance, development and behaviour.

Proving the utility of a phenotype is a critical step because early adoption of unproven phenotypes in a clinical setting is not helpful, he said. In order to be useful in relation to a disease, a phenotype should improve diagnosis, prognosis, treatment selection, prevention, pharmaceutical research and

suggest new treatment pathways. Phenotyping may hold the key to improving treatment outcomes and facilitating research.

Conclusions from this workshop:

Hunner lesion is a valid phenotype but why is Hunner prevalence so variable?

Should the appearance (cystoscopic definition) be standardised to images of Hunner lesions prior to bladder distension?

Hunner lesion is the most important finding as it determines treatment strategy.

There was general agreement that Hunner lesion is a disease and not just a phenotype.

Hunner lesion etiology may be multifactorial and it may itself have phenotypes within the designation, i.e. there may be different types of Hunner lesion.

It was felt by one participant that pain may be a phenotype itself in patients with frequency, urgency and nocturia. Bladder capacity might be another phenotype, possibly differentiating patients with bladder centric and non-bladder centric disease. Voiding dysfunction and pelvic floor dysfunction may define another phenotype. Presence of somatic syndromes also. While glomerulation is not a phenotype, its severity may be important in prognosis.

This workshop felt that an international patient registry would perhaps help find answers. Furthermore, a great deal of data has been collected in different parts of the world and it would be very valuable to collect this together. However, this is difficult if there is no international standardization.

WORKSHOP C. HYPERSENSITIVE BLADDER AND IC/BPS

Professor Yukio Homma from Tokyo presented the summary of the workshop on hypersensitive bladder.

For the sake of clarity, the following terms and abbreviations are used in East Asia:

HSB – Hypersensitive Bladder

IC – Interstitial Cystitis

HIC – Hunner type IC

NHIC – Non-Hunner type IC

MBAD – Mucosal bleeding after distension

Professor Homma noted that it is becoming increasingly evident that Hunner lesion (HIC) is a distinct disease with characteristic cystoscopic findings and dense inflammation associated with B-cell clonal expansion. HIC should be separate from/not combined with other conditions with similar symptoms such as BPS.

The East Asian guideline, updated in 2016, defines IC and hypersensitive bladder but does not use symptom syndromes (BPS and PBS). Hypersensitive bladder was defined here as a disease of the bladder with HSB symptoms (pain, discomfort or pressure usually associated with increased urinary frequency) in the absence of obvious pathology. Interstitial cystitis (IC) is defined as a disease of the bladder with HSB symptoms in the presence of bladder pathology (Hunner lesions or mucosal bleeding after distension (MBAD)).

Professor Homma said that the multiple terms and combinations of terms being used around the world are not only confusing but also often inaccurate. He quoted the ICS definition of syndrome which states that “syndromes... cannot be used for precise diagnosis. ...are functional abnormalities...” BPS or PBS cannot therefore be an umbrella term including disease, he said. Common issues for HSB and BPS include the fact that they are not a diagnosis for which insurance reimbursement is made.

He concluded by proposing that:

- HSB is a symptom-alone condition with painful and non-painful symptoms
- BPS is a condition with symptoms but without IC or other obvious disease.

WORKSHOP D. HUNNER LESION AND NON-HUNNER LESION

This workshop summary was presented by Professor Magnus Fall from Sweden who explained that the situation is complex and data available are neither clear nor coherent.

Questions include: how often is a diagnosis of Hunner lesion missed and are additional diagnostic tools needed for assessment conformity? Classic IC with Hunner lesions is an entity with typical features and has a more favourable response to specific treatments than non-lesion disease.

There was a discussion as to whether hydrodistension is necessary to diagnose Hunner lesions or whether an office cystoscopy without hydrodistension is sufficient. Professor Fall's view was that while in the majority of cases Hunner lesions can be recognized without hydrodistension, some cases may be missed.

Professor Whitmore added that since we do not know what percentage of lesions are not visible without hydrodistension under anaesthesia, it would be difficult to validate not using anaesthesia.

The group had looked at Narrow Band Imaging (NBI) for identification of Hunner lesion and had found that bladder lesions are easily and clearly recognized by NBI (in comparison with conventional white light).

Glomerulation and/or mucosal bleeding is not a type of lesion, it may be a question of urothelial fragility and may later prove to be a specific phenotype. But we do not yet know, said Professor Fall.

Genetic Modulation of Chronic Pelvic Pain Symptoms – speaker David Klumpp

USA researcher David Klumpp noted that while genetic susceptibility to IC has long been postulated, genetic modulators of pelvic pain are not well characterized.

Interstitial Cystitis/Bladder Pain Syndrome/Hypersensitive Bladder: Worldwide Confusion! What has gone wrong and how can we put it right for the sake of the patients? – speaker Jane Meijlink, International Painful Bladder Foundation, Netherlands

IPBF Chair Jane Meijlink pointed out that patients are confused, doctors are confused, pharma companies are confused and unfortunately the all-important health, regulatory, and insurance authorities are also confused. There are multiple guidelines, standardization documents, classifications, taxonomies with different nomenclature and definitions from all the different medical societies and while all may overlap and have similarities, they are not the same. Unfortunately, the fact that each society is convinced that its way is the right way means that there is no international consensus. This is damaging for research, for international data sharing and comparing, and ultimately for proper treatment for the patient. Because treatment trials have produced conflicting data, health and regulatory authorities are refusing to approve and reimburse treatments. We now need an international plan, she said, to determine how to proceed further to achieve real international consensus and real progress to help the real patients and ensure that every patient has affordable access to the best possible treatment. The complex problem of non-reimbursement has to be seriously tackled at the highest levels and not simply left to the patient and/or support groups to deal with.

Immunological mechanisms of BPS/IC/HSB - speaker Tomohiro Ueda, Japan

It is not clear whether bladder epithelial damage and GAG abnormalities are the cause or result of BPS/IC/HSB.

Pathophysiology of IC with or without Hunner lesion – speaker Akira Furuta, Japan

Significant inflammation in urine specimens and bladder tissues was confirmed in both HIC and NHIC patients compared with controls.

Subtyping and Phenotyping of Interstitial Cystitis and Bladder Pain Syndrome – speaker Yoshiyuki Akiyama, Japan

Dr Yoshiyuki Akiyama from the University of Tokyo emphasized that there are no internationally standardized terminology, definitions, diagnostic criteria or classification systems. There is no shared disease concept in the world. Furthermore, he said, any distinction between the subtypes has been downplayed. Looking at the UPOINT system, he noted that this system does not differentiate the Hunner lesion subtype.

Role of urinalysis in the diagnosis of IC – speaker Atsushi Sengiku

Patients with IC are routinely examined with urinalysis. While this is useful to confirm UTIs, it is not sufficient for the diagnosis of IC. Cystoscopy is recommended, regardless of the results of urinalysis.

Effects of GO-SHAKU-SAN for bladder pain syndrome – speaker Yuki Sekiguchi, Japan

KAMPO is a traditional Japanese form of treatment. Derived from traditional Chinese medicine, it was introduced into Japan around the 7th century. Today it is mainly concerned with herbal medicine and is integrated into the Japanese national health care system. Go-shaku-san is an anti-inflammatory and analgesic treatment traditionally used for gastrointestinal disorders. This study tried it for urological and pelvic pain with some success.

Low bladder capacity is an important predictor for comorbidity of IC with Hunner lesion in patients with refractory chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) – speaker Masakatsu Ueda, Japan

This study concluded that in refractory CP/CPPS patients, performing NBI-assisted urethrocytoscopy should be considered, especially when their voided volume is low.

The IC Care Provider in Taiwan – IC/BPS/HSB need BPS model – speaker Ming Huei Lee, Taiwan

There is a close working relationship between the patient organisation TICA (Taiwan Interstitial Cystitis Association) and the medical professionals who operate in a multidisciplinary care team. Dr Ming Huei Lee discussed the advantages of a “telecare” system in patients with chronic diseases. It can increase the patient’s compliance with treatment, make the patient aware of factors that may trigger a flare and promote the active involvement of the patient in disease management. All of this can lead to a reduction in the number of visits to the doctor/hospital and consequently in the cost of management. The e-health system was developed to help change the lifestyles of patients and manage their condition. The video-based m-health (mobile health) system is aimed at alleviating symptoms and improving quality of life.

25 years ICA-Deutschland – speaker Barbara Muendner-Hensen, ICA-Deutschland

Germany is one of the largest countries in Europe and its patient association, founded in 1993, led the way in Europe, organizing seven international congresses attended by medical professionals and patients from all over Europe, thereby playing a huge role in raising awareness at all levels. Since 2009, the ICA-Deutschland has been carrying out a survey on the care situation for IC patients using a comprehensive questionnaire and the results were presented here by Barbara Hensen. While there is a large range of treatment options available in Germany, treatment needs to be individually tailored per patient and multimodal treatment is usually the best option. Multidisciplinary centres are the ideal way to treat these patients who may have multiple comorbidities. Since 2017, the ICA-Deutschland has been certifying centres for IC and pelvic pain.

Understanding Interstitial Cystitis – speaker Juergen Hensen, ICA-Deutschland

Juergen Hensen looked at the consequences of confusion regarding nomenclature since it is ultimately always the patient who suffers with no reimbursement of treatment for patients with the diagnosis of “interstitial cystitis”. A specific major concern is that this confusion is resulting in inaccurate “indication” for drugs by the relevant drug authorities. The speaker gave the example of the recent

EMA approval of Elmiron in Europe but with an indication which makes it unprescribable and non-reimbursable for the very patients for whom it is most suited.

Bladder pain syndrome: World Guidelines and Harmonization – speaker Philip Hanno, USA

At the present time, there is still little or no agreement worldwide. Professor Hanno took a look at the different guidelines, diagnosis, glomerulations, Hunner lesion and the difference between CP/CPSS and IC/CPSS. He noted that the clinical characteristics which define CP/CPSS are similar to IC/BPS. The diagnosis of IC/BPS should be strongly considered in men whose pain is felt to be related to the bladder. Both conditions can occur together and treatment should reflect this.

Professor Hanno also reported that at the end of 2017 the FDA (USA Food & Drug Administration) Advisory Committee had voted unanimously in favour of combining patients with and without Hunner lesions in clinical trials. This initially seemed rather difficult to follow since everyone else had been urging precisely the opposite and recommending phenotyping and subtyping as a matter of urgency for clinical trials. Global harmonisation then still seems quite a long way off! However, more details can be found in the commentary paper: *Nickel JC, Moldwin R. FDA BRUDAC 2018 Criteria for Interstitial Cystitis/Bladder Pain Syndrome Clinical Trials: Future Direction for Research. J Urol. 2018 Feb 13. pii: S0022-5347(18)30208-8. doi: 10.1016/j.juro.2018.02.011. [Epub ahead of print] PMID: 29452126*

GYN associated disorders and management – Kristene Whitmore, USA

Professor Kristene Whitmore from Philadelphia looked at all types of chronic pelvic pain, noting that it is often complex and difficult to treat. Furthermore, in 30% of cases, no cause is ever determined. This presents a huge challenge for the doctor with regard to treatment.

The importance of histopathological evaluation to diagnose Hunner's disease, BPS/IC type 3C – speaker Christina Kabjorn-Gustafsson, Sweden

Pathologist Christina Kabjorn-Gustafsson from Gothenburg, Sweden who has had many years of experience in the field of IC and Hunner lesion said that it is possible to histologically diagnose Hunner lesion (also known as Classic IC or Hunner's disease or ESSIC Type 3C) and separate it from other cystitis with similar clinical symptoms.

Interactive audience discussion with a panel and audience to discuss FDA perspectives, problems in BPS diagnosis and treatment with case presentations.

Panelists: Rajesh Tanja, India, Sandor Lovasz, Hungary, Michael Pontari, USA and Debuene Chang, USA

Dr Debuene Chang, representing the USA Food & Drug Administration (FDA), looked at the worldwide differences in the rates of Hunner lesion. In the USA this varies from 3-20%, with some USA clinicians even doubting its existence, while European and Asian clinicians publish rates 30-57%. What is the reason for this?

There are also worldwide differences in cystoscopy with hydrodistension. Countries and regions with high rates of cystoscopy with hydrodistension (e.g. Asia, Sweden/Scandinavia, Russia) report the highest rates of Hunner lesions. In the USA, cystoscopy + hydrodistension is not widely practiced in many clinical centres as the widening target patient population no longer requires bladder findings to be included in the diagnosis for treatment. So, does cystoscopy + hydrodistension lead to higher detection rates of Hunner lesion?

Hunner lesion cannot be distinguished from non-lesion by signs and symptoms alone. Specific therapies are available for Hunner lesion. Is the lesion type a distinct population, she asked?

WEDNESDAY 18 APRIL – KARASUMA KYOTO HOTEL

Conference day 2 was held at the Karasuma Kyoto Hotel and included the SICJ Joint Seminar.

Future projects and meetings of the INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS JAPAN (ICICJ) – speaker Tetsuji Asao, Japan

Dr Asao emphasized that it is very important to secure a sound financial basis for organizing periodic international ICICJ meetings. It has been becoming increasingly difficult to continue organizing the meeting, he said, due to difficulties faced in fund raising, particularly support from industry. This funding problem was also an issue raised by other speakers, and in informal talks throughout the meeting.

He explained to us that the International Consultation on Interstitial Cystitis Japan (ICICJ) was formally registered as an incorporated association in April 2016. The mission and purpose of ICICJ, he said, was to “harmonize an ambitious, effective, efficient, comprehensive and practical definition diagnosis of IC through the ICICJ meetings and to accelerate development of novel therapies for the treatment of an unmet medical need through translational research”. The activities of this association include organizing and hosting periodic international ICICJ meetings, research and development of diagnosis and a novel drug for treatment of IC, global collaboration in research for IC, maintenance and management of the intellectual properties which the Association may have and all matters relating to the conduct of business related to the above. Its financial basis will include membership fees with both individual members and corporate members, government grants, donations, business, consulting and a clinical trial network.

Urothelium and cell-cell interactions – speaker Lori Birder, USA

Professor Lori Birder explained that the urinary bladder consists of 3 main layers: the mucosa, the muscularis propria and the adventitia/serosa (external). The urothelium is a type of epithelium which allows the bladder to expand and contract. One of its functions is as a barrier to prevent toxic elements penetrating the bladder wall. In addition, the urothelium has sensory functions. Chronic inflammation or injury can disrupt the mucosal barrier and subsequently alter the ability of the urothelium to act as a barrier and lead for example to increased permeability and decreased ability to repair as well as bladder instability, hyperactivity and altered sensations. Professor Birder suggested that both physiological and psychological stress may result in failure of urothelial and sub-urothelial defence systems, thereby promoting changes that could trigger urgency, increased frequency and pain during bladder filling and voiding.

Pain phenotypes of bacteria in the bladder – speaker David Klumpp, USA

The fact that many IC patients have a history of urinary tract infection led Klumpp and colleagues from Chicago to examine mechanisms of pain of bladder infection using a mouse model.

Quantitative histological analysis of interstitial cystitis: a novel approach to elucidate IC pathophysiology – speaker Yoshiyuki Akiyama, Japan

Quantitative analysis-based histological characterization of IC/BPS was carried out to clarify the distinct histology between IC subtypes for further investigation of the pathophysiology. It was concluded that Hunner IC and non-Hunner IC manifest distinct histology.

Minimally invasive device for intravesical instillations (MID-ii) for catheter-free drug delivery into the bladder – speaker Sandor Lovasz, Hungary

Intravesical instillation of various therapies or cocktails using a catheter is a common and very effective way of treating IC/BPS. It has a high local drug concentration, a low rate of systemic side effects, and drugs penetrate the bladder wall by passive drug diffusion (can be enhanced by various techniques). It is possible to standardize the whole process. Some of the drugs adhere to the surface of the mucosa, remaining efficacious for a longer time. However, many IC/BPS/HSB patients also suffer from pain or tenderness in the urethra (according to Dr Lovasz around 70%) and catheterization can trigger more pain, superficial lesions and even bleeding. This may lead them to refuse this type of treatment. Dr

Lovasz and his team have therefore invented a syringe adapter – the MID-ii - with a special drip-free collar which can be attached to Luer-lock and Luer-slip syringes and used instead of a catheter. It avoids irritation of the urethra and at the same time ensures that the treatment reaches not only the bladder but also the urethra. Can be successfully used in the majority of patients, both males and females. Patients can benefit from local drug delivery without the disadvantages of urethral catheterization.

The quantitative sensory testing in phenotyping patients with chronic pelvic pain – Andrei Zaitcev, Russia

The aim of this study from Russia was to determine the possibilities of a method of quantitative sensory testing in phenotyping patients with chronic pelvic pain (CPP) which allows evaluation of A-delta and C-fibers. They found that this method presents a combination of a quantitative method and a physical examination suitable for both research and clinical applications. Phenotyping patients into similar groups can be used clinically to assess prognosis, evaluate potential treatments or suggest further diagnostic evaluation.

SICJ JOINT SEMINAR I

SICJ – State of the Art – Yukio Homma, Japan

SICJ – the Society of Interstitial Cystitis of Japan (<http://sicj.umin.jp>) – was established 17 years ago in April 2001, making it most probably the oldest medical society worldwide specializing in IC. It started with just 4 members, but currently has around 160, said Professor Homma. SICJ forms the core of clinical and research activity into IC and related conditions in Japan.

In 2002, the society organized a satellite symposium on IC at the 90th Japanese Urological Association (JUA) Congress and it also published a book on IC for both physicians and patients. Its first annual meeting was organized in the same year and this year marks the 17th meeting of SICJ.

In 2003, 2007, 2013 and 2018, SICJ supported the International Consultation on Interstitial cystitis in Japan (ICICJ) in Kyoto and in 2016 organized a workshop on IC during the 46th International Continence Society Annual Meeting held in Tokyo.

The first Clinical Guideline for Interstitial Cystitis in Japanese was published in 2007, followed in 2009 by the Clinical Guideline for Interstitial Cystitis and Hypersensitive Bladder co-worked with Korean and Taiwanese urologists and known as the East Asian Guideline. The guideline was updated at the end of 2015 (Int J Urol. 23: 542-9, 2016). In 2013, a national survey on the clinical practice of IC was carried out (Transl Androl Urol. 4:486-490, 2015).

In 2015 a major step was achieved with the approval of IC as an intractable disease by the Japanese Ministry of Health and in 2017 a patient registry system was set up, supported by the Ministry.

Professor Homma then looked at the terminology and definitions being used by Japan, Taiwan and Korea. They use two terms: interstitial cystitis (IC) and hypersensitive bladder (HSB). They do not use the symptom syndromes PBS or BPS.

Hypersensitive bladder is symptom-based with pain, discomfort, or pressure (i.e. without or without pain) related to the bladder usually associated with increased urinary frequency in the absence of obvious pathology.

Interstitial cystitis is a disease of the bladder with HSB symptoms in the presence of bladder pathology (Hunner lesions or mucosal bleeding after distension (MBAD)).

There are currently 3 categories in East Asia: HSB, non-Hunner type IC and Hunner type IC. However, Professor Homma put forward a proposal for consideration for a possible new East Asian classification divided into just 2 main types to bring this in line with IC/BPS.

Professor Homma discussed the issue of glomerulations, and said he agreed with the article by Wennevik et al, 2016 (*Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in*

Bladder Pain Syndrome – A review. J Urol 2016 Jan 01;195(1)19-25) saying that there is indeed no convincing evidence that glomerulation should be used diagnostically, but emphasized that, since the biological explanation and the clinical meaning are still unknown, it would be wise to document glomerulation and mucosal bleeding after distension (MBAD) until its biology and clinical significance have been elucidated. The data could prove useful in the future when it is better understood.

He also noted that there is often confusion between glomerulation and mucosal bleeding after hydrodistension (MBAD):

- Glomerulations = small petechiae/submucosal hemorrhages after hydrodistension
- MBAD = mucosal bleeding after hydrodistension during emptying. Also known as waterfall, weeping bladder etc.

While they are not identical, Professor Homma suggested that they probably refer to the same phenomenon.

Dr Nagendra Mishra from India emphasized that a thorough study is needed to look into glomerulation.

Like previous speakers, Professor Homma noted that a bladder with Hunner lesions is a distinct disease and should stand alone.

SICJ JOINT SEMINAR II

How to perform hydrodistension of the bladder for treatment of interstitial cystitis with Hunner lesions. A procedure in our clinic that we learned from failure – Masaharu Nanri, Japan

This presentation led to a discussion about biopsy and distension, with the experts stressing that biopsy should not be performed before hydrodistension since there is a risk of perforation. The authors felt that fulguration of lesions may be safer than TUR.

Cystoscopic diagnosis in female patients – Atsushi Sengiku, Japan

This presentation took a look at different videos and once again the urgent need for a comprehensive atlas was stressed by everyone. Dr Sengiku noted that NBI-assisted cystoscopy is useful for easy and clear identification of abnormal vascular changes on the urothelium.

Cystoscopic diagnosis in male patients – Masakatsu Ueda Japan

Dr M. Ueda suggested that Hunner lesions are more common in male patients.

Optimizing results of Interstitial Cystitis/Bladder Pain Syndrome – Nagendra Mishra, India

Dr Mishra emphasized that their experience in India has shown that a meticulous approach to IC/BPS results in a very good patient outcome. The average follow-up was 20 months.

Intravesical Tacrolimus in Intractable Interstitial Cystitis/bladder pain syndrome: our experience – Nagendra Mishra, India

The purpose of this pilot study was to discover if tacrolimus dissolved in DMSO or sterile water instilled in the bladder is effective in the treatment of IC/BPS without side effects. 14 of 24 patients showed an improvement. Other than post-instillation symptoms flares, no side effects were observed. He noted for the first time that although tacrolimus is believed to be insoluble in water, it is nevertheless absorbed by the urothelium. He felt that it should be offered to patients before contemplating surgery.

Patch cystoplasty in refractory interstitial cystitis/bladder pain syndrome – Nagendra Mishra, India

Patch cystoplasty was performed in a small group of patients with refractory IC/BPS at this centre in India. It was found to be a safe and effective treatment, even in long-term follow-up.

Clinical presentation of IC/BPS patients with and without Hunner lesions – Jos Houbiers, The Netherlands

This study data was presented by Dr Jos Houbiers, Executive Director in Global Medical Science at Astellas Pharma Global Development. 286 female patients from 60 sites in 12 EU countries were included in a randomized, controlled drug trial. Disease characteristic were compared between those with and without Hunner lesion. Disease severity was found to be worse in HL+ compared to HL-. Interestingly, no evidence of a relationship between pain and glomerulation was found. The research is continuing and it is planned to test urine samples of the same sub-populations for microbiome composition and whole genome gene expression profiling/TRDA/RT assays.

What is to be expected in the treatment of IC/BPS in the future? – speaker Hikaru Tomoe, Japan

Professor Hikaru Tomoe from Tokyo Women's Medical University Medical Center East reviewed the current situation of treatment.

She noted that while transurethral resection (TUR) or coagulation (TUC) is recommended and has a clear effect, recurrence is probable and there is a risk of serious complications. Non-surgical treatment is desirable wherever possible.

As emphasized by many speakers in Kyoto, the situation with clinical trials currently leaves much to be desired. Professor Tomoe said there is a need for prospective, randomized double-blind controlled studies with a large sample size, no selection bias and long-term follow-up.

She stressed that IC/BPS needs to be classified with or without Hunner lesions.

There is a need for standardized treatment evaluation.

What tendencies are to be expected in the treatment of interstitial cystitis/bladder pain syndrome in the future? – speaker Sandor Lovasz, Hungary

Extensive research by urologists and increasing awareness raised by patient organizations has led to a steadily increasing growth in the number of patients diagnosed with IC/BPS. GAG-layer replenishment therapy is proving effective, he said, and particularly in the form of instillations which are likely to play a determining role in the treatment of IC/BPS.

With lack of reimbursement, the cost is going to be high. We do not have adequate information on the cost of IC treatment, which varies significantly between different countries, depending on the medication used and different treatment protocols, he said.

Local bladder instillation is long-lasting but a great expense to the patient, preventing many of them from receiving treatment. There are countries where social insurance does not cover the cost of any IC/BPS treatment and an even higher percentage of patients are unable to afford instillation treatment. In Germany, for example, 40% of the patients had to stop treatment due to financial problems.

This means that there will need to be more self-instillation and consequently IC/BPS centres should organize courses to teach patients how to do this themselves in their own homes. They need to learn about catheterization, catheter-free instillation technique, a basic knowledge of sterility etc. Treatment has to be more patient-focused and pharmaceutical companies need to develop ready-to-use, pre-filled, patient-friendly syringes with cocktails of the optimal drug composition. Personal contact with the doctor and treatment follow-up can be maintained using internet software (see for example <http://bladderpain.eu>) which will also be a time- and cost-saving option for patients with limited financial resources.

Dr Lovasz is critical of the fact that guidelines all begin with non-invasive treatment which is likely to be relatively ineffective, while intravesical therapy may be more effective with a lower risk of systemic side effects and can be adapted to the individual patient's needs. However, good clinical trials are urgently needed, he emphasized, since we do not yet know the optimal timing and dosage of instillations and this may even be leading to overtreatment.

Dr Lovasz concluded by saying: "the future is approaching, let's get prepared for it!"

Conclusions and discussion points

This conference and consultation was particularly lively and interactive. The many discussions after each presentation revealed not only a lack of consensus worldwide on terminology and definitions but also a lack of internationally standardized diagnostic procedures. For example, office cystoscopy versus hospital with anaesthetic and hydrodistension was extensively debated. Is hydrodistension under anaesthesia necessary for diagnosis of lesions? Can hydrodistension actually cause harm? But if we don't do hydrodistension, will we miss specific lesions? More research is needed.

A pre-conference survey of participating clinicians by Dr Nagendra Mishra showed that there is little agreement on anything and that this underlined that guidelines are not clear and have their own biases. It is evident, he says, that there is a need to draw up an international guideline.

While on the one hand treatment is likely to be a local issue and dependent on culture as well as what is available, on the other hand terminology, definitions, diagnostic criteria and basic diagnostic methods are not local issues. International collaboration in research is dependent on consensus.

It was realized by all that clinical studies have to be improved with the aim of achieving reliable and comparable data.

Attention was drawn by the patient advocates to the lack of reimbursement and consequent lack of access to treatment by patients. This was strongly picked up by many other speakers and it was agreed that something has to be done to sort out this problem with the regulatory authorities. The best treatment in the world is of little use if it is unavailable and/or unaffordable.

Good clinical studies with evidence are essential. Without them there is neither approval nor reimbursement. Phenotyping and subtyping are essential elements here to try to ensure homogeneous study groups. There is likewise an urgent need for standard nomenclature and standard definitions of that nomenclature. This is vital in an electronic world. While valuable research is being done at many centres, the lack of internationally accepted standard criteria makes it difficult either to compare data or to organize the large trans-border, multi-centre studies and clinical trials which are now required.

Another aspect discussed extensively was the worldwide shortage of funding for IC/BPS/HSB at all levels. How do we tackle this?

We also have to ensure that IC/BPS/HSB stays on/returns to the agenda of the urological societies!

It was clear that a great deal of time and effort is now needed to cover some of the many issues, controversies and confusion worldwide. In order to be able to achieve any solutions and the urgently needed international consensus which should form the basis of clinical studies, it is also evident that not only is structured global collaboration needed, but also – most importantly - a willingness to do this. Without this, there will be no progress and it will ultimately be the patients who suffer. For the sake of the patients, something has to be done and quickly. As Dr Lovasz said: we must prepare for the future!

Jane Meijlink

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