REVIEW OF THE VIRTUAL ANNUAL MEETING OF THE GLOBAL INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SOCIETY (GIBS), INDIA, 5 & 6 SEPTEMBER 2020

Virtual meetings and conferences allow far more health professionals and patient advocates to participate than a face-to-face conference. And this 2-day virtual meeting of GIBS, in cooperation with the Urological Society of India (USI), was no exception. With many participants from countries worldwide, it was a global virtual event and an ideal way of educating a maximum number of people, including patient advocates. It was also multidisciplinary with urologists, gynaecologists and other specialists and therapists speaking, including a number of well-known international experts from ESSIC. Participants were able to submit written questions both in advance and during the meeting online and this led to lively panel discussions.

This review looks at just a few highlights of this 2-day virtual meeting.

Dr Sanjay Pandey, urologist and Organizing Secretary of GIBS, introduced the conference on the 1st day by emphasizing the problems faced by GIBS when it was first set up in 2015 and still faced today by both doctors and patients: the true global prevalence of IC/BPS is unknown, it has a significant impact on the patient's quality of life, it is under-reported, under-diagnosed, under-studied and under-treated.

Dr Amit Agarwal, speaking on What is new in IC/BPS, was the first of many speakers to say how immensely confusing it is to have so many terms and definitions for this condition. GIBS opted for the following definition: *"Pain/discomfort in the lower abdomen and/or urogenital area of more than 3 months duration, usually worse with a full bladder, associated with one or more lower urinary tract irritative symptoms such as frequency, urgency, nocturia, with/without standard stigmata on cystoscopy, provided that other identifiable pathology likely to cause the symptoms has been excluded."*
Looking at the evidence of inflammation, Dr Agarwal discussed the possible role of inflammasomes which are cytosolic multiprotein oligomers of the innate immune system responsible for the activation of inflammatory responses. Recent studies, however, indicate high levels of inflammasome component expression in epithelial barrier tissues, where they have been shown to represent an important first line of defence (see https://en.wikipedia.org/wiki/Inflammasome). The speaker noted that the most studied inflammasome is NLRP3. This could potentially lead to targeted therapies in his view. He (and many speakers to follow) underlined the inconsistencies in guidelines regarding cystoscopy with some societies recommending it as a mandatory part of the initial evaluation while others (AUA and ICI) suggesting it is optional and should only be performed if another pathological process is suspected.

Professor Jean-Jacques Wyndaele from Belgium, President of ESSIC, looked at the issue of GAG replenishment, asking: can GAG replenishment work, is there a rationale for using it, does a GAG layer exist, can a deficiency cause IC/BPS and is replenishment possible? Indeed, it does exist, he said. The bladder lining (urothelium) is covered by a glycosaminoglycan (GAG) layer whose natural constituents include hyaluronic acid (also known as sodium hyaluronate or hyaluronan)), chondroitin sulfate, heparin sulfate/heparin, keratan sulfate and dermatan sulfate. The GAG layer forms a barrier that

protects the underlying tissue from urinary toxins and pathogens. Disruption or deficiency of the GAG layer allows toxic elements to penetrate the bladder wall, causing pain and inflammation. The pathophysiology of IC/BPS involves epithelial dysfunction. GAG replenishment has been shown to work in animal studies. Clinically it can be done either intravesically or orally. PPS can be used either orally or intravesically. Sub-cutaneous heparin can be added to increase the effect. Intravesical treatments include hyaluronic acid, chondroitin sulfate, combinations of these, DMSO and PPS as well as many cocktails. Heparin is often used as a cheaper alternative. Professor Wyndaele emphasized that intravesical treatment can play an important role in management of IC/BPS today. A problem has been that different studies have given different results, once again underlining the need for subtyping.

Gynaecologist Dr Tanvir Singh emphasized the importance of taking a comprehensive history for each IC/BPS patient. Diagnosis is based on symptoms and exclusion. Symptoms include pain related to the bladder, urinary urgency and frequency, pain on filling, dyspareunia, there also may be anal discomfort, multiple triggering factors (diet, stress, certain activities) and failed treatment for other suspected diseases. Exclusion in India particularly has to include stone and tuberculosis. Cystoscopy is mandatory to exclude other conditions and to diagnose Hunner lesion. She also stressed the importance of a bladder voiding diary. There are many associated and overlapping disorders. This means that a multidisciplinary approach is essential.

Dr Amit Shah noted that many patients are being wrongly diagnosed as recurrent urinary tract infection. Phenotyping is important and treatment can be targeted to the phenotype. Multimodal treatment is likely to be needed. Dr Shah discussed heparin and lidocaine. Heparin is a sulphated GAG believed to replenish the urothelial GAG layer. It also acts as an anti-inflammatory, inhibits fibroblast proliferation and promotes angiogenesis and smooth muscle cell proliferation. Lidocaine is a topical anaesthetic and is used either as a single-agent instillation or – more commonly – in combination with heparin or other instillations. It is given in a variety of formulations and concentrations and often in combination with an alkalising agent (sodium bicarbonate) to avoid ionisation within the urine and to better penetrate the urothelium. Heparin + alkalinised lidocaine can give better immediate relief. On the subject of oral PPS which is an oral heparinoid, he noted that its main disadvantage is that only a relatively small amount of the oral drug will actually reach the bladder and it can take up to 6 months before oral PPS shows any improvement. He also discussed the role of hyaluronic acid (HA) and chrondroitin sulfate (CS) in facilitating the repair of the deficient GAG layer, reducing urothelial permeability and counteracting inflammation. DMSO is an industrial solvent in use since the 1970s, given either as a single-agent instillation or as a cocktail with methyl prednisolone/hydrocortisone or heparin and alkalinised lidocaine. Likely to exert a clinical effect through reduction of inflammation, analgesic effect and facilitating detrusor relaxation. Botulinum toxin is a potent neurotoxin, still experimental in IC/BPS. He emphasised that patient selection is very important in relation to intravesical instillation. Dr Shah was one of many doctors in this virtual conference who stressed that these patients need extra consultation time and a lot of empathy.

Dr Sandor Lovasz from Hungary discussed a topic close to all our hearts: how to reduce the often exorbitant cost of IC/BPS treatment!! He pointed out that IC/BPS is a life-long, incurable disease which can cause serious symptoms. It can adversely affect the ability to work, rest and recreation, social life, sexuality, resulting in a continuously intolerable quality of life which needs regular, long-lasting, expensive treatment. It can involve innumerable visits to different specialists, the loss of employment leading to financial crisis, loss of friends and family, divorce, depression and a 70% higher rate of suicide. The often long delay in diagnosis can also cause huge expense due to misdiagnosis and often multiple inadequate therapies.

The cost of treatment varies significantly between different countries depending on the type of treatment used and different treatment protocols. However, **the cost is intolerably high in all countries.** He quoted the example of Germany where 40% of IC/BPS patients have been forced to stop their treatment due to financial difficulties. It is therefore important to seek different ways of reducing costs.
While guidelines suggest going from less invasive to more invasive forms of treatment, less invasive may mean less effective, particularly bearing in mind that since it may have taken years to get the right diagnosis the IC/BPS may already be at a serious level. Since a deficient GAG layer is a typical feature of IC/BPS, Dr Lovasz suggested starting treatment with the most effective treatment for a deficient GAG layer: bladder instillation therapy. However, this is expensive therapy. He suggested that the current recommended dosages are unreasonably high, potentially leading to overtreatment. A dose reduction can reduce the expense significantly.
Furthermore, most patients have to travel long distances to their specialist involving high travel costs. This means that it is necessary to reduce face-to-face appointments, instead using online communication wherever possible. Patients can learn how to do self-instillation in their own home. There is then no need to travel and they can perform the instillation as and when they need it. This can greatly reduce costs and enable far more patients to take advantage of beneficial therapy.

Professor Philip Hanno (USA) discussed the history of nomenclature, the situation today and the very topical issue of the current status of both Hunner Lesion and glomerulations. Glomerulations cannot be used as a diagnostic tool. Hunner lesion disease should not be evaluated with non-Hunner disease in clinical studies. On the subject of phenotypes: phenotyping may hold the key to improving treatment outcomes and facilitating research. The only proven phenotype in 2020 is the Hunner lesion. The Hunner lesion patient population seems to be different to non-Hunner lesion patients. Its histology is also quite different.
Referring to the new IASP (International Association for the Study of Pain) 2019 proposed classification of chronic pain for ICD-11, he noted that it may impact IC/BPS. See below:

- Chronic primary pain syndrome: pain as the sole or leading complaint, i.e. fibromyalgia, low back pain.
  - IC/BPS without Hunner lesion could fit in here
- Chronic secondary visceral pain
  - Pain secondary to an underlying disease (i.e. cancer, post traumatic, post surgical)
  - Pain as a symptom of another problem
  - Hunner lesion could fit in here as the cause of pain.

He concluded by stressing that it is time for urology associations to make HL a disease and it is also time for governments to give it its own coding.

Professor Mauro Cervigni (Italy), Vice-President of ESSIC and a urogynaecologist, discussed “What a urologist should know about female pelvic pain”, beginning with an overview of chronic pelvic pain, its high prevalence and economic impact and its substantial impact on quality of life.
Chronic pelvic pain syndromes include:

- Lower urinary tract pain
- Female genital pain
- Gastrointestinal pain
- Musculoskeletal pain
- Neuropathic pain
- Psychological overlay
- Sexual pain
- Extra-pelvic comorbidities.

Gynaecologic conditions associated with IC/BPS include vulvodynia, endometriosis, pelvic floor dysfunction and pudendal neuropathy. Professor Cervigni pain special attention to endometriosis which can occur inside the bladder and on the outer bladder wall. While endometriosis is listed as a confusable disease, it can also appear concurrently with IC/BPS, but may be being underdiagnosed. Both cystoscopy and laparoscopy may be needed to detect bladder endometriosis. Endometriosis can be in the bladder wall and not always visible. Professor Cervigni also stressed that there are many unknown factors and work that needs to be done in this field. He described the field of IC/BPS very aptly as being "full of holes"!

Dr Sanjay Pandey (Mumbai), Organizing Secretary GIBS, looked at the role of cystoscopy in IC/BPS and its methodology. In its diagnostic role, it is used both to diagnose and to exclude pathologies with similar symptoms to IC/BPS, including lesions other than Hunner lesions. Cystoscopy + hydrodistension is used therapeutically and can provide relief in some patients. It is also used for surveillance to monitor progression and changes in refractory cases.
Dr Pandey drew everyone's attention to the new Cochrane review: *Imamura M, Scott NW, Wallace SA, et al. Interventions for treating people with symptoms of bladder pain syndrome: a network meta-analysis. Cochrane Database Syst Rev. 2020;7:CD013325. Published 2020 Jul 30. doi:10.1002/14651858.CD013325.pub2.*

The second virtual conference day was introduced by Dr Anant Kumar, President of USI, who noted that IC/BPS is a difficult disease for both patients and the doctors looking after them. This kind of virtual conference can play an important role in educating and training, he said. Dr Rajeev TP, Secretary of USI, noted that IC/BPS can substantially reduce a woman's health.

The first speaker of this 2nd day was Dr Nagendra Mishra, Senior Consultant Urology, who is also a Board Member of the International Painful Bladder Foundation. Dr Mishra spoke about newer types of treatment for IC/BPS, focusing on intravesical tacrolimus, an innovation in India. Tacrolimus is an immunosuppressant and also used as a topical medication in the treatment of T-cell-mediated diseases such as eczema and psoriasis. Tacrolimus has the same mechanism of action as Cyclosporine A which has been shown to be effective in intractable cases of BPS/IC. The advantage of intravesical tacrolimus is that it is delivered at the site of action. It is not soluble in water but is soluble in DMSO.

See also: *Mishra NN, Riedl C, Shah S, Pathak N. Intravesical tacrolimus in treatment of intractable interstitial cystitis/bladder pain syndrome - A pilot study. Int J Urol. 2019;26 Suppl 1:68-72. doi:10.1111/iju.13978*

Dr Navita Purohit is a pain consultant in Mumbai and spoke about management of chronic pain of bladder origin. The aims of management are to alleviate pain and to improve quality of life. There are four treatment cornerstones: pharmacological, physical therapy, psychological/counselling and interventional pain management.

Dr Vikky Ajwani, urologist, discussed his experience in a urologist's practice in India. He emphasized that the doctor must listen to the patient with compassion. Patient education is important, he said. Be positive to the patient, while at the same time being realistic. Every patient is different so you need to be flexible in your approach to the patient. Diet plays an important role in disease management. There is a need for greater awareness among both doctors and patients. Knowledge at present is still suboptimal. Patients expect a cure but they are not getting it.

This was followed by a panel discussion led by Dr Shivam Priyadarshi and a quiz in which everyone could take part.

Dr Ariel Scafuri, speaking from Brazil, gave a glimpse of what it is like working with IC/BPS patients in Brazil where they have many patients. He says there has been no progress in treating the disease in the past 20 years. This has to change.

Dr Rajesh Taneja gave a presentation on the current status of oral PPS in the treatment of IC/BPS. There had already been some discussion the previous day on how to approach the problems regarding the risk of pigmentary maculopathy with long-term use.

Dr Amita Jain presented an IC/BPS algorithm as recommended by GIBS. Her take-home message was:

- Multiple treatment options – but lack of high level evidence
- Multimodal treatment approach
- Phenotype treatment plan to achieve maximum response
- Ineffective multimodal therapy should always raise suspicion
- AVOID: long-term antibiotics, oral steroids, long duration high pressure hydrodistension, intravesical BCG.

Further information about GIBS: https://gibsociety.com/