

# Interstitial Cystitis/Bladder Pain Syndrome

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## Chapter Outline

- ◆ Augmentation cystoplasty
- ◆ Bladder pain syndrome
- ◆ Cystoscopy
- ◆ Guideline
- ◆ Hunner's lesion
- ◆ Hydrodistention
- ◆ Hypersensitive bladder syndrome
- ◆ Interstitial cystitis (IC)/bladder pain syndrome (BPS)
- ◆ Interstitial cystitis
- ◆ Intractable IC/BPS
- ◆ Intravesical therapy
- ◆ Painful bladder syndrome
- ◆ Phenotyping
- ◆ Reconstructive surgery
- ◆ Tacrolimus

## Abstract

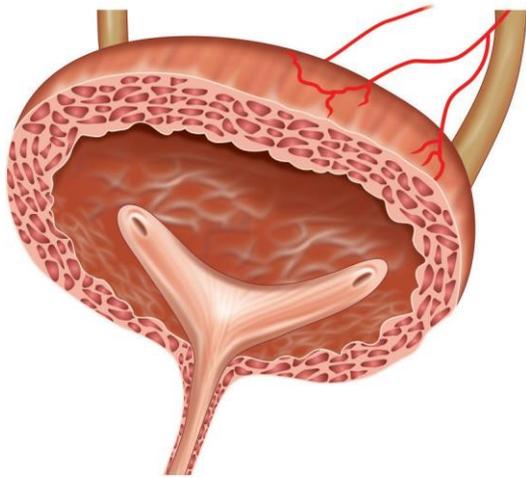
Interstitial cystitis (IC)/bladder pain syndrome (BPS) is a chronic disease characterized by pain, urgency, and frequency. Patient having severe symptoms experiences a very miserable life. Even after so many years of research exact etiopathology has not been determined. There is no cure available and the treatment is directed toward control of symptoms. Most of the physicians believe that it is very difficult to treat IC/BPS and patients continue to suffer. Patients present in different permutations and combinations of symptoms. In spite of increased awareness IC/BPS patients still have to move from one physician to other for years before diagnosis is made. In 2024 there is an international consensus regarding the name and definition of the disease IC/BPS. Bladder diary, urine routine examination and culture and sensitivity, ultrasonography of kidney-ureter-bladder and cystoscopy are commonly performed investigations, but no test can diagnose IC/BPS.

Based on findings of cystoscopy patients can be divided in Hunner's lesion (HL-IC/BPS) and non-Hunner's lesion (NHL-IC/BPS) depending on the presence or absence of Hunner's lesion. Therapeutic hydrodistention and treatment of HL can be done at the time of diagnostic cystoscopy. IC/BPS is considered as heterogenous disease so there is an attempt to identify different phenotypes of IC/BPS in order to treat individual patient in best possible way.

A policy of staged treatment is adopted where various treatment modalities are applied to the patient one after other, starting with less invasive and progressing to more invasive. Lifestyle changes, biofeedback physical therapy and diet also play a part in management of IC/BPS. Orally amitriptyline, hydroxyzine hydrochloride, pentosan polysulfate sodium (PPS), gabapentin, etc., are prescribed. PPS has a black box warning from United States Food and Drug Administration (USFDA) for the development of retinal maculopathy and patients should be cautioned about it. Dimethylsulfoxide (DMSO), intravesical cocktail, and intravesical tacrolimus are used after failure of oral therapy. Oral cyclosporine A, intravesical Botox injection, neuromodulation, and reconstructive surgery are reserved for nonresponsive patients. The results of surgery are good but should be used as last resort because of surgical morbidity and there is a fear of persistence of symptoms in few patients.

International consensus guidelines, biomarker for diagnosis and effective oral treatment are the most important unmet needs of IC/BPS and efforts should be made to achieve that in near future.

## INTRODUCTION



Interstitial cystitis/bladder pain syndrome (IC/BPS) is a neglected debilitating chronic, inflammatory disorder of the urinary bladder characterized by variable degree of bladder pain, frequency, and urinary urgency.<sup>1</sup> There are still many physicians worldwide who do not believe in existence of this disease. There is a consensus all over the world that IC/BPS is difficult to diagnose and treat. The worst scenario is that there are no diagnostic symptoms, signs, or investigations. In last 35 years all the over the world, particularly in USA, in spite of spending unlimited money and effort, there is no clear direction toward pathology and treatment even at distance. But these efforts have helped in increasing the awareness about the disease. It is a unique disease with no clue to etiology,<sup>2</sup> its pathology is unknown,<sup>3</sup> and no specific treatment exists to affect a cure.<sup>4</sup>

## HISTORY

In early 19th century this disease was defined as a painful bladder inflammatory disease producing the symptoms same as bladder stone. However, the term interstitial cystitis was mentioned for the first time in 1986.<sup>5</sup>

In 1918 Guy Hunner described the term elusive ulcer of the bladder which was later named as Hunner's ulcer. Cystoscopes in 1918 had primitive design and limited vision. Now it is realized that what he said as ulcer are not true ulcers but red lesion.

In 1951, JP Bourque from Canada used the term “painful bladder”—sometimes also referred to as “painful bladder disease”—not as a synonym for IC, but as an umbrella term for all disorders causing pain in the bladder.<sup>6</sup>

For the first time in 1978 one full chapter was devoted to interstitial cystitis in Campbell's Urology, 4th edition and for the first time word glomerulations was coined for dot-like bleedings.<sup>7</sup>

In 1987, Magnus Fall et al., described two types of IC as ulcerative and nonulcerative with different clinical picture.<sup>8</sup>

In the same year the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) formed a consensus definition of IC which was later revised in 1988. The aim of drawing these guidelines was to have an international standard to compare patients of different geographical areas. Unfortunately, these NIDDK guidelines were very rigid and diagnosed only 40% patients of IC/BPS.<sup>9</sup>

In 2002 International Continence Society used the term painful bladder syndrome.

European Society for the Study of Interstitial Cystitis (ESSIC) was founded in Copenhagen in 2004. ESSIC changed the name to bladder pain syndrome in 2006 to meet the taxonomy criteria.<sup>10</sup>

In 2009 hypersensitive bladder syndrome was the term used in Japanese guidelines as there is no word like pain in Japanese language.<sup>11</sup>

In 2010 ESSIC changed the name to the International Society for the Study of Bladder Pain syndrome but decided to continue to use the acronym ESSIC.

American Urological Association (AUA) for the first time framed the guidelines for interstitial cystitis in 2011 used the term IC/BPS.<sup>12</sup> It is to be noted that all the terms IC, BPS/ IC, BPS, and HBS are used for the same syndrome. AUA guidelines were amended in 2014 and 2022.

2017 Bone, Reproductive, and Urological Drugs Advisory Committee (BRUDAC) criteria for IC/BPS were framed by USFDA.<sup>13</sup>(BOX 1)

The 2022 European Association of Urology (EAU) guidelines for chronic pelvic pain added the word “primary” to BPS, making it primary bladder pain syndrome (PBPS).

In 2024 we can write that though there is no consensus internationally on the name, IC/BPS is used by a good majority of physicians.

### BOX 1: Summary of BRUDAC criteria.

- Symptoms of HL-IC/BPS and NHL-IC/BPS are indistinguishable and can be combined in clinical trial
- HL can be identified with patients under local anesthesia\*
- Urodynamic evaluation is not a requirement of diagnosis
- Glomerulations are not a pathognomonic feature of classical IC
- Hallmark symptom of IC/BPS is 6 months (rather than 12 months) of (bladder) pain associated with urinary symptoms

\*Not acceptable by many urologists including the author  
(HL-IC/BPS: Hunner lesion-interstitial cystitis/bladder pain syndrome;  
NHL-IC/BPS: non-Hunner lesion-interstitial cystitis/bladder pain syndrome)

## DEFINITION

Keeping in mind the historical perspective it is expected that there will be multiple definition of same syndrome. According to (ESSIC)—“bladder pain syndrome (BPS) is diagnosed on the basis of chronic pelvic pain, pressure, or discomfort perceived to be related to 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.”<sup>10</sup>

In June 2009, the Indian IC/BPS society under my chairmanship framed the Indian IC guidelines which defined, IC/BPS as recurrent pelvic pain or discomfort (pressure, burning, throbbing, etc.), of at least 4–6 weeks duration, which increases with bladder filling and/or decreases with micturition associated with urinary frequency and/or urgency in the absence of definable pathology.

The American Urological Association published its guideline in 2011, naming the disease IC/BPS. The condition was defined as “an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of >6 weeks duration, in the absence of infection or other identifiable causes.”<sup>12</sup>

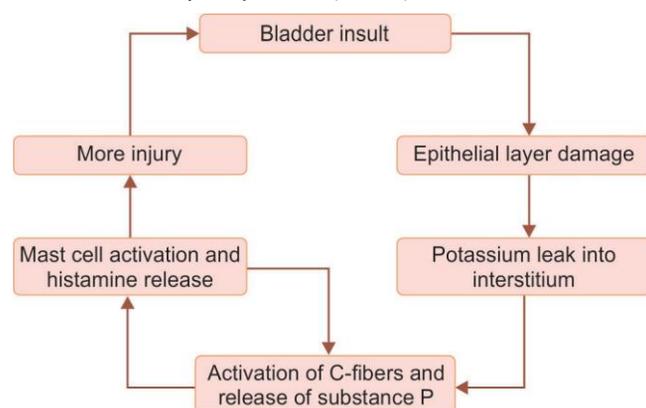
Japan, Taiwan, and Korea have their own **guidelines** and label it as “hypersensitive bladder” (HSB)<sup>11</sup> defined as “bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain.”

## INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME ETIOPATHOLOGY

The underlying cause of IC is not well understood and mechanism of causation is not clear. There are many theories but exact explanation is still elusive (**Flowchart 1**).

- Epithelial paracellular permeability<sup>14,15</sup>
- Glycosaminoglycan layer impairment (GAG theory)<sup>14-16</sup>

**Flowchart 1:** Pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS).<sup>23</sup>



- Occult infection
- Neurogenic inflammation<sup>17</sup>
- Mast cell activation<sup>17</sup>
- Autoimmunity<sup>18</sup>
- Abnormality of stretch receptors in urothelium and detrusor.

## Epithelial Paracellular Permeability

The symptoms in IC/BPS could be ascribed to the increase of urothelial paracellular permeability, thereby leaking the irritants into intermediate layers and eliciting inflammatory responses.<sup>14</sup> The barrier integrity of tight junctions (TJs), adherens junctions (AJs), and urothelium is essential to prevent the solutes from moving into the intercellular space.<sup>15</sup>

## Glycosaminoglycan Layer Abnormality

The bladder permeability barrier (BPB) is an impenetrable barrier between the blood and the urine, and its function is similar to the blood-brain barrier. The BPB is comprised of the urothelium and glycosaminoglycan (GAG) layer. The loss of the GAG layer attracts irritants from urine to attach onto the epithelium. An increase in urothelial permeability could trigger chronic inflammatory responses and eventually damages BPB. The urothelium not only has a barrier function but also acts as a “mechanical sensor” of bladder distention and a “chemical sensor” of urine acidity, osmolarity, and composition.<sup>16</sup>

## Mast Cell Activation

Recent studies have indicated that mast cells (MCs) could be activated by multiple biological substances such as drug molecules, chemokines, bacteria, viral components, immunoglobulin E (IgE), and other biologics. The activated MCs secrete a variety of bioactive compounds, including biogenic amines, enzymes, proteoglycans, growth factors, cytokines, and chemokines.

Among these secreted factors, histamine specifically targets and activates histamine receptor 3 (H3R), which subsequently leads to hyperinflammation in the bladder. The infiltration and activation of MCs can induce the inflammatory response, disrupt the BPB and trigger the signaling pathway in pathological pain during the development of IC/BPS.<sup>14,17</sup>

## Autoimmunity Activation

Interstitial cystitis/bladder pain syndrome is chronic in nature, has remissions and flare ups and is associated with many autoimmune diseases. There is a strong association

between IC/BPS and autoimmune disease such as Sjogren syndrome (SS), ulcerative colitis, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). There's increasing evidence showing that the bladder tissue of IC/BPS patients has an abundance of CD4<sup>+</sup>, CD8<sup>+</sup>, and  $\gamma\delta$  T cells, as well as IgA, IgG, and IgM plasma cells.<sup>18</sup> These studies have opened up antibodies as a treatment for IC/BPS but still future research is needed to confirm these options.

### Central Nervous System Sensitization

In the peripheral nervous system, to respond to the stimulus of an extracellular environment, urothelial cells would release transmitters such as adenosine triphosphate (ATP), acetylcholine (ACh), and prostaglandin (PG). Then, these transmitters activate the afferent nerves, which convey the sensory information to the central nervous system. Persistent peripheral insults may lead to the alteration in the peripheral nervous system.

Pelvic pain is one of the typical symptoms of IC/BPS. Recently, central sensitization has been demonstrated to lead to chronic pain. Central sensitization is a pathologic state wherein the central nervous system augments the signaling in response to the peripheral stimulus. The effect of central sensitization can act as a vicious cycle leading to hyperexcitability during the progression of IC/BPS.<sup>19,20</sup>

### Abnormality of Stretch Receptors in Urothelium and Detrusor

During physiological tension mechanoreceptors (A $\delta$  fibers) respond to distention, resulting in a reproducible series of increasing bladder sensations, which culminate with initiation of the micturition reflex. The normal frequency/volume relationship of afferent nerve firing may be modulated by the stretch-dependent release of mediators from the urothelium, e.g., acetylcholine, adenosine triphosphate, and nerve growth factor. Many of these mediators are increased in patients with IC/BPS, which may lower the threshold for initiation of afferent nerve firing or increase the rate of afferent nerve firing in response to bladder filling. This results in pain and desire to micturate at small urinary volume in the bladder filling.<sup>21</sup> This hypothesis is basis of success of surgery in intractable IC/BPS patients.

### Summary: Multifactorial Etiology of Interstitial Cystitis/Bladder Pain Syndrome

Interstitial cystitis/bladder pain syndrome is a chronic condition. This refractory disease is multifaceted-urothelial and GAG defect, BPB breakage with increased permeability, MC infiltration, infection autoimmunity response, and

central sensitization are various hypotheses. The exact cause, however, remains unknown. A nonmicrobial inflammation is widely recognized as a key pathological mechanism that mediates or promotes the development of bladder pathology associated with urinary symptoms and IC/BPS symptoms. Despite that, it cannot be ruled out that the very initial steps of IC/BPS are provoked by pathogens.<sup>22</sup>

Initially epithelial damage takes place following infection, inflammation, pelvic surgery, childbirth, or urological instrumentation. Normally epithelial surface heals following treatment but, in some patients, epithelial healing does not take place leading to abnormalities in the GAG layer. Defective GAG layer allows potassium and other urinary metabolites to pass the submucosal layer and cause inflammation leading to activation of mast cells which elicits local tissue damage and vascular constriction. This sets up a cascade of events and leads to more bladder damage, injury to detrusor smooth muscles and fibrotic changes. Final result is small capacity bladder. There is also neural up regulation and development of neural changes in the spinal cord.<sup>23</sup>

The latest research is pointing towards autoimmunity as the probable cause of IC/BPS

### PREVALENCE OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Bladder pain syndrome/IC is a rare disease and prevalence differs from nation to nation. As awareness of the disease is increasing more patients are being diagnosed. IC/BPS is underdiagnosed. China has minimum prevalence of 100/lac<sup>24</sup> to USA where it is estimated to be 2,600/lac.<sup>25</sup> When the criteria to diagnose changes the prevalence changes. Even in the USA Clemens in 2007 reported an incidence of 197/lac.<sup>26</sup> Whereas Finland<sup>27</sup> and Austria<sup>28</sup> have prevalence of 300 and 307/lac respectively.

A recent study utilizing Veteran Health Administration data estimated US national prevalence 0.87% with female and male prevalence of 1.08 and 0.66% respectively.<sup>29</sup>

In India there are no epidemiological studies, but even going by minimum population prevalence, India has 1.35–1.4 million patients with IC/BPS.<sup>30</sup>

### SYMPTOMS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Triad of pelvic discomfort urinary urgency and frequency is most common presentation of IC/BPS. Pain is most important cause of pelvic discomfort but patients also complain of unusual pressure sensation, burning, throbbing or, piercing or childbirth like pain. Urinary discomfort is related to micturition meaning increases with bladder filling and decreases on voiding. In severe cases pelvic discomfort is continuous. It is felt in the suprapubic, retropubic, infrapubic, urethral, genital, rectal region, and/or deep pelvic

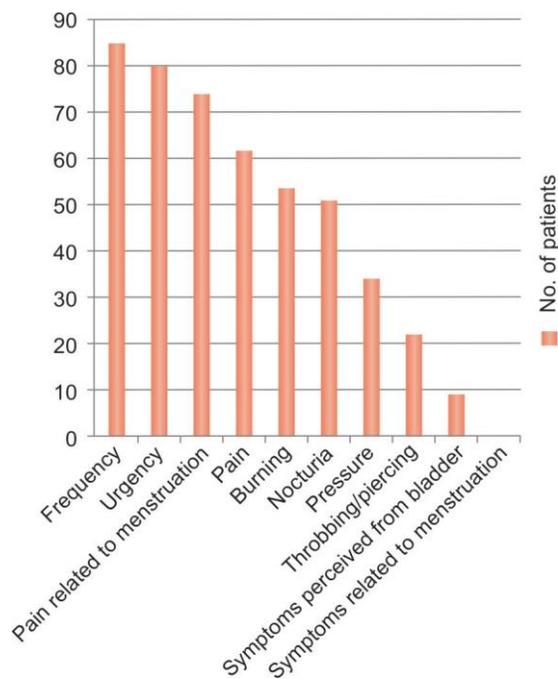
area. Most of the patients pass urine >8 times in a day. Once the patient gets desire to pass urine, they cannot postpone it because of increasing discomfort. Patient has urgency but not urge incontinence. This is an important point to differentiate IC/BPS from overactive bladder (OAB). In IC/BPS patients has severe urinary discomfort but urine does not leak. In IC/BPS patient's urgency is fear of pain but in OAB there is fear of leak. To start with patient may have only one symptom initially but develop fully fledged syndrome over next 4–5 years. Some of the patients find it difficult to perceive the organ of origin of pain, i.e., bladder and they simply mention that it comes from pelvis (**Fig. 1**) depicts the common symptoms with which the patients presented in our series. Total number of patients included here is 92.

In a very severe presentation patient prefers to stay home and not travel. When there is need to travel, they prefer to move by train and not by road as toilets are available in train. There is no quality of life for the patients of severe IC/BPS.

### Unusual Symptoms

Interstitial cystitis/bladder pain syndrome is basically a disease of sensation. In spite of little urine in the bladder patients feel that bladder is full and they cannot evacuate it totally. In severe cases patients sit in the toilet for hours as they feel that bladder is full and there is continuous urge to pass urine.

Patients may present with unusual obstructive symptoms such as thin stream, incomplete evacuation,



**Fig. 1:** Symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS) n = 92.<sup>31</sup>

dribbling, obstruction and straining, and desire to pass urine immediately after micturition. This is why sometimes presentation is like urethral stricture. Even with minimal urine in the bladder patients feel they have full bladder (**Fig. 2**). Irritative symptoms are hall mark of IC/BPS but it should be realized that around 50% of patients present with unusual obstructive and sensory symptoms.

### Unusual Nonurinary Symptoms of Interstitial Cystitis/Painful Bladder Syndrome

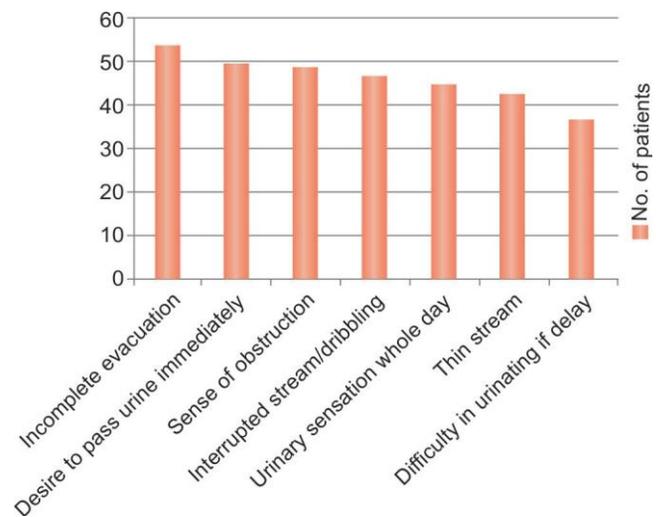
Patients complain of anal discomfort, vulvar and penile glans pruritis and burning, dyspareunia, painful ejaculation, and difficulty in walking and sitting. In both male and female some patients complain of flare up after intercourse. Increased tone of pelvic muscles or inability to relax pelvic muscles may be responsible for some of these symptoms (**Fig. 3**).

### ASSOCIATED DISEASES

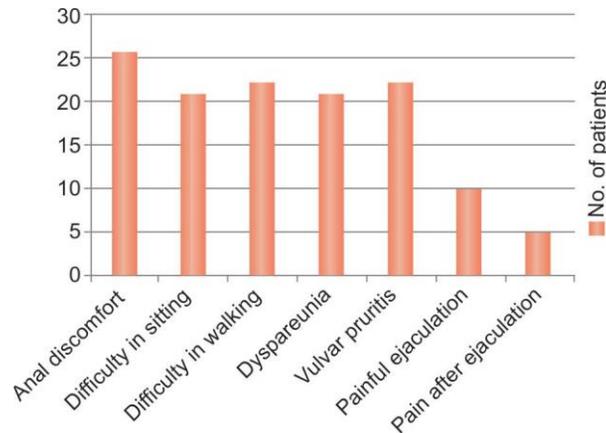
Some of the diseases are found more commonly in patients of IC/BPS than normal population. **Figure 4** lists those diseases and the frequency with which they are found in a series of 92 patients. Most common problem is gas, acidity, muscle and joint pain, backpain, and chronic fatigue.

### INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND CHRONIC ABACTERIAL PROSTATITIS: SAME DISEASE

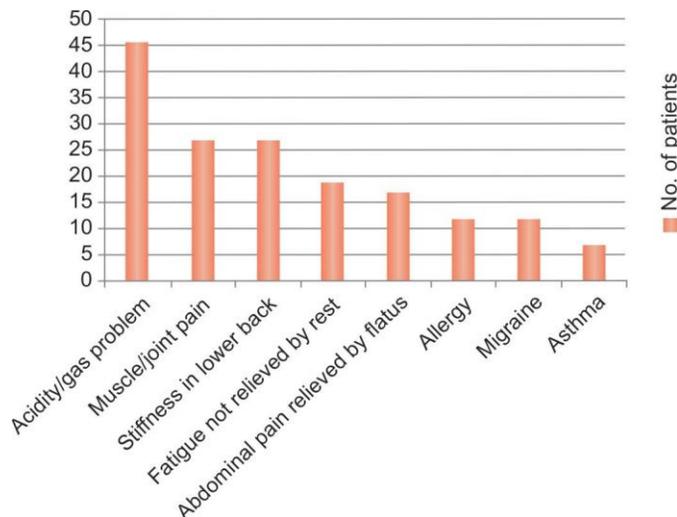
Interstitial cystitis/bladder pain syndrome is more common in men than originally thought. In fact, male patients with IC/BPS are diagnosed as chronic abacterial prostatitis



**Fig. 2:** Unusual obstructive and sensory urinary symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). Total n = 92.<sup>31</sup>



**Fig. 3:** Unusual nonurinary symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS) total patients n = 92.<sup>31</sup>



**Fig. 4:** Associated disease with interstitial cystitis/bladder pain syndrome (IC/BPS) total n = 92 patients.<sup>31</sup>

(CAP) or NIH type 3 prostatitis.<sup>32</sup> At our center patients with pelvic discomfort, suprapubic, perineal and penile tip pain, urgency and frequency related to micturition are initially treated with a quinolone and  $\alpha$ -blocker for 6–8 weeks and if there is no improvement they are considered as suffering from IC/BPS and treated accordingly. If the patient has only pelvic discomfort not related to micturition he is considered as suffering from chronic prostatitis and these patients are not treated as IC/BPS. Many researchers consider IC/BPS and CAP as similar diseases. In 2007, the NIDDK began using the umbrella term “urologic chronic pelvic pain syndrome (UCPPS),” to refer to pain syndromes associated with the male and female pelvis. Previously, the female version was called painful bladder syndrome/interstitial cystitis, or PBS/IC, and the male version was called chronic prostatitis/chronic pelvic pain syndrome, or CP/CPPS.

#### BOX 2: Quick guide to diagnose IC/BPS.

*Suspect IC/BPS in patients having:*

- Lower abdominal discomfort with urinary urgency and/or frequency
- Increase/decrease in discomfort with filling/evacuation of bladder
- Cannot postpone the initial desire to pass urine
- Absence of any other pathology to account for the above symptoms
- Also consider if this discomfort is present in urethra/vagina in female and glans/shaft of penis/urethra in male
- Discomfort means pain, pressure, burning, piercing, and childbirth like pain

Cystoscopic appearance of IC was found in 70% of men with symptoms of nonbacterial prostatitis and prostatodynia when scoped under anesthesia<sup>33,34</sup> In our series 80% patients have petechiae and ecchymosis on cystoscopy and hydrodistention. In the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) study which enrolled men and women with IC/BPS and/or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), about 3 out of 4 men had symptoms of “painful bladder filling” and/or “painful urgency,” consistent with IC/BPS.<sup>35</sup> Historically, both of them were considered totally different diseases. An important clinical point is that it is very difficult to diagnose IC/BPS in male patients where the symptoms of CAP and IC/BPS overlap. The best strategy is to think IC/BPS in all patients with CAP when the initial therapy for prostatitis fails. Quick guide to diagnose IC/BPS is enumerated in Box 2.

### INVESTIGATIONS (BOX 3)

#### Frequency Volume Chart

- Very useful investigation
- Patients are instructed to make a chart mentioning the time and amount of urine passed each time.
- IC/BPS patients void small amounts of urine frequently
- The average urinary volume per void is around 50 mL.
- A 3-day log preferred.
- This type of log is especially useful when there is suspicious of IC/BPS but patients do not have frequency.

#### Urine Routine and Culture

- Urine culture may not be done if urine routine and microscopic test is totally normal.
- If any suspicious of infection, then urine culture is a mandatory investigation.
- In patients with IC/BPS urine culture does not show any growth
- If culture positive diagnosis of urinary tract infection is made and treated with adequate antibiotics.

**BOX 3: Investigations.**

- Frequency volume chart
- Urine routine and culture
- Sonography of kidney, ureter, and bladder with postvoid residual (PVR)
- Cystoscopy under anesthesia

- Consider IC/BPS if patient does not improve with adequate treatment and symptoms persist.
- Role of expanded qualitative urine culture (EQUC), urinary polymerase chain reaction (PCR), and next generation sequencing (NSG) is not clear and not recommended in clinical use. Both of these EQUC and NGS provide a plethora of information. However, the clinical applicability of these data is unclear as the presence of a microbe does not render it causative of symptoms or necessarily indicate pathogenicity. Further research will throw light on use of these new technologies in clinical use.<sup>36</sup>

### Ultrasound of Kidney Ureter and Bladder with Postvoid Residual

- Upper tract normal, normal bladder wall and no or minimal postvoid residue.
- Some patients will have small capacity bladder as they are not able to hold more urine.
- In patients with small capacity bladder with normal bladder wall thickness and normal upper tracts IC/BPS should be first differential diagnosis.
- Tuberculous small capacity thimble bladder has thick bladder wall with upper tract changes. This point is very important in differentiating tuberculosis from IC/BPS.

### Cystoscopy

- Cystoscopy is important investigation and has a diagnostic, management, and prognostic role. It should always be done under general or spinal anesthesia. Office cystoscopy under local anesthesia has minimal role and should be discouraged as it is painful. I do not believe that Hunner's lesion can be diagnosed by performing flexible cystoscopy under local anesthesia<sup>37</sup> as mentioned in BRUDAC criteria.
- Spinal anesthesia is preferred as it keeps the pelvis muscles relaxed for 60–90 minutes keeping patient comfortable after the procedure while in general anesthesia post procedure after waking up patient feels severe pelvic pain and desire to pass urine and cannot tolerate Foley's urethral catheter. Post procedure the catheter is removed as soon as patient starts moving legs.<sup>30</sup>

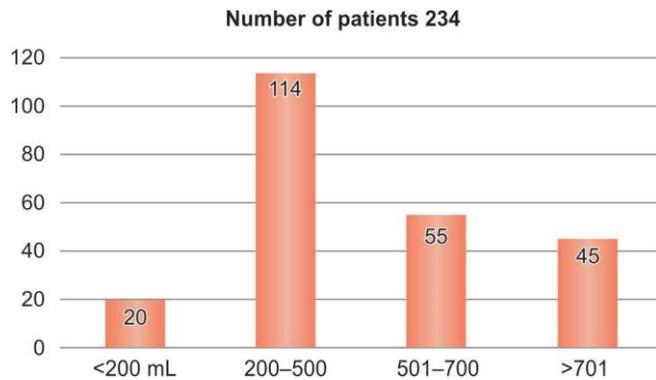
- *Advantage of cystoscopy:*

- To rule out any other disease as cause of symptoms, e.g., bladder carcinoma, carcinoma in situ, tuberculosis, and uroepithelial dysplasia.<sup>8</sup>
- To biopsy any suspicious lesion present before the bladder is distended. There is no need to biopsy red petechial hemorrhage and ecchymosis that develop as the bladder is distended or after bladder is evacuated.
- To measure capacity of bladder. If bladder capacity is <150 mL under anesthesia it is better to advise patient for surgical therapy. Patients with maximum bladder capacity >701 mL have good prognosis and <201 mL have poor prognosis.<sup>37,38</sup>
- Therapeutic hydrodistention can be performed at the same sitting
- If Hunner's lesion is present biopsy is done from the lesion, and can be fulgurated or resected or treated with laser at the same time. Even triamcinolone could be injected at the base of HL. We coagulate the Hunners Lesion in our practice.

- *Technique:* Cystoscopy is done under spinal anesthesia using saline as an irrigation solution. The reservoir is kept at a height of 80 cm from pubic symphysis and the bladder is filled under gravity. The bladder is then evacuated and refilled again. The color and volume of the evacuated fluid is noted. It is necessary to distend the bladder again as the petechiae and ecchymosis usually develops on evacuation of the bladder and can be observed only when the bladder is redistended. In few cases petechiae and ecchymosis develop even on first distention. Some patients start bleeding from all over the mucosa while distention is being performed. In therapeutic hydrodistention (HD), the bladder is kept distended for 3 minutes during second distention and then evacuated again. The reservoir height is not increased as it will hydrodilate the bladder. Our aim is to hydrodistend the bladder, not hydrodilate.<sup>30</sup> Hydrodilatation causes breaches in the bladder mucosa. Following this, bladder biopsies can be taken. Bladder capacity under anesthesia varies from <100 mL to around 1,000 mL. We do not distend the bladder >800 mL for fear of rupture. Foley catheter is retained in all the cases.

- *Important points about cystoscopy:*

- Patients with normal capacity under anesthesia can also have IC/BPS. **Figure 5** shows distribution of IC/BPS patients as per cystoscopy capacity under anesthesia. Around 10% of patients will have small capacity bladder (<200 mL). Important point to note is that 43% of patients have maximum cystometric bladder capacity (MBC) >500 mL (**Fig. 5**).



**Fig. 5:** Under anesthesia maximum bladder capacity (MBC) in mL. Total number of patients is 234.

- Bladder mucosa can be normal in around 20% cases of IC/BPS. Prevailing concept that normal bladder on cystoscopy rules out IC/BPS is wrong. In my series 17% of patients had normal bladder mucosa and 17% patients had grade 4 lesion HL (**Table 1**) (**Fig. 6**).
- There are no pathognomonic changes on bladder biopsy to diagnose IC/BPS. Bladder biopsy can be absolutely normal in IC/BPS. The belief that a normal bladder biopsy rules out IC/BPS is false. Cold cup biopsy will mostly show changes of inflammation.
- **Complications of cystoscopy and HD:** Following complications occurred in my series of 482 patients from January 1992 to September 2022.
  - No perforations requiring laparotomy in any patients.
  - Three near perforations requiring catheterization for 1 week
  - Two patients went in retention post procedure and needed catheter for 2–3 days
  - Two patients required hospitalization and clot evacuation for postprocedure clot retention
  - One patient needed hospitalization for mild bleeding
  - No long-term surgical morbidity in any patient

### Glomerulations and Hunner's Lesion

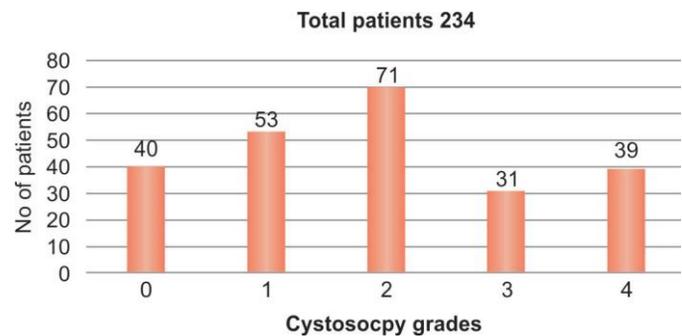
On cystoscopy we find either normal mucosa or three types of lesions. One is pinpoint bleeding spots (PH and glomerulations), second is ecchymosis, and third is Hunner's lesion (HL). In few patients there will be excessive oozing of blood from all over the bladder. Glomerulations were first time mentioned in Campbell Urology 1978 edition and represent pinpoint submucosal hemorrhages. It is now realized that Hunner's ulcer identified by Guy Hunner is not an ulcer but a lesion with specific characteristics and the terminology ulcer, lesion, and fissures represents same lesion on cystoscopy in IC/BPS.

Glomerulations were long considered to be the hallmark of IC/BPS<sup>2</sup>, but it is not true. In my own series out of 234

**TABLE 1:** Cystoscopic classification of bladder mucosa.

**Copenhagen cystoscopic classification of bladder mucosa (May 2003)<sup>43</sup>**

Grade 0	Normal mucosa
Grade 1	Petechiae in at least two quadrants
Grade 2	Large submucosal bleeding (ecchymosis) ( <b>Fig. 7</b> )
Grade 3	Diffuse global mucosal bleeding
Grade 4	Mucosal disruption, with or without bleeding/edema



**Fig. 6:** Cystoscopic grades in 234 patients of interstitial cystitis/bladder pain syndrome (IC/BPS) in author's series.

patients of IC/BPS syndrome group 40 did not have any glomerulations/ecchymosis/HL/fissures or excessive oozing. In a study at my center cystoscopy was done in 40 cases with nonbladder diseases and none of them developed any lesion at all even on second distention or hydrodistention.<sup>39</sup> But there are opposite finding too. Glomerulations have also been found in normal women undergoing tubal ligation.<sup>40</sup> Although the term glomerulations is associated with IC/BPS, there is no correlation between them and the degree of histological inflammation<sup>41</sup> and symptoms.<sup>42</sup> Glomerulations and HL are not standard terminologies and moreover, these findings are very subjective and differ from observer to observer. In an attempt to standardize cystoscopic findings, the International Society for the Study of BPS (ESSIC) has described various grades of bladder mucosa appearance on cystoscopy<sup>43</sup> (**Table 1**). Grade 4 is considered as HL. In author's series of 234 patients most common grade was grade 2 and are around 17% patients had grade 0 while other 17% had HL (**Fig. 6**).

**Cystoscopic appearance of Hunner's lesion:** Hunner's lesion is distinctive inflammatory lesion with characteristics central fragility, which ruptures on hydrodistention. Usually, a solitary lesion is present but 2 or 3 can also be present. Most important point is that HL is present in the bladder before it is distended. For detection of HL, abnormal bladder mucosa must be present in the initial inspection of bladder at the start of cystoscopy when bladder is minimal filled. On cystoscopy, it is seen as a circumscribed reddened mucosal area with small

vessels radiating toward a central scar. This site ruptures with increasing bladder distention, with petechial oozing blood from the lesion in a waterfall fashion (Figs. 8A to D).



**Fig. 7:** Cystoscopic appearance of interstitial cystitis/bladder pain syndrome (IC/BPS) grade 2 changes.

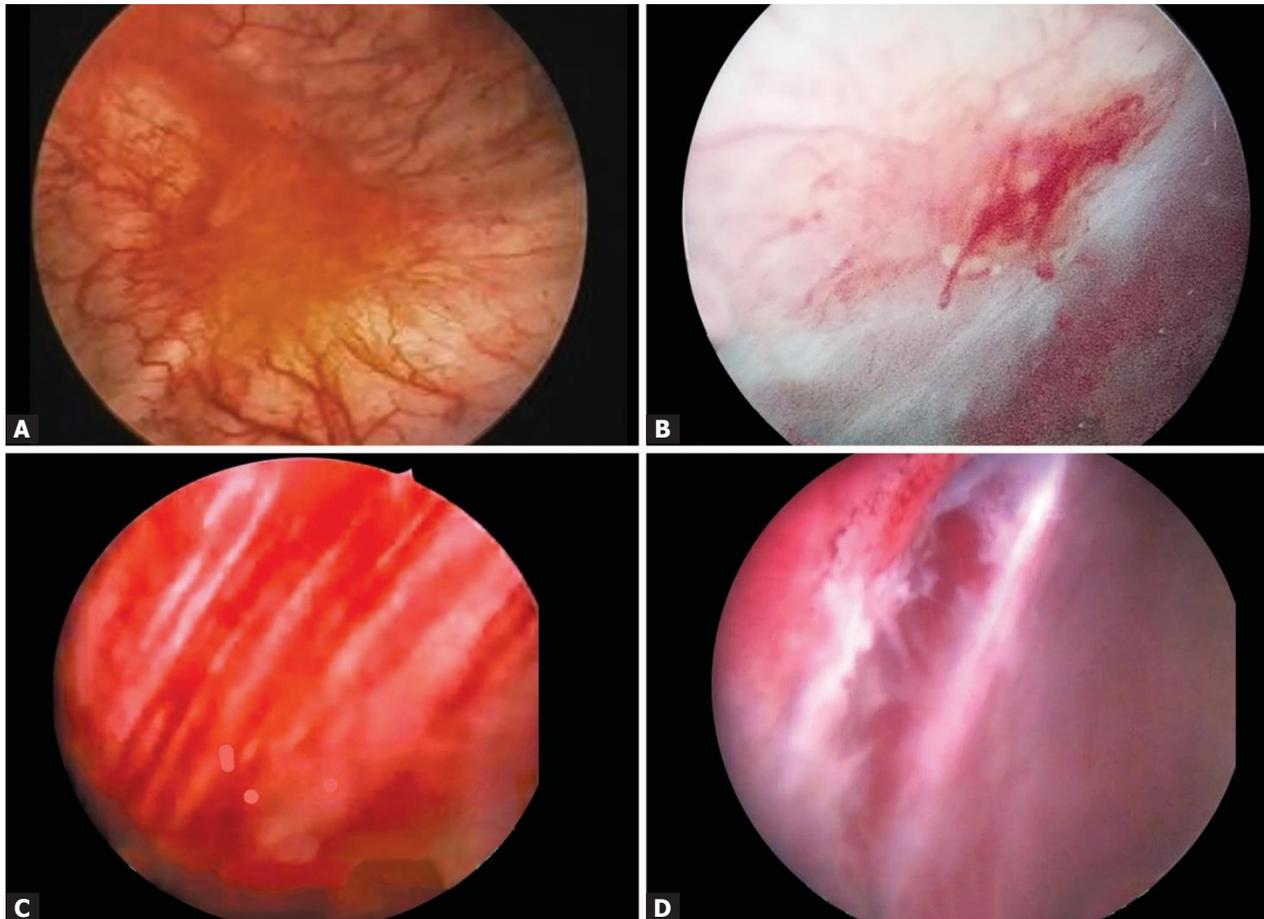
Visualization of HL requires experience. We were unable to identify any HL in our cystoscopies till 2013.<sup>30</sup>

### URODYNAMICS

- Not recommended (BRUDAC 2017 criteria).
- No diagnostic features on urodynamic studies (UDS).
- The procedure is invasive and painful
- Awake bladder capacity is small
- Sometimes patients cannot micturate due to pain and a wrong interpretation of atonic bladder with residual urine is made.

### TREATMENT OPTIONS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

As the etiopathology is multifactorial, it is logical to treat the patients with multimodal therapy.<sup>23</sup> At our center once we suspect IC/BPS we do cystoscopy under anesthesia in all patients. Treatment options available are hydrodistention, oral therapy, intravesical therapy, InterStim, fulguration,



**Figs. 8A to D:** Typical cystoscopic appearance of Hunner's lesion with—(A) Central scar, (B) Mucosal rupture, (C) Waterfall bleeding, and (D) Fissure.

resection, or triamcinolone injection of Hunner's lesion, behavioral, physical therapy, and lifestyle modification.

### Staged Treatment Policy

The problem with IC/BPS is its uncertainty in treatment response. There is no way to know which patient will respond to which treatment. Multiple treatment options are available. We follow staged treatment policy in all our patients for last 30 years and all the patients are subjected to same protocol.<sup>30</sup> Protocol is modified depending on advances in our understanding of the disease, the response of the patient and the availability of the therapeutic agent. Though AUA Guideline 2011 recommended managing patients based on 1–6 lines of treatment starting from simple therapy and moving toward more invasive one,<sup>12</sup> but the recent amendment to the guidelines (2022) has not mentioned any lines of treatment recommendation.

The protocol developed and followed at our center from last 30 years is represented in **Flowchart 2**. All the patients are advised about lifestyle and diet modifications and stress management at the first consultation and it is followed throughout the treatment duration. We do not have specialist available for biofeedback and special physical therapy

so do not recommend it to the patients. We do not follow AUA guidelines as only 6 out of 26 guideline statements are evidence based and others are either option, clinical principle or expert opinion. There is evidence for what not to do rather than what to do. This is because there is very less evidence available for management of IC/BPS in literature.<sup>35,37</sup>

### Staged Therapy Protocol

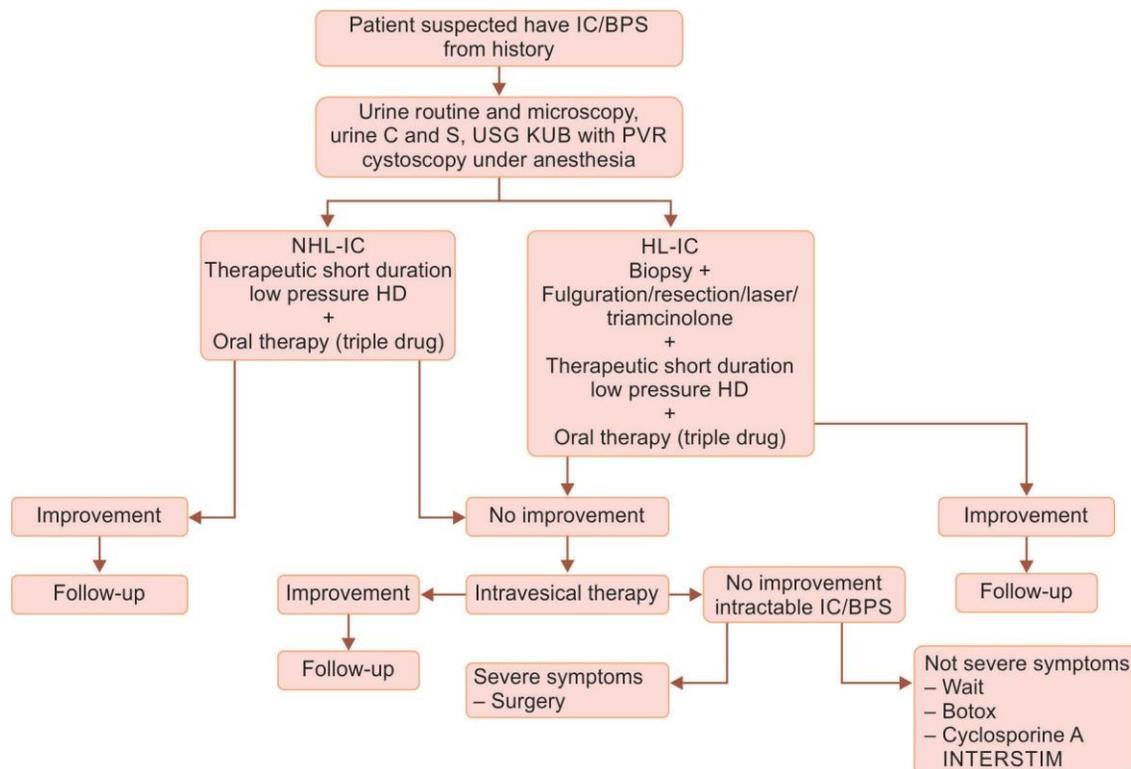
- Stage 1: Cystoscopy hydrodistention with oral therapy
- Stage 2: Intravesical therapy
- Stage 3: Reconstructive surgery

Our experience with injection BoNT-A is not good so do not recommend it. InterStim is not a popular therapy in India due to cost and instrument limitations but believe that both these treatment modalities do have a role in management of patients.

#### Stage 1: Cystoscopy Hydrodistention with Oral Therapy

All suspected IC/BPS patients with normal urine and sonography report are subjected to cystoscopy and therapeutic hydrodistention. In cystoscopy under anesthesia, patient having <150 mL MBC capacity is advised

**Flowchart 2:** Mishra's simplified treatment algorithm for the management of IC/BPS.



(HL-IC: Hunner lesion interstitial cystitis; HD: hydrodistention; IC/BPS: interstitial cystitis/bladder pain syndrome; KUB: kidney, ureter and bladder; NHL-IC: non-Hunner's lesion interstitial cystitis; PVR: postvoid residual; USG: ultrasonography)

reconstructive surgery. Hunner's lesion is fulgurated at the same sitting.<sup>44,45</sup> All patients are put on triple drug therapy including amitriptyline, hydroxyzine, and gabapentin for 3 months. Pentosan may or may not be added to the triple therapy. After 3 months, management is reviewed and changes made accordingly.

### Stage II: Intravesical Therapy

If the first stage treatment fails, intravesical therapy is employed as a second stage. Intravesical anesthetic cocktail (40 cc bupivacaine 5%, 25,000 unit heparin, and 2 cc dexamethasone) is offered as first choice intravesical therapy, and on its failure, tacrolimus (0.1 mg/kg dissolved in sterile water) is instilled in the bladder as a second choice of intravesical therapy.<sup>46</sup> Initially DMSO was used to dissolve the tacrolimus powder, but now we use distilled water to dissolve the tacrolimus since it is more patient-friendly and increases compliance.<sup>47</sup> In case of flare up of disease anesthetic cocktail can also be used as rescue solutions. DMSO, hyaluronic acid, chondroitin sulfate, etc., are other solutions which have been used for intravesical therapy.

### Stage III: Surgery

Surgery is offered as a last resort to those patients who have a miserable life and have failed all other therapies. Procedures including patch cystoplasty, substitution cystoplasty, and neobladder with or without cystectomy are done with varying success. We have experience of patch cystoplasty in IC/BPS with very good results.

### Intravesical Botox Injection

- As BoNT-A involves inhibition of suburothelial neurotransmitter release of sensory neuropeptides and neurotransmitters; there is a rationale for its use in IC/BPS.
- BoNT-A injection relaxes the smooth muscles and increases functional bladder capacity through the inhibition of acetylcholine release. After a BoNT-A injection, both motor and sensory nerves are affected and patients experience symptomatic relief. It also has an anti-inflammatory effect.<sup>47</sup>
- Indicated if patient continues to suffer after adequate treatment with oral and intravesical agents.
- Invasive procedure performed with cystoscopy under spinal/general anesthesia.
- 100 or 200 unit of BoNTA is injected in detrusor muscle or submucosally either in the bladder wall or trigone
- Will benefit around 50% of the patients
- Need for repetition every 6–9 months
- Short-term efficacy with serious side effect profile

- Common AEs are dysuria, the need for abdominal straining to void, large postvoid residuals (>100 mL), and the need for clean intermittent self-catheterization (CISC) that may persist for one to three months and in some cases longer
- BoNTA may not work if pain is main symptom.
- Based on the inconstant results available in the literature and the lack efficacy in randomized clinical trials (RCTs), no clear statement on the efficacy on BoNT-A in the treatment<sup>48</sup> of IC/BPS can be drawn.
- My initial experience with Botox was not encouraging so do not use it routinely in my practice.

## ■ NEUROMODULATION

Neuromodulation is electrical stimulation of nervous system to accomplish therapeutic effect. Different types of neuromodulations are mentioned in **Box 4**.

### Salient Features of Sacral and Pudendal Neuromodulation

Sacral or Pudendal neuromodulation is not USFDA approved for IC/BPS. The procedure is invasive and is indicated only in patients of intractable IC/BPS. Change in device implantation technique and technology has made the procedure minimally invasive. Recent developments are like better lead placement, better programming including cycling, body compliant leads, rechargeable batteries and MRI compatible equipment. InterStim micro and InterStim 2 are advanced models. This procedure is not popular in India due to cost and complications such as relapse of symptoms, explanations, and resurgery.

- Two different types of trial—(1) PNE and (2) staged tined lead implantation
- How SNM works in IC/BPS is not understood?
- In first stage, trial with temporary stimulation of nerves done and if patient's symptoms improve >50%, then permanent implant is placed.
- After testing only around 50% of patients will be eligible for SNM
- SNM showed improvement in pain score, urgency, frequency, and increase in bladder capacity in a meta-analysis

#### BOX 4: Types of neuromodulations.

- SNM: Sacral neuromodulation
- PNM: Pudendal nerve stimulation
- PTNS: Percutaneous tibial nerve stimulation
- TTNS: Transcutaneous tibial nerve stimulation
- TENS: Transcutaneous electrical nerve stimulation
- EA: Electroacupuncture

- Improvement was less in IC/BPS group than pain from other causes
- Adverse event in 30% of cases
- About 5% device failure or removal
- About 10% underwent implant revision/replacement
- About 3% needed battery change

Both intravesical BoNT-A treatment and SNM have been shown to have positive effects in patients with IC/BPS. However, firm conclusions cannot yet be drawn.<sup>49</sup>

Principles of multimodal therapy are enumerated in Box 5.

## COMPONENTS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME THERAPY (BOX 6)

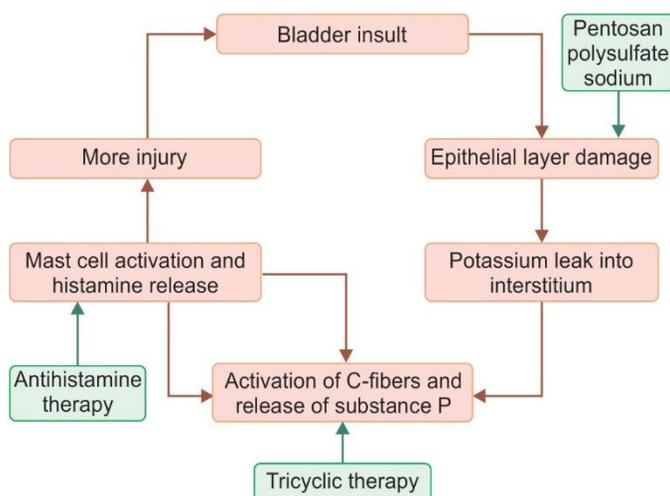
### Pentosan Polysulfate Sodium<sup>50</sup>

- Heparin analog, USFDA approved oral therapy.
- Doubtful evidence for effectiveness of pentosan as meta-analysis results from various trials are contradictory.
- Black box warning for pentosan by USFDA for irreversible retinal maculopathy.
- Corrects the deficiency of GAG layer decreases potassium leak in the interstitial space. PPS also induces broad anti-inflammatory actions, including the inhibition of mast cell induced histamine release in the bladder.
- Recommended dose is 100 mg TDS empty stomach. One trial did not find any difference in efficacy between 100 mg OD, 100 mg TDS, and placebo. Bioavailability of the drug is very poor.

#### BOX 5: Principles of multimodal therapy (Flowchart 3).

- Repair endothelial dysfunction
- Modulate neural function
- Stabilize mast cell

Flowchart 3: Multimodal therapy in a nutshell.<sup>23</sup>



- Full efficacy may not be seen before 5–6 months.
- Side effects headache, gastrointestinal (GI) upset, hair loss, rectal bleeding, and retinal maculopathy.
- Concern is finding of retinal maculopathy associated with chronic PPS use.
- Baseline retinal exam to be done before starting medication.
- Start retinal screening at 500 g of exposure (4.5 years with standard dose of 100 mg TDS) and then annually.
- About >1,500 g high risk.
- Concern for bleeding when taken with clopidogrel or high dose Ecosprin. Can be safely taken with low dose Ecosprin
- Patient compliance a major problem.
- We use PPS in few patients and for <1 year.
- RCOG had recently stopped recommending PPS

### Amitriptyline Hydrochloride

- Amitriptyline hydrochloride is the most commonly used drug
- Due to its antihistaminic and anticholinergic effects elevates mood; decreases pain; aids in sleeping
- Improves pain by inhibiting the reuptake of serotonin and norepinephrine
- Generally given at night in a dose of 10–100 mg
- More effective in >75 mg dose but side effects common

#### BOX 6: Components of IC/BPS therapy.

##### Oral therapy:

- Amitriptyline (antidepressant)\*
- Hydroxyzine hydrochloride (antihistaminic)\*
- Gabapentin\*
- Pentosan polysulfate sodium\*
- Steroids
- Cyclosporine A

##### Intravesical agents:

- Anesthetic cocktail\*
- Tacrolimus\*
- DMSO\*
- Hyaluronic acid
- Chondroitin sulfate
- PPS

##### Surgical therapy:

- Hydrodistention\*
- Transurethral resection or fulguration, laser, injection triamcinolone of Hunner's lesion\*
- Intravesical Botox injection
- InterStim
- Substitution cystoplasty or urinary diversion with or without

\*used by the author

(DMSO: dimethyl sulphoxide; PPS: pentosan polysulfate)

- Use 25 mg HS dose in most of the patients and in some patients 50 mg
- Common side effects are nausea, constipation, and drowsiness
- If patients cannot tolerate amitriptyline, then nortriptyline can be used
- Antidepressants can cause retention of urine due to anticholinergic properties and should not be used in patients with glaucoma.

### Hydroxyzine Hydrochloride

- Hydroxyzine hydrochloride is a most effective agent for the management of mast cell dysfunction
- Generally administered at night due to sedative effect
- Side effects are drowsiness, dry mouth, and constipation
- Dose 25–75 mg
- Use dose of 25 mg HS
- Dose of 10 mg in highly sensitive patients.

### Gabapentin

- Used for neuropathic pain or patients with severe pain
- Can decrease neurogenic inflammation
- Dosage 100–2,400 mg in divided doses
- Use dose of 100 mg HS.
- Side effects are nausea, constipation, and drowsiness.

### Cyclosporine A

- Calcineurin inhibitor
- Have been successful in treatment of autoimmune disease so tried in IC/BPS
- Cyclosporine more effective in HL-IC/BPS
- More effective than PPS<sup>51</sup>
- AEs common with cyclosporine and need close monitoring
- Renal toxicity, hypertension, and alopecia are common side effects
- Many patients stop treatment due to AEs.
- Symptoms come back after stopping treatment
- It is difficult to subject patients to long term CyA
- Patients taking CyA should have close monitoring, especially for renal function and blood pressure. A monitoring protocol should also take into account the risks of hepatotoxicity, hyperuricemia, hypomagnesemia, hematologic abnormalities and malignancies, and especially skin cancer and lymphomas.

### Certolizumab Pegol<sup>50</sup>

- New molecule being tried for treatment of IC/BPS based on the etiopathology hypothesis of antibody activation

- Novel anti-TNF  $\alpha$
- Treats autoimmune diseases such as Crohn's disease and rheumatoid arthritis
- Subcutaneous injections 400 mg
- Side effect has been UTI
- Can cause serious infections like tuberculosis as per USFDA label.

### Intravesical Therapy

- Anesthetic cocktail (N Mishra)
  - Marcaine 40 mL 0.5% (Sensorcaine)
  - Heparin sulfate 25,000 IU
  - Dexamethasone 2cc
  - Total 47 mL solution mixed and instilled in bladder
  - Dwell time 30 minutes
  - Total six instillation at interval of 15 days
- DMSO is the only USFDA approved intravesical therapy
  - DMSO promotes smooth muscle relaxation inhibits collagen and has anti-inflammatory effect.
  - About 50 mL of 50% DMSO instilled in bladder six times at an interval of 15 days
  - The dwell time should be limited to 15–20 minutes because holding for more time is associated with pain
  - Initially releases and depletes substance P from bladder wall
  - Stimulates mast cell deregulation
  - Medical grade DMSO is not available in India
- Intravesical tacrolimus
  - Formulation developed by N Mishra
  - 0.1 mg/kg body weight tacrolimus instilled in bladder
  - Capsule opened up and powder mixed in 20 cc of distill water
  - Dwell time 30 minutes
  - Three instillations at the interval of 15 days
  - AE is flare of symptoms for 2–3 days
  - Used in 71 patients
  - Takes time to act may be 6 months
  - Effective in 50% of patients.

### DIET AND LIFESTYLE CHANGES

- Ask patient to avoid diet which causes flare.
- Common food items causing flare—tomatoes, tomato products, soy, tofu product, spices (pepper, curry powder, mustard, horseradish, etc.), excessive potassium, citrus, high-acidity-inducing substances (caffeine, carbonate, and citric acid)
- Carbonated drinks and alcohol
- Green chilies
- Chocolates
- Sugar very rarely

**TABLE 2: Risk profile of various treatment modalities in pregnancy.**

PPS	Low risk
Hydroxyzine	High risk
Intravesical heparin	Recommended
Intravesical alkalized lidocaine	No data on safety
DMSO and systemic steroids	Known teratogens
Sacral nerve stimulator	Not to be placed during pregnancy and if already placed to be switched off

(DMSO: dimethyl sulphoxide; PPS: pentosan polysulfate)

- **Elimination diet:** A procedure used to identify foods which a person is intolerant of, in which all suspected foods are excluded from the diet and then reintroduced one at a time is recommended.
- Always advise patients to take less fluid which reduces frequency but some patients cannot tolerate concentrated urine and will need more fluid
- Stress reduction
- Pelvic floor relaxation
- **Yoga:** Only those *asanas* are advisable which do not cause contraction of pelvic muscles. *Kapalbhati* and *moolbandh asanas* are to be avoided.

## PREGNANCY AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

In our series 15 patients became pregnant in the last 30 years. The pregnancy did not affect the course of the disease. Neither the responders among this group worsened after pregnancy nor did the nonresponders improve after pregnancy. Although, some of them did have temporary benefits during the pregnancy none of the patients had moderate or marked improvement due to pregnancy<sup>37</sup> (Table 2).

### Treatment Safety in Pregnancy<sup>52</sup>

Refer Table. 2

## INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PHENOTYPES

Phenotype means an observable trait. Bladder pain syndrome is believed to be a heterogeneous syndrome.

Proper phenotyping is essential for the diagnosis and treatment of IC/BPS and for facilitating research. Physicians believe that if IC/BPS patients can be divided in different groups it will be easy to treat them by focusing on one trait.

In 1987, Magnus Fall et al. described two types of IC as ulcerative and nonulcerative with different clinical picture.<sup>8</sup>

In 2009 UPOINT was proposed by Shoskes and Curtis Nickel.

- *U:* Urinary
- *P:* Psychological
- *O:* Organ specific
- *I:* Infection
- *N:* Neurological/systemic
- *T:* Tenderness/tightness of muscles

This was modified by Shoskes to INPUT meaning infection, neurological, psychological, Hunner's ulcer, and tenderness of muscles.

In 2015 Chris Payne divided IC/BPS in following subtypes:<sup>53</sup>

- Hunner's lesion subtype
- Pelvic pain primary—bladder predominant
- Pelvic pain primary—pelvic floor/myofascial predominant
- Pelvic pain primary—pudendal neuralgia predominant
- Pelvic pain primary—mixed
- Systemic pain syndromes primary.

## HL-IC/BPS AND NHL-IC/BPS

In 2024 there is trend for dividing patients of IC/BPS two groups. Hunner's lesion disease is a bladder-centric condition with distinct cystoscopic, and pathological features, whereas non-Hunner's disease is a broader, systemic condition associated with other somatic and psychosocial syndromes. Patients with HL are called HL-IC/BPS and patients without HL are called as non-HL IC/BPS.<sup>54</sup> It is also being believed that HL-IC/BPS may be a different disease and there is need to take it out of the umbrella of IC/BPS. I believe that both are the same disease and have seen conversion from one to other in my patients. Evolution of HL is not very clear. HL-IC/BPS is a severe form of the disease and responds to same treatment options, except that the lesions can be resected or coagulated. In our experience HL-IC/BPS patients are a decade older, have less bladder capacity, require more rigorous management, and the response rate is less<sup>37</sup> (Table 3). I believe that HL are a severe form of IC/BPS. There is a need to identify HL by doing cystoscopy under anesthesia in the initial stages of management of IC/BPS.<sup>55</sup>

## INTRACTABLE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

It has not been defined in international literature. Our proposed definition of intractable IC/BPS is:

- Persistence of severe IC/BPS symptoms after adequate treatment with conservative/minimal invasive modalities such as oral therapy, intravesical therapy, and therapeutic hydrodistention which also includes endoscopic treatment of HL.

**TABLE 3:** Comparison of patients of HL-IC/BPS and NHL-IC/BPS in author's series. Total patients 181 (NHL-IC/BPS 144 patients and HL-IC/BPS 37 Patients).<sup>37</sup>

Points	NHL-IC/BPS	HL-IC/BPS
Average age (years)	44	52
Average capacity (mL)	566	288
<200 mL capacity (% of patients)	04	35
>701 mL capacity (% of patients)	22	0
Intravesical cocktail treatment (% of patients)	35	72
Intravesical tacrolimus treatment (% of patients)	19	46
Recystoscopy (% of patients)	09	22
Surgery (% of patients)	4	8
Marked improvement at follow-up (% of patients)	74	38
No improvement at follow-up (% of patients)	11	44

- The treatment options for intractable IC/BPS are oral cyclosporine A, injection BoNT-A, neuromodulation (sacral or pudendal), or reconstructive surgery.

### INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN CHILDREN

The diagnosis of IC in children is controversial. About 25% of IC patients report that they had chronic urinary tract problems in childhood.<sup>56</sup> Children do indeed present with dysfunctional voiding. There is no theoretical reason why IC cannot exist in children<sup>57</sup> and should be suspected in a child who presents with irritative symptoms and pelvic pain and has no definite diagnosis and has not responded to symptomatic treatment.

The presentation and treatment of IC/BPS in children is similar to Adults PPS, amitriptyline, hydroxyzine, and gabapentin are options for oral therapy. Dose has to be adjusted for pediatric patient intravesical options are anesthetic cocktail or DMSO in reduced doses.<sup>58</sup>

I am an adult urologist and have seen only four patients who would fit in the pediatric IC/BPS presentation in my 30 years of practice. I believe that most of these patients are managed as dysfunctional voiding by pediatricians.

A separate condition of extraordinary urinary frequency has been reported in children. This condition is described as abnormally increased diurnal frequency in a completely toilet-trained child with normal urinalysis. Onset is sudden and there is complete resolution in few months. I have seen one patient like this.

### WHAT NOT TO DO WHILE MANAGING IC/BPS PATIENTS?

- Long term oral antibiotics
  - Systemic (oral) long-term steroid administration
  - Intravesical BCG
  - Long duration high pressure hydrodistention (>10 minutes)
  - Repeat HD under anesthesia at short interval like 1–3 months
  - Hydrodilatation by raising the height of reservoir at the time of cystoscopy under anesthesia
  - Oral steroids
  - Painful procedure such as potassium test, office cystoscopy, and urodynamics
- The first four are also mentioned in AUA guidelines on IC/BPS.<sup>35</sup>

### AUTHOR'S CRITERIA FOR DIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN 2024

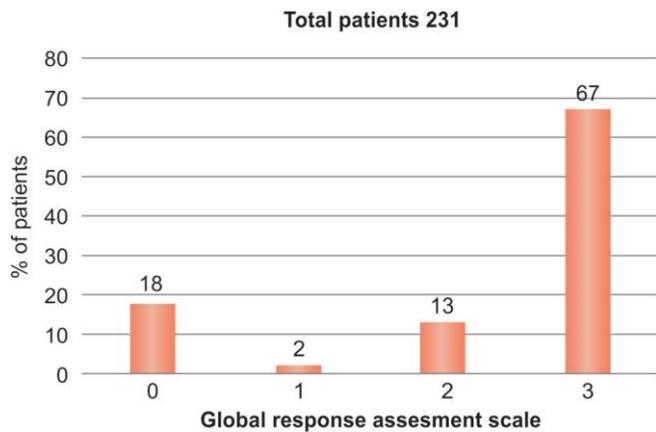
Interstitial cystitis/bladder pain syndrome should be suspected in a patient presenting with lower abdominal, penile, vaginal, and urethral perineal discomfort related to micturition:

- Discomfort means pain, pressure, burning, throbbing pain, piercing pain, or childbirth-type of pain
- Discomfort increases with bladder filling and reduces with bladder emptying
- Nocturia may or may not be present
- These symptoms are present for at least 1 month.
- USG (KUB) is normal, there **is** postvoid residue and urine culture is negative.
- No other disease responsible for the above symptoms.
- Under anesthesia, cystoscopy is either normal or shows the presence of pinpoint hemorrhage or ecchymosis or both. Hunner's lesion may be present.
- Diagnosis of IC should also be entertained in following group of patients:
  - Patients with culture positive urinary infection, but in whom the symptoms do not disappear after adequate treatment with a culture sensitive antibiotic
  - Patients of CAP who do not improve with treatment
  - OAB patients not responding to standard oral treatments.

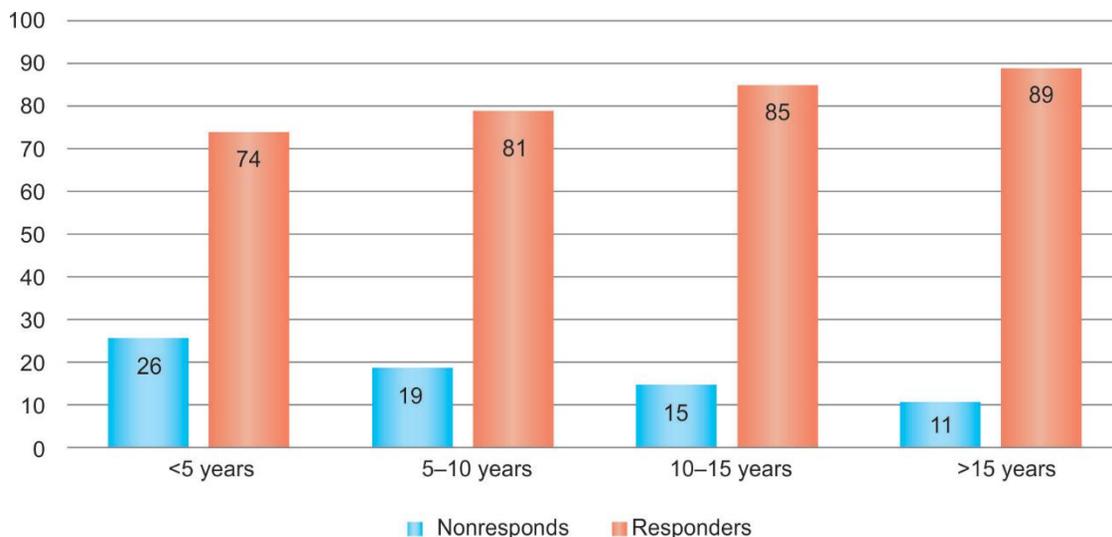
### EXPERIENCE AT AUTHOR'S CENTER

Since 1993 (till Dec. 2023) we have seen around 1,500 patients of IC and done cystoscopy in 521 patients. About 315 females and 206 males. Female:male ratio is 1.6:1. In

June 2021 we were able to telephonically contacted 231 out of 380 patients who presented to our center between 2001 and 2020 and asked them about their present disease in comparison to what they had at the time of first consultation with us. Mean follow up was 6.7 years and median 14 years. Out of these 231 contacted patients, cystoscopic data were available for 181 patients. Around 18 patients out of 231 died during this period. The response was evaluated on 7-point global response assessment scale. About 67% of patients had marked improvement, 13% had moderate improvement, 2% had mild, and 18% patients had no improvement. These patients were treated with modalities of treatment which were available at the time of presentation (Figs. 9 and 10).



**Fig. 9:** 20 years long-term follow-up of patients treated at the center from 2001 to 2020. Total number of patients 231. Note: GRA grade—0 no improvement, 1 mild improvement, 2 moderate improvement, and 3 marked improvements.



**Fig. 10:** 20 years long-term follow-up of patients treated at the center from 2001 to 2020. Total number of patients is 231. Responders mean moderate and marked improvement and nonresponders mean mild or no improvement on a 7-point GRA score. Very good result even inpatients followed for >15 years.

Recystoscopy is done if the patient responds to the treatment for >1 year and then starts developing symptoms again. During the same period 30 patients underwent recystoscopy and re-hydrodistention for recurrent disease. We have seen HL developing in patients with NHL-IC/BPS and also HL disappearing in patients of HL-IC/BPS. In some patients HL have changed location in bladder and also there is increase of decrease in number of HL. We believe that HL-IC/BPS and NHL-IC/BPS are part of one syndrome and treat them in similar way. We fulgurate the HL as basic treatment. About 18% of patients in our series have HL. This is more than the normal 10% incidence of HL as we are tertiary referral center for IC/BPS.

Our experience with BoNT-A injection is not good. InterStim (neuromodulation) has not been performed by us in any patient.

Reconstructive surgery is our preferred modality of treatment for patients of intractable IC/BPS. From January 2012 we have performed patch ileocystoplasty in 19 patients of intractable IC/BPS. Two patients died due to causes unrelated to surgery sodata from 17 patients (11 females and 6 males) were analyzedand their present condition was assessed on a 7-point GRA scale. The mean age was 48 (23–61) years at the time of surgery. Average pre surgery maximal bladder capacity (MBC) under anesthesia was 310 mL (100–600). 11 patients had Hunner's lesion (HL). Mean follow-up was.38 years and median were 3 years. About 14 patients void with minimal residue and 3 patients need clean intermittent catheterization. 14/17 patients have marked improvement and this improvement is maintained in long term also. First patient operated in 2012 is symptom-free after 11 years. I recommend reconstructive surgical therapy in all patients

of intractable IC/BPS who have not improved despite multiple adequate treatment as results of surgery are very good. For example, all the patients in our small series of 17 patients have improved after surgery and have very good quality of life. There is a misconception in IC/BPS world that patients can have pain even after surgery and due to this urologists are reluctant in operating patients of intractable IC/BPS. I agree that there can be few patients who have not got relief from reconstructive surgery and continue to suffer without treatment. I believe that most patients of intractable IC/BPS should not be denied surgery because few patients have not improved, but surgery should be offered only as last resort. Results of all types of reconstructive surgery are very encouraging and range from 70 to 90%. We prefer patch cystoplasty as it has minimum morbidity in comparison to other surgical options available for IC/BPS and equally good results. Patch cystoplasty does not involve extensive resection, so patients have minimum surgical morbidity and complications. About 80% patients void naturally with minimum residue. No long-term medication is needed for metabolic complications as very small intestinal segment is used. There is no effect on sexual functions in both males and females. Surgical complications of patch cystoplasty are minor and can be managed easily.

### ■ TAKE HOME MESSAGES

- IC/BPS should always be in the mind while managing a patient with pain, urinary urgency, and frequency.
- Pelvic discomfort means pain, pressure, burning, piercing, and throbbing sensation.
- Initial patient management must include cystoscopy under general or spinal anesthesia to find out and treat HL.
- No procedures which give pain to patient are justified.
- Treatment should be done in a planned manner and in justified timeline.
- Both HL-IC/BPS and NHL-IC/BPS can have severe disease.
- Both small capacity and large capacity bladder can have severe disease.
- Even patients with large capacity bladder benefit from reconstructive surgery.
- Patients should be offered surgery if they not improve after adequate treatment.
- Results of surgery are better in comparison to other modalities of treatment.
- Persistence of pain in one patient should not deny surgery to 99 patients.
- The approach of physicians should change from negative to positive while dealing with IC/BPS patients.
- We have proved that long-term good results are possible.

- The initial diagnostic and therapeutic cystoscopy should be done by most experienced urologist in the team so important findings are not missed.

### ■ CONCLUSION

In 2024 there is consensus regarding name of disease and definition of IC/BPS. Etiopathology is elusive and no standard management protocol is defined yet. We have positive results in treating IC/BPS in long run. Introduction of intravesical tacrolimus and good results of surgery has given us confidence in managing IC/BPS patients. Immediate future need is to unlock etiopathology and prepare a simple and effective management algorithm. There is unmet need to develop drugs for curing IC/BPS. I hope that scientist all over the world will work harder to give IC/BPS patients very good quality of life.

### ■ REFERENCES

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