

Interstitial cystitis (IC) Or Painful bladder syndrome (PBS)

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- What is IC/PBS?
- What is the cause of interstitial cystitis?
- What are the signs and symptoms of interstitial cystitis?
- How is interstitial cystitis diagnosed?
- What is the treatment of interstitial cystitis?

What is IC/PBS?

Interstitial cystitis (IC) or painful bladder syndrome (PBS) is a chronic disease characterized by :

- * Urinary urgency
- * Frequency
- * **Discomfort**, pressure or **pain** in the bladder, suprapubic, and the surrounding pelvic region

Although the term "cystitis" but there is **no infectious organism** has been identified in people with interstitial cystitis.

The International Continence Society (ICS) criteria state:

Painful bladder syndrome is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased day-time and night-time frequency, in the absence of proven urinary infection or other obvious pathology.

The ICS believes this to be a preferable term to "interstitial cystitis." Interstitial cystitis is a specific diagnosis and requires confirmation by typical clinical cystoscopic and possibly histological features.

In 2006, another set of diagnostic criteria were proposed by the European Society for the Study of IC/BPS, suggesting the use of the term bladder pain syndrome (BPS):

A diagnosis of **IC/PBS** is made on the basis of the symptom of chronic discomfort, pressure or pain related to the urinary bladder accompanied by at least one other urinary symptom such as day-time and night-time frequency, AND exclusion of confusable diseases as the cause of the symptoms, AND cystoscopy with hydrodistension and biopsy if indicated (to document the type of **IC/PBS**).

What is the cause of interstitial cystitis?

Various etiologies have been proposed, none of which adequately explains the variable presentations, clinical courses, or responses to therapies.

* It is not known for sure what causes PBS/IC, but many believe that, there is normally a thin layer covers the inner surface of the bladder to prevent the contact of urine and its toxic harmful content to protect the inner lining surface of the bladder, this layer called **glycocalyx**, it consists of substances called glycosaminoglycans (GAGs) and mucins.

Cracks in this layer allow substances in urine to pass into the bladder wall, local chemical inflammatory reaction, scarring of bladder wall, loss of its elasticity, turn rigid, decrease of its capacity, dysurea, frequency and chronic pelvic pain.

* IC/PBS may be due to neurological hypersensitivity, it means increase the sensitivity of sensory nerves of the bladder wall.

* Also, there is substance named " antiproliferative factor (APF) " inhibits the normal growth of cells of the layer that lining of the bladder. Detection of " antiproliferative factor (APF)" in the urine of the majority of patients complaining of IC/PBS .

* Autoimmune disorder

* Pathogenic role of mast cells in the muscles and/or mucosal layers of the bladder

* Production of a toxic substance in the urine.

* The urologic pelvic pain syndromes, such as IC/BPS and CP/CPPS, may have no initial trigger other than anxiety, often with an element of Obsessive Compulsive Disorder or other anxiety-spectrum problem. (6)

What are the signs and symptoms of interstitial cystitis?

Symptoms:

The symptoms of PBS/IC vary greatly from one patient to another.

The symptoms of PBS/IC have some similarities to those of a urinary tract infection.

IC/PBS is more common in women than in men.

The most common symptoms of IC/PBS are :

- * Urinary urgency
- * Frequency
- * Discomfort, pressure or pain in the bladder, suprapubic, and the surrounding pelvic region.

The **pain**, is found in 100% of patients, **frequency** (82% of patients), **urgency** and nocturia (62%).(7) **Dyspareunia** , and discomfort and difficulty driving, travelling or working.

Patients with interstitial cystitis are more likely to have:

* Previous gynecologic surgery.

* History of urinary tract infections and bladder problems.

* PBS/IC could be associated with several chronic illnesses, including inflammatory bowel disease, systemic lupus erythematosus, irritable bowel syndrome, fibromyalgia, and atopic allergy. Psychiatric conditions associated with interstitial cystitis include anxiety disorder, depression, and adjustment reactions.

Most patients suffering from PBS/IC have both **urinary frequency/urgency and pelvic pain**, although these symptoms may also occur singly or in any combination. In most women, **symptoms usually worsen around the time of their periods**.

The symptoms usually have a slow onset, and urinary frequency is the most common early symptom. As PBS/IC progresses over a few years, **cycles of pain (flares) and remissions occur**. Pain may be mild or so severe as to be debilitating. **Symptoms can vary from day to day**.

How is interstitial cystitis diagnosed?

No specific physical findings are associated with PBS/IC, except tenderness of the bladder either when pushing on the abdomen over the bladder or during the pelvic examination in women.

There is no definitive diagnostic investigations to identify PBS/IC. Symptoms of PBS/IC are similar to many of other urinary system disorders, in many cases the diagnosis is made by **exclusion**. Among the disorders to be excluded are urinary tract infections, cancer bladder, overactive bladder, urithritis, urethral syndrome, trigonitis, eosinophilic and tuberculous cystitis, urinary tract stones, neurological disorders ... etc

If urine analysis and urine culture revealed **sterile urine** for weeks or months while symptoms persist, a diagnosis of PBS/IC is consider.

The **previous** gold standard test for IC/BPS was the use of hydrodistention with cystoscopy. During cystoscopy, only 5 to 10% of patients who have IC/BPS are found to have Hunter`s ulcers.

Some researchers, however, determined that **cystoscopy is not specific for IC/BPS** and the cystoscopy itself can contribute to the development of small glomerulation (petechial hemorrhages) often found in IC/BPS.

Thus, a diagnosis of IC/BPS is one of exclusion, as well as a review of clinical symptoms.

In general, cystoscopy is performed while the patient is under anesthesia in order to provide sufficient distention to examine for coexisting urethral and bladder pathology (eg, transitional cell carcinoma) and features of interstitial cystitis, such as **Hunner ulcers and glomerulations**. Bladder capacity values are also recorded.

No pathognomonic histologic findings exist for interstitial cystitis.

Urodynamic studies are **not** part of the routine interstitial cystitis evaluation.

Potassium Sensitivity Test: Some authors have found that certain subgroups of patients with interstitial cystitis have increased urothelial permeability to certain intravesical constituents. This potential property is exploited in the potassium sensitivity test as a diagnostic test for interstitial cystitis.

In patients with interstitial cystitis or other conditions of the bladder that affect urothelial permeability, the patient experiences acute and severe pain with intravesical instillation of the potassium chloride solution. Patients who do not have interstitial cystitis experience little or no pain from the solution. Due to its lack of sensitivity and specificity, this test does not usually alter clinical decision-making and thus is generally **not** recommended.

Diagnosing interstitial cystitis remains difficult even more than a century after it was described by Skene, in 1887. No pathognomonic findings exist

with regard to patient history, physical examination findings, laboratory findings, or cystoscopy findings.

The exclusion of other clinical entities remains the foremost goal of the work up and evaluation of patients thought to have this condition.

The differential diagnosis of urinary frequency, urgency, and/or pain includes the following types of conditions:

- Infectious or inflammatory
- Gynecologic
- Urologic
- Neurologic

Infectious or inflammatory conditions to consider include the following:

- Recurrent urinary tract infection (UTI)
- Urethral diverticulum
- Infected Bartholin gland or Skene gland
- Vulvovestibulitis
- Tuberculous/eosinophilic cystitis
- Vaginitis (eg, bacterial, viral [eg, herpes])
- Schistosomiasis

Gynecologic causes to consider include the following:

- Pelvic malignancy or mass (eg, fibroid, endometrioma)
- Endometriosis
- Mittelschmerz
- Pelvic inflammatory disease
- Genital atrophy

Urologic causes to consider include the following:

- Bladder cancer or carcinoma in situ (CIS)

- Radiation cystitis
- Overflow incontinence
- A contractile detrusor
- Chronic pelvic pain syndrome
- Bladder outlet obstruction (eg, urinary retention with overflow incontinence)
- Large postvoid residual volume
- Open bladder neck (eg, intrinsic sphincteric deficiency, urolithiasis, urethritis)

Neurologic causes to consider include the following:

- Neurogenic detrusor overactivity
- Parkinson disease
- Lumbosacral disk disease
- Spinal stenosis
- Spinal tumor
- Multiple sclerosis
- Cerebrovascular accident

Other possible diagnoses to consider include the following:

- Dysfunctional voiding
- Vulvodynia
- Pelvic floor myalgia
- Degenerative joint disease
- Hernia
- Inflammatory bowel disease
- Gastrointestinal neoplasm
- Diverticulitis
- Adhesions from prior surgery

In 2006, the ESSIC (International Society for the Study of BPS) society proposed more rigorous and demanding diagnostic methods with specific classification criteria so that it cannot be confused with other, similar conditions.

Specifically, they require that a patient must have **pain** associated with the bladder, accompanied **by one other urinary symptom**. Thus, a patient with just frequency or urgency would be excluded from a diagnosis. Secondly, they strongly encourage the exclusion of confusable diseases through an extensive and expensive series of tests including (A) a medical history and physical exam, (B) a dipstick urinalysis and various urine cultures, (C) flowmetry and post-void residual urine volume by ultrasound scanning and (D) cystoscopy. A diagnosis of IC/BPS would be confirmed with a hydrodistention during cystoscopy with biopsy.

Diagnosis has been greatly simplified in recent years with the development of two new methodologies. The Pelvic Pain Urgency/Frequency (PUF) Patient Survey, created by C. Lowell Parsons, is a short questionnaire that will help doctors identify if pelvic pain could be coming from the bladder.

In 2009, Japanese researchers identified a urinary marker called **phenylacetylglutamine** that could be used for early diagnosis.

What is the treatment of interstitial cystitis?

Ongoing reassurance and physical and emotional support are important as the diagnostic evaluation progresses and therapies are applied.

Oral medications

** Oral **pentosan polysulfate** is the most popular oral medication is the heparinoid (heparin-like) drug named pentosan polysulfate sodium (PPS); its brand name **Elmiron**.

PPS is chemically similar to the substance that lines the bladder, and it is believed that PPS assists in the repair or restoration of the lining tissues in the bladder.

Even after therapy with PPS has begun, patients may still experience symptoms for some time because the sensory nerves in the bladder have been hyperactive, and it takes time for the nerves to return to their normal

state of activation. Therefore, it is recommended giving up to one year of PPS treatment in mild PBS/IC and two years in severe PBS/IC, before deciding if the drug is effective or not. Between one-third and two-thirds of patients will improve after three months of treatment.

Oral **pentosan polysulfate** is believed to provide a protective coating in the bladder, but there are some studies show it is not statistically significant compared to placebo. (9)(10) However, some studies have found that a minority of patients do respond to pentosan polysulfate. (11)(12)

** **Antidepressants of the tricyclic group** may be used to treat PBS/IC along with other oral medications. This is not due to a belief that PBS/IC is a psychological condition; rather, tricyclic antidepressants can help reduce the hyperactivation of nerves within the bladder wall.

Amitriptyline

Amitriptyline can reduce symptoms in patients with IC/BPS. (13) Patient overall satisfaction with the therapeutic result of amitriptyline was excellent or good in 46%. (14) A May 2010 study concluded in part that amitriptyline may be beneficial in doses greater than 50 mg.(15)

Duloxetine

The newest entry into the field of antidepressants is duloxetine (Cymbalta), a drug that also has FDA approval for use in nerve injury pain. This is the first drug that the FDA had indicated may be useful as a single agent against depression and pain.

There are some reported the antidepressant duloxetine (Cymbalta) was found to be ineffective as a treatment. (16)(17) There is a U.S. Patent 6150396 for the use of duloxetine for treatment of interstitial cystitis although one study found positive outcomes in only a small proportion of cases.(18)

There has been further work to suggest that neuropathic pain localized in the pelvic region may respond to neurotransmitter re-uptake inhibitors.

** **Antiseizure** medication gabapentin (Neurontin, Gabarone) has also been used to treat nerve-related pain and has sometimes been used to treat the pain of IC/PBS.

** **Oral antihistamines** may also be prescribed to help reduce allergy symptoms that may be worsening the patient's PBS/IC. (19)(20)(21)(22)

** Aspirin and ibuprofen are sometimes used as a first line of defense against mild discomfort. However, they may make symptoms worse in some patients.

** Over-the-counter, forms of phenazopyridine hydrochloride may provide some relief from urinary pain, urgency, frequency, and burning.

Intravesical therapy

Bladder instillation is considered a bladder wash or bath. In which, the bladder is filled with a solution that is kept for varying periods of time, from a few seconds to 15 minutes, before being drained.

In severe cases of PBS/IC, intravesical solutions may be administered along with oral medications to provide relief until the oral medication has had time to take effect.

Solution used for bladder instillation composed of **pentosan polysulfate or heparin, sodium hyaluronate, lidocain and sodium bicarbonate**, has generated considerable excitement in the IC/BPS community because it is the first therapeutic intervention that can be used to reduce a flare of symptoms. Published studies report a 90% effectiveness in reducing symptoms. (23)

Sometimes these bladder instillations are given on a regular basis for treatment. It is important to note that this is off-label use for both pentosan polysulfate and heparin, as neither medicine has been approved to be used this way.

Drugs that have been used for bladder instillations include **dimethyl sulfoxide** (DMSO, RIMSO-50), **heparin**, **sodium bicarbonate**, **pentosan polysulfate sodium (Elmiron)**, and **hydrocortisone**.

DMSO

DMSO (dimethyl sulfoxide), a wood pulp extract, is the only approved bladder instillation for IC/BPS yet it is much less frequently used in urology clinics. Research studies presented at recent conferences of the American Urological Association by C. Subah Packer have demonstrated that the FDA approved dosage of a 50% solution of DMSO had the potential of creating irreversible muscle contraction. However, a lesser solution of 25% was found to be reversible. Long term use is questionable, at best, particularly given the fact that the method of action of DMSO is not fully understood. (24)

Bladder coatings

Other bladder coating therapies include **Cystistat** (sodium hyaluronate) and **Uracyst** (chondroitin). They are believed to replace the deficient **glycosaminoglycans** (GAG) layer on the bladder wall. Like most other intravesical bladder treatments, this treatment may require the patient to lie for 20 – 40 minutes, turning over every ten minutes, to allow the chemical to 'soak in' and give a good coating, before it is passed out with the urine.

Cystistat is not currently available in the United States or Canada, though testing has recently started in Canada. Testing has also begun for Uracyst in both Canada and the United States. Uracyst is available in Canada.

Diet

In 2007, a study done at Long Island University reported that over 90 percent of interstitial cystitis patients experience an increase in symptoms when they consume certain foods and beverages, especially coffee, tea, soda, alcoholic beverages, citrus fruits and juices, artificial sweeteners and hot pepper. (25)

The American Urological Association states that most (but not all) people with IC find that certain foods make their symptoms worse. (26)

The challenge with diet triggers is that the harmful diet vary from person to person, the best way for a person to discover her own regimen aiming to avoid those foods which can further irritate the damaged bladder wall.

The mechanism by which how can stop taking some food dietary benefits patients with IC is **unclear**. Researchers hypothesize that integration of neural signals from pelvic organs mediates the effects of diet on symptoms of IC.

A study done at University of South Florida found that IC/BPS patients do not have to be overly restrictive of their diets. This study recommended that patients avoid **citrus fruits, tomatoes, coffee, tea, carbonated and alcoholic beverages, spicy foods, artificial sweeteners, and vitamin C**.

It also found that many patients had reduced sensitivity to trigger foods if they consumed **calcium glycerophosphate** and/or **sodium bicarbonate**. (27)

The certain foods that make symptoms worse, **including alcohol, foods containing acid, for example, tomatoes, vitamin C, carbonated beverages, citrus fruits and beverages, cranberries, grapes, mango, guava, strawberries, pineapple, and vinegar** are believed to aggravate PBS/IC.

Other foods that may increase symptoms because they contain the **natural chemical tyramine** include **wine, beer, cheese, nuts, yogurt, bananas, soy sauce, chicken livers, raisins, sour cream, avocados, canned figs, corned beef, fava beans, brewers' yeast, and chocolate**.

Some patients with PBS/IC also have noticed a worsening of symptoms after eating or drinking products containing **artificial sweeteners**.

Patients may try eliminating such all mentioned products from their diet and, if there is a reduction of symptoms, they can reintroduce them one at a time to determine which product seems to be aggravating their symptoms.

Smoking

Many PBS/IC patients feel that smoking worsens their symptoms. (Because smoking is the major known cause of bladder cancer, one of the best things a smoker can do for the bladder is to quit smoking.)

Exercise

Many PBS/IC patients feel that regular exercise, helps relieve symptoms and, in some cases, hastens remission.

Bladder training

People who have found some relief from pain may then be able to reduce frequency using bladder training techniques. Methods vary but basically the patient decides to urinate at designated times and uses relaxation techniques and distractions to help keep to the schedule. Gradually, the patient lengthens the time between urinations. A diary usually is helpful in keeping track of progress.

Acupuncture

A 2002 review study reported that Acupuncture alleviates pain associated with IC/BPS as part of multimodal treatment. (28) While a 1987 study showed that 11 of 14 (78%) patients had a >50% reduction in pain, (29) another study (published in 1993) found no beneficial effect. (30) A 2008 review found that although there are hardly any controlled studies on alternative medicine and IC/BPS, "rather good results have been obtained" when acupuncture is combined with other treatments. (31)

Biofeedback

Biofeedback, a relaxation technique aimed at helping people control functions of the **autonomous nervous system**, has shown some benefit in controlling pain associated with IC/BPS as part of a multimodal approach

that may also include medication or hydrodistention of the bladder.
(32)(33)(34)

Surgical therapies for interstitial cystitis

Surgical interventions are **rarely** used for IC/BPS. In severe cases of PBS/IC that do not respond well to oral medications or to bladder distension or instillation, more invasive surgical procedures may be attempted.

A procedure known as **Sacral Neuromodulation** has been shown to be effective in controlling symptoms in some people with PBS/IC.

Sacral neuromodulation is a new treatment for women with urgency and urge incontinence. “Sacral neuromodulation is a very important new breakthrough in the treatment of the overactive bladder. It provides an effective solution for women when conservative treatment has not worked. It avoids the risk of catheters with major surgery.” Jeremy Ockrim, Consultant Urologist, Harley Street Urology.(4)

The term "neuromodulation" refers to an alteration of the nervous system. In sacral neuromodulation, a device is implanted that allows for electrical impulses to stimulate the nerves in the sacral area. Sacral neuromodulation is believed to work by inhibiting the hyperactive signals from the sensory nerves within the bladder wall.

Minimally invasive sacral neuromodulation implant technique. After the percutaneous nerve evaluation test, a small longitudinal incision (3 cm) is made, and a catheter cannula segment is inserted through the sacral foramen beside an insulated needle. The electrode is introduced into the catheter cannula, which is then removed and fixed to the sacrum by means of small anchors. The proximal part of the lead is tunneled into the subcutaneous tissue, reaching the pocket made to accommodate the neurostimulator. (5)

Therapies that also have been used include **Transcutaneous Electrical Nerve Stimulation (TENS)**, a form of neuromodulation that does not involve surgical placement of wires or an impulse generator. With TENS, mild electric pulses enter the body for minutes to hours two or more times

a day either through wires placed on the surface of the lower back or the suprapubic region, between the umbilicus and the pubic hair, or through special devices inserted into the vagina in women.

It is believed that the electric pulses may increase blood flow to the bladder, strengthen pelvic muscles that help control the bladder, and trigger the release of hormones that block pain. TENS is generally more effective in reducing pain than in reducing urinary frequency.

Other surgical interventions for IC/BPS include transurethral fulguration and resection of ulcers, using electricity/laser; bladder denervation, where some of the nerves to the bladder are cut (Modified Ingelman-Sundberg Procedure); bladder removal (cystectomy).

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