

Bladder pain syndrome/interstitial cystitis

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Introduction

The European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC) has recently suggested a change of the name to *bladder pain syndrome* (BPS) to differentiate it from other urologic pain syndromes such as urethral pain syndrome, prostate pain syndrome, and others.^{1,2} The Washington DC Consensus Group on IC/PBS favoured retaining the name *interstitial cystitis/painful bladder syndrome*.³

Definitions

- **Bladder pain syndrome (BPS)**
BPS is chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder and accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency, in the absence of infection or other pathology.^{1,2,3}
- **Interstitial cystitis (IC)**
Interstitial cystitis is BPS with typical cystoscopic and/or histological features.⁴

Incidence

BPS/IC is mainly found in women (90%). Prevalence: 60 per 100 000 women. Men may be incorrectly diagnosed as having non-bacterial prostatitis, or prostatodynia (pain in the prostate).⁵

Pathogenesis of BPS/IC (How does it start?)

In the normal bladder the epithelium is covered with a mucous lining called glycosaminoglycans (GAG layer). It provides an impermeable barrier. The process that leads to the development

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of BPS/IC is triggered by an insult to the urothelium, such as bacterial cystitis, childbirth or surgery. In people prone to BPS/IC this protective GAG layer disappears and allows leakage and absorption of urinary solutes to occur; the major solute being potassium (Figure 1). Ongoing exposure of the bladder wall to potassium and other urinary metabolites cause inflammation, irritation and injury. Histamine and other pro-inflammatory chemical substances are released by the mast cells. Histamine activates C-nerve fibres, which release substance P and other neuropeptides that cause further cell damage and mast cell activation (neurogenic inflammation) (Figure 2). This results in local inflammation with tissue damage and irritation of the sensory nerves located in the bladder wall. This could be part of an autoimmune condition.^{6,7,8}

Symptoms

The primary symptom of BPS/IC may be the persistent urge to void, which leads to urinary frequency during daytime and at night. The average patient with BPS/IC voids 16 times per day (and may be as often as 60 times a day). Patients often experience bladder pain,

pressure or spasm that may increase as the bladder fills and urinating usually alleviates the pain and gives a temporary sense of relief. Bladder pain may be associated with suprapubic pain, pelvic pain, sometimes extending to the lower part of the back and groins and thighs. In women there may be pain in the vagina and in men pain in the penis, testes, scrotum and perineum. Both men and women may experience pain in the urethra and pain with sexual intercourse. The pain may be constant or intermittent. Although some patients may have a small bladder, other patients may have a normal-sized bladder with frequency due to hypersensitivity of the bladder.⁹

Flares

In the early stages of the disease the symptoms may only occur in attacks known as 'flares'. This leads many patients and their doctors to think that it may be an infection (bacterial cystitis), but urine cultures are negative. However, patients with BPS/IC may also develop infection, which can cause severe irritation of the already painful bladder. Symptoms may be exacerbated just before or during menstruation, during ovulation, taking contraceptive

pills or going through the menopause. Physical and emotional stress may exacerbate the symptoms but there is no proof that emotional stress causes the condition. The pain, frequency and persistent urge to void and lack of sleep may themselves be a significant cause of stress. Patients may notice an increase in symptoms after consumption of specific foods especially coffee, alcohol, carbonated drinks, citrus (vitamin C), tomatoes or chocolate.

Diagnosis

Symptoms

Pain, persistent urge to void and frequency for more than six months.²

Clinical examination

- Suprapubic tenderness
- Tenderness of the bladder base during vaginal examination of the anterior vaginal wall
- High tone pelvic floor muscle dysfunction with tenderness of the levator muscles in the lateral vaginal walls.

Voiding diary

Accurate recording of fluid intake and urine output for 24 to 72 hours.

Laboratory studies

Many of the tests and investigations are aimed at eliminating other confusable diseases such as urinary tract infections, kidney or bladder stones, bladder cancer, vaginal infection, sexually transmitted infections, radiation cystitis, chemical cystitis, eosinophilic cystitis, tuberculosis, schistosomiasis, endometriosis, prostatitis (in men), neurologic disorders including pudendal nerve entrapment, overactive bladder and urethral diverticulitis.

- Urinalysis and urine culture
- Urine cytology
- Vaginal cultures for Chlamydia, Herpes or other sexually transmitted infections if clinically indicated.

Potassium sensitivity test

Instillation of potassium into the bladder can cause significant pain but is now no longer considered to

Figure 1. Bladder wall

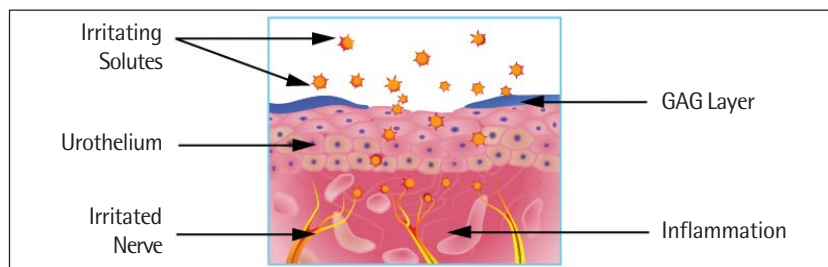
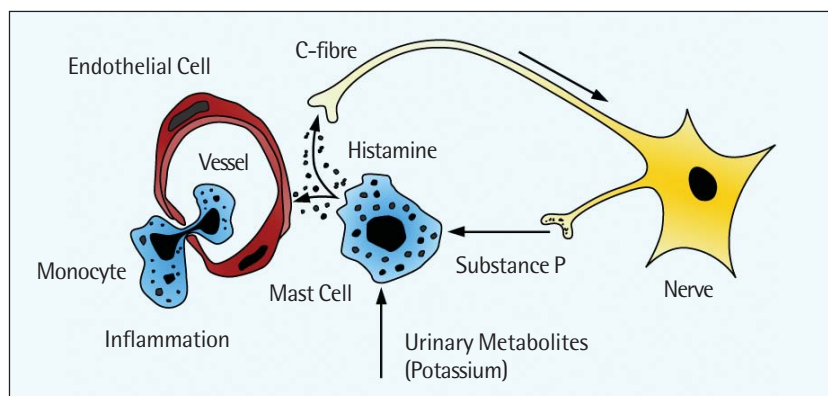


Figure 2. Mast cells



be sufficiently reliable for diagnostic purposes.

Urodynamic studies

Usually show a decreased maximum bladder capacity (less than 350ml). It is not considered essential in all women with BPS/IC, but is considered mandatory in men.

Cystoscopy with hydrodistension under general anaesthesia

This is recommended as a standard investigation for BPS/IC. Other causes of symptoms such as tumours and stones are excluded by cystoscopy. Hydrodistension is carried out by filling the bladder twice at the pressure of 80 to 100cm H₂O. As the walls of the bladder are stretched, pinpoint patchial haemorrhages, also known as glomerulations, or larger areas of submucosal bleeding (ecchymoses) are seen in about 90% of BPS/IC patients. Hunner's lesions are seen in less than 10% of people. In advanced cases there is tearing of the bladder mucosa during filling with rather typical development of bul-

lous edema. Hydrodistension of the bladder may improve symptoms in 60% of patients.⁶ Bladder volume under general anaesthesia in patients with BPS/IC may be as high as 850ml, but is usually less.

Bladder biopsy

Bladder biopsy may reveal inflammatory infiltrates, granulation tissue, increase in mast cells in the detrusor muscle and/or intrafascicular fibrosis.¹

All the above tests can temporarily exacerbate the symptoms and cause burning in the bladder, urethra and blood may be visible in the urine.

Treatment

Treatment is aimed at alleviation of the symptoms as no curative treatment has yet been found.

Patients with BPS/IC may be anxious, sleep deprived and frustrated. There is great therapeutic value simply in being a concerned clinician who understands BPS/IC. Most treatment regimes are multifactorial and highly individual.

Conservative therapies

Diet modification

Alphabetic list of potential bladder irritants: Alcoholic drinks, apples or apple juice, artificial sweeteners, avocados, bananas, beans, cantaloupe (melon), carbonated drinks/soda, citrus fruit and juices, cranberry juice, caffeine, chili, chocolate, cheese (aged), corned beef, grapes, peaches, plums, prunes/raisins, spicy food especially containing hot pepper, sour cream, tea, tomatoes, rye bread, vinegar, vitamin supplements such as vitamin C, yoghurt.^{6,9,10}

Smoking and certain oral drugs such as antibiotics may also irritate the bladder.

Urinary alkalinisation

Half a teaspoon of baking soda dissolved in a glass of water taken three times a day may be helpful, but as it has a high salt content it cannot be used in patients with salt restriction. Ural or Citravescent. Patients who desire some leniency in their diet can use Prelief (Calcium glycerophosphate).^{11,12}

Fluid intake

It is important to maintain a balanced fluid intake as concentrated urine may aggravate the pain. Restricting drinking in the evening may reduce the need for nighttime urination.

Bladder retraining (physiotherapy)

This may be helpful in patients with urinary frequency and urgency when the pain is controlled with medical treatment.

Exercise

A gentle exercise programme such as low impact aerobics, walking, swimming and pelvic floor muscle exercises may relieve symptoms. Patients with high tone pelvic floor dysfunction, spasms and tenderness in the levator ani muscle group may need to avoid tension in the pelvic floor muscles.

Avoid constipation

Constipation can exacerbate symptoms by causing pressure in the pelvic floor area. Many patients also

suffer from irritable bowel syndrome (IBS). They may experience bloating and in these patients treatment with a high fibre diet, painkillers and tricyclic antidepressants may aggravate the problem.

Stress avoidance & relaxation therapy

Avoid situations which make them physically or emotionally exhausted.

Clothing and hygiene

They should wear loose clothing and cotton underwear. Washing products and fabric softeners containing perfume can cause irritation. No perfumed products or bubble baths should be used near the urogenital area.

Heat/cold

Heat and cold packs; either can help when applied to the lower abdomen or perineum. Warm baths are also an option.

Travel

Use soft pillow. Plastic funnel available to pass urine standing up.¹³

Complementary therapies

- Herbal remedies – Chondroitin and glucosamine, CystoProtec, Aloe vera, Cysta-Q⁸
- Acupuncture
- Massage therapies
- Hypnotherapy.

Oral medications

Pentosan polysulfate sodium (Elmiron, Tavan, SP54)

These drugs repair the damaged GAG mucous lining of the bladder. Three to six months of therapy or more may

be needed to achieve symptom relief. Side effects include gastrointestinal upset, headache and hair loss.

Anti-inflammatory drugs

- **Corticosteroids** (hydrocortisone, prednisolone and dexamethasone); prednisone may be very effective in pain control in refractory patients.
- **Non-steroidal anti-inflammatory drugs** (aspirin, diclofenac and ibuprofen); NSAIDs inhibit the production of prostaglandins, which play an important role in stimulating inflammation.
- **Montelukast** (Singulair) – asthma drug inhibits the release of leukotrienes from mast cells.
- **Histamine-receptor antagonists:**
H1-receptor blockers: Hydroxyzine (Atarax), Promethazine (phenergan), Loratadine; Antihistamines for allergy may also be beneficial for the bladder condition.
H2 blockers: Cimetidine and Ranitidine. These drugs inhibit the release of histamine from mast cells.

Antispasmodics and anticholinergics/antimuscarinics

Oxybutynin, Vesicare (Solifenacin) and Tolterodine.

Anticonvulsants

Tegretol, Gabapentin (Neurontin). These drugs reduce nerve sensitivity.¹²

Tricyclic antidepressants

Amitriptyline, imipramine and nortriptyline. These drugs block the release of histamine, reduce nerve sensitivity, sedate pain and have a relaxing effect on the bladder muscle.

Figure 3. Glomerulations

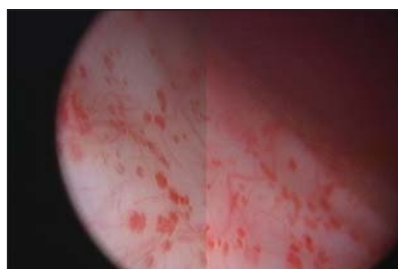
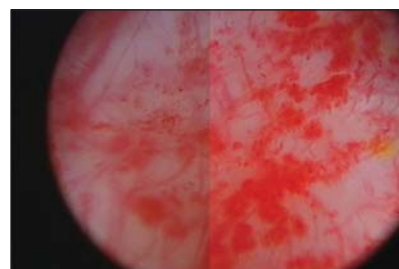


Figure 4. Ecchymoses



Analgesics

Normal painkillers are often not effective in many patients. In cases of extreme pain, long acting opioids may be necessary (morphine). Painkillers can be given as suppositories (paracetamol or paracetamol with codeine).

Bladder instillations (intravesical treatment)

This means that the medication immediately reaches the right place and far higher concentrations come into contact with the bladder wall than in the case of oral medication. Adverse effects are limited as there is relatively little absorption from the bladder into the bloodstream. Application of Lignocaine gel in the urethra before insertion of the catheter reduces pain on catheterisation.

DMSO (dimethyl sulfoxide)

This is an organic liquid with anti-inflammatory, analgesic and muscle-relaxant properties. The usual dose is 50ml, 50% DMSO intravesically every one to two weeks for four to eight weeks. It can be mixed as a 'cocktail' with heparin, hydrocortisone, sodium bicarbonate and lignocaine to increase its effects.

Heparin

This has an anti-inflammatory effect and can temporarily repair the GAG mucous lining of the bladder. It can take two to three months to produce an effect. It can be mixed with local anaesthetics and corticosteroids to increase the anti-inflammatory effect.

Chondroitin sulfate & Hyaluronic acid

These are believed to repair the bladder GAG layer. (Cystistat)

Heparin injections

Heparin can be injected underneath the skin three times per week.

The three components of BPS/IC should be treated simultaneously. These are:

1. GAG layer dysfunction
2. Mast cell hyperactivity
3. Neurogenic inflammation.⁸

Botox (Botulinum toxin A) injections

This blocks the nerves in the bladder and relaxes the smooth muscle of the bladder and reduces bladder pain and inflammatory reaction. In several small studies subjective improvement was observed in 69 to 85% of people.¹⁴

Hyperbaric oxygenation

Studies have produced encouraging results.

Neuromodulation/ electrostimulation

This is a very expensive option and not effective in patients with nerve damage as in the cases of diabetes, autoimmune diseases or damage to the spinal cord.

Percutaneous tibial nerve stimulation

This sends a mild electric current via the posterior tibial nerve to the sacral roots that control bladder function. It may help for selective patients suffering from urinary urgency and frequency and urgency incontinence.

Surgery

Removal of most of the bladder and replacement with bowel or removal of the whole bladder and urethra with urinary diversion or neo-bladder made from bowel. These procedures are not recommended and should only be performed as a last resort as patients may have 'phantom pain' even after removal of the bladder.

BPS/IC and other disorders⁹

Many patients with BPS/IC may also have one or more associated disorders:

- Allergy: Skin or systemic allergies may be present in 50% patients with BPS/IC
- Asthma
- Fibromyalgia
- Irritable bowel syndrome: This occurs in 40% of patients with BPS/IC. The reason for this association may be a common aller-

gen, similar nerve supply of the bowel and bladder and hormonal factors. Mast cells are increased in the intestine of IBS patients. In both conditions, mast cells were seen in close proximity to local nerve endings⁷

- Inflammatory bowel disease (Ulcerative colitis and Crohn's disease)
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjogren's syndrome
- Chronic fatigue syndrome: One should distinguish between tiredness resulting from a lack of sleep due to nightly excursions to the toilet
- Chronic non-bacterial prostatitis (prostatodynia): Men with ongoing 'prostatitis symptoms' should have a cystoscopy under general anaesthesia with hydrodistension of the bladder to exclude this condition
- Sensitive skin: Patients should avoid chemicals and perfumes
- Vulvodynia (Vulvar pain syndrome)¹⁵
- Endometriosis: 65% of women with chronic pelvic pain syndrome had BPS/IC and endometriosis.¹⁶
- Migraine¹⁷
- Detrusor overactivity.

Pregnancy and BPS/IC

Approximately 70% of women may experience remission during pregnancy although in others symptoms may get worse or symptoms may only start during pregnancy.

Treatment

Of the intravesical treatments, heparin is the safest as it is unlikely to be absorbed from the bladder or to cross the placenta. Intravesical lignocaine has minimal systemic absorption.

Hydroxyzine and amitriptyline have the lowest risks during pregnancy. Pentosan poly sulfate may be used during pregnancy but should preferably be discontinued.^{8,18}

Competing interests

None declared.

References

1. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. *Eur Urol* 2008 Jan; 53(1):60-67.
2. van de Merwe JP et al. ESSIC consensus on criteria, classification, and nomenclature for PBS/IC. 2007; www.essic.eu
3. Hanno PM. Re-imagining interstitial cystitis. *Urologic Clinics of North America* Feb 2008; 35(1):91-99.
4. van de Merwe JP et al. Interstitial cystitis: definitions and confusable diseases. ESSIC meeting 2005 Baden. *Eur Urol Today* March 2006; 4,5,18,19.
5. Warren J. Interstitial cystitis/painful bladder syndrome: An update for clinicians. www.medscape.com/viewprogram/5535_pnt
6. Penzera AK. Interstitial cystitis/painful bladder syndrome. *Urol Nurs* 2007; 27(1):13-19.
7. Theoharides TC. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J Neuroimmunol* 2004; 146:1-12.
8. Evans R. Diagnosing and treating interstitial cystitis: An interactive case. www.medscape.com/viewprogram/7199_pnt
9. Meijlink J. Painful bladder syndrome/interstitial cystitis (PBS/IC). International Painful Bladder Foundation 2007; www.painful-bladder.org 1-38.
10. Understanding Diet and IC. www.ic-network.com/handbook/diet.html
11. www.prelief.com
12. Milne D. New Zealand Painful Bladder Support Group Newsletters. weedot@xtra.co.nz
13. Plastic funnel. www.shewee.co.nz
14. Giannantoni A et al. Botulinum A intravesical injection for painful bladder syndrome. *Eur Urol* 2006; 49:704-9
15. www.nva.org
16. Chung MK et al. Interstitial cystitis and endometriosis in patients with chronic pelvic pain: The 'Evil Twins' syndrome. *JSLS* 2005; 9(1):25-9.
17. Tietjen GE et al. Endometriosis is associated with prevalence of comorbid conditions in migraine. *Headache* 2007 Jul-Aug; 47(7):1069-78.
18. Erickson DR et al. Pregnancy and interstitial cystitis/painful bladder syndrome. *Urologic Clinics of North America* Feb 2007; 34(1):61-69.