

# Painful bladder syndrome/interstitial cystitis: Aetiology, evaluation and management

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**Summary** *Interstitial cystitis or bladder pain syndrome (BPS) is often a chronic debilitating condition characterised by predominantly storage symptoms and associated frequently with pelvic pain that varies with bladder filling. The aetiology is uncertain as the condition occurs in the absence of a urinary tract infection or other obvious pathology. Resulting discomfort may vary and ranges from abdominal tenderness to intense bladder spasms. Diagnosis and management of this syndrome may be difficult and is often made by its typical cystoscopic features. This review discusses the diagnosis and management of interstitial cystitis according to the current available best evidence and advises a multimodal approach in its management.*

**KEY WORDS:** Bladder pain syndrome; Interstitial cystitis; Chronic Pelvic; Treatment; Management; Diagnosis.

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## INTRODUCTION

Interstitial cystitis (IC)/painful bladder syndrome (PBS) was defined in 2005 by the *International Society of Bladder Pain Syndrome (ESSIC)* as “the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology”. The definition of IC is the same as PBS, while also including “typical cystoscopic and/or histological features”. The ESSIC collectively term IC and PBS as *Bladder Pain Syndrome (BPS)*, however it's important that the distinction is made as this can affect patient management (1). To further define BPS, it's important to recognise that it is a form of *chronic pelvic pain (CPP)*, and therefore this review investigates not only its role but also other factors relating to CPP (2). CPP is difficult to classify, as it is defined by the symptom of pain and has no obvious associated cause, much the same as BPS (2). *Rackow et al.* define CPP as ‘pain that persists for six months requiring medical evaluation and intervention’. They concluded that in young women BPS is an aetiological factor for

CPP (3). This highlights the importance of considering both of them together by examining other factors beyond the bladder, as the cause of BPS. In their case study, *Warren et al.* found that the strongest risk factor for BPS is non-bladder syndromes (4). Therefore, studying the pathogenesis of non-bladder syndrome, of which CPP is included, might reveal the pathogenesis of BPS (4).

## Prevalence

*RAND Interstitial Cystitis Epidemiology (RICE)* conducted 146,231 household telephone calls in the United States and found that, according to the high sensitivity definition, 6.53% (95% CI 6.28, 6.79) of women met the symptom criteria of a BPS sufferer. Based on the high specificity definition, 2.70% (95% CI 2.53, 2.86) women met the criteria of a BPS sufferer. The study showed that BPS is an under-diagnosed condition and its prevalence may be higher in the population (5). *Parsons et al.* concur with RICE's study in as much that IC/PBS has a substantially underestimated prevalence (6). After surveying 8 studies, carried out between 1975 and 2005, they suggested that the prevalence over the last decade was 197 for every 100,000 women and 41 for every 100,000 men in the United States (6). *Nickel et al.* found the prevalence of interstitial cystitis to be 7.9% in women and 0.4% men when 48 urologists completed an audit on the cases seen in their outpatient practice, showing it's a condition that affects women more often than men (7).

## Aetiology

A lack of consensus on how to classify BPS means that its aetiology is still uncertain. A number of theories have been proposed as the mechanisms involved are poorly understood and in order to obtain a clear understanding, it is imperative that the risk factors are fully evaluated. *Kennedy et al.* surveyed 645 women, and noted a positive correlation with smoking, irritable bowel syndrome (IBS) and generalised pain disorder (8). A twins study by *Tettamanti et al.* contradicted this result, concluding that smoking is likely to be the confounding factor. They however found that tea consumption increased the likelihood of experiencing BPS (9). *Nickel et al.* noted IBS is

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more prevalent in sufferers of BPS (10). This association is important, the understanding of which may be significant in comprehending the aetiology of BPS. One suggestion put forward was that the clinical components of sufferers of BPS, IBS or systemic pain syndromes could be the three stages of a single combined syndrome. This proposed syndrome progresses from being organ specific initially, which is the bladder in the case of BPS, then progressing regionally and finally eventually leading to systemic pain syndrome (10). This theory is similar to that proposed by *Butrick et al.* who described the bladder as a 'symptom generator' for CPP (11).

### 1a. Genetics

The importance of genetic factors responsible for BPS is mounting and is based on the high prevalence of BPS in first degree relatives (12). In a study of 25,000 twins, *Altman et al.* found that there was a genetic component to the aetiology of BPS. For the first time, they were able to assess the importance of genetic and environmental influences on the possibility of developing BPS in a large population of monozygotic and dizygotic twins (13).

### 1b. Previous Surgery

*Ingber et al.* found in a survey carried out on women with BPS, that there was a statistically higher prevalence of pelvic surgeries. They state that most of the surgeries were carried out before the diagnosis of BPS, inferring that the increase in surgeries observed is not due to the BPS diagnosis (14). *Langenberg et al.* study shows more BPS sufferers have had pelvic surgery than the control group. However, the study does conclude that there is a high chance that the reason for the pelvic surgery is a confounding factor. The study provides evidence that CPP in particular may be the reason for many of the surgeries whilst also being the cause of it (15).

### 1c. Infection

*Warren et al.* carried out a case-control study and found that 18% to 36% women showed evidence of a urinary tract infection (UTI) at the onset of BPS (16). *Warren et al.* proposed two hypotheses for the pathogenesis of UTIs that could cause BPS.

The first hypothesis is that the acute symptoms are the start of the chronic disease. The other possibility is that UTI causes a physiological response that result in BPS (16).

### 1d. Glycosaminoglycan layer defects

*Urothelial Glycosaminoglycans (GAGs)* line the bladder's surface and it has been hypothesised that a deficiency in GAGs reduces protection of the bladder wall, resulting in BPS. *Engelhardt et al.* describe the GAG layer as the urine-tissue barrier and showed the long-term efficacy of treatment with intravesical hyaluronan; this successful treatment is the best indication that the urine-tissue barrier hypothesis is correct (17). *Maccari et al.* conducted a study that shows that this hypothesis cannot be proven by levels of urinary GAGs, as they are not representative of the amount of urothelial GAGs. This study is important to oppose the use of urinary GAGs concentration as a diagnostic tool (18).

### 1e. Neurobiology/NO metabolism

In a study by *Aizawa et al.* it was found that nitric oxide (NO) has a major role in the control of bladder filling by modulating the afferent nerves in rats. NO signalling may therefore play a major role in the hypersensitivity of BPS (19). *Kumar et al.* found that adenosine triphosphate (ATP) is released from the urothelium of bladders with overactive detrusor activity; which has been observed in BPS sufferers (20).

*Daly et al.* concluded that recent studies showed further evidence of the role of excitatory and inhibitory mediators, from the urothelium, which act on afferent nerves. These afferent nerves have been implicated in the symptoms of urgency and frequency in BPS. The review concludes that a better understanding of the afferent system of the bladder will provide a good therapeutic target for BPS (21).

### 1f. Mast cells/autoimmunity

Whilst experimenting on mice, *Chen et al.* showed that BPS is associated with the activation of distinct mast cell pools in the bladder. This release was found to be mediated by tumour necrosis factor (TNF). The pain in BPS may be attributed to the release of the inflammatory mediators from the mast cells. It has been further hypothesised that an autoimmune response may be responsible for the irritation of the bladder (22, 23).

### Patient evaluation

In the AUA guidelines by *Hanno et al.*, the complications with diagnosis of BPS become apparent. The variety of definitions, the complex aetiology and the insufficient number of publications makes its diagnosis complex. Therefore, diagnosis is partly based on the exclusion of other diseases. Diagnosis is often based on a 'clinical principle' which is an informal consensus among urologist that may or may not be based on evidence from within the medical literature (24).

When a patient presents with symptoms of CPP, a full history and examination must first be carried out with the elimination of differential diagnoses. In the event of a complicated diagnosis, a cystoscopy and/or urodynamics should be considered (25).

When taking a full history, physicians should put emphasis on the symptoms and common risk factors. *Nipkow et al.* describe the symptoms to be urgency, frequency and suprapubic pain (26). *Hanno et al.* reported that the pain sufferers of BPS describe is related to bladder filling and occurs suprapubically but in can include pain in the urethra, vulva, vagina and the rectum (24). It is important to recognise that this pain can be described as a feeling of 'pressure'. The symptoms can be affected by the consumption of specific food and drinks and the presence of these symptoms strongly suggests BPS.

*Hanno et al.* state that, alongside the patient's pain history, the general history should include assessment of risk factors such as: previous pelvic operations, urinary tract infections (UTI), history of urological diseases, previous pelvic radiation treatment and the presence of autoimmune diseases (24). In a cohort study by *Butrick et al.*, significant number of patients presented not with pain but with either stress/urge urinary incontinence or pelvic

organ prolapse. Therefore, these should also be considered during evaluation (11).

A common physical exam of the lower abdomen should be followed by assessment of bladder fullness and suprapubic tenderness. In female patients, a vaginal exam should be carried out and the presence of pain involving the vulva, vagina or the surrounding organs should be carefully documented. In men, digital rectal exam is recommended with pain mapping of the scrotal-anal region (24). A urine dipstick should be used to eliminate the differential diagnosis of an infection. If 'sterile pyuria' is detected then, a culture for tuberculosis and fastidious organisms should be performed (25).

In complicated presentations, it is recommended that urodynamics and cystoscopy should be included. *Kuo et al.* found that the common urodynamic findings in BPS sufferers were the presence of early sensory urgency and reduced bladder capacity. Their study showed that symptoms of urgency and pain coupled with a small cystometric bladder capacity of less than 350 ml and a positive potassium chloride test is diagnostic of BPS with a positive predictive value of 91.2% (27).

The ESSIC define IC based on the classic findings of ulcer's noted on a cystoscopy (28). The classic patch of red urothelium with radiating small blood vessels was first described by *Hunner* in 1914 (29). The presence of these lesions is associated with pain and urinary urgency and removal of these lesions can improve these urinary symptoms. Glomerulations can also be identified during cystoscopy of patients affected by BPS (30, 31).

The cystoscopic features are considered in the context of the ESSIC standardised procedure for cystoscopy involving systematic inspection of the bladder wall and grading of the lesions based on the lesion type (Table 1) (28).

**Table 1.**

ESSIC grading based on lesion type identified by cystoscopy (28).

Grade	Lesion type
0	Normal mucosa
1	Petechiae in at least 2 quadrants
2	Large sub-mucosal bleeding
3	Diffuse global mucosal bleeding
4	Mucosal disruption with or without bleeding/oedema

## MANAGEMENT

The poorly understood aetiology of BPS has brought about many different treatment and management options. They include different types of behavioural, dietary, interventional, pharmacologic and surgical therapies.

## CONSERVATIVE

Conservative therapy options should be exhausted before providing less reversible surgical therapies. Initial therapy for BPS should focus on educating the patient and providing them with an understanding of the com-

mon exacerbating factors and treatment options. *Hanno et al.* state that behaviour modification can improve symptoms and therefore should be the first avenue of treatment. Patients should be told to avoid certain foods and drink; commonly, coffee and citrus products as these are irritants.

Certain types of exercise, sexual intercourse, stress, tight-fitting clothing and constipation may also be exacerbating factors in some patients.

Relieving factors should be explained such as local heat or cooling over the bladder region and pelvic floor relaxation techniques (24).

## ORAL THERAPY

### 2a. Pentosan polysulfate

Oral *pentosan polysulfate* (PPS) is the only oral medication approved by the US Food and Drug Administration (FDA) for BPS. It has a structure similar to that of the GAGs in the urinary tract and therefore allows restoration of the urothelial layer, reducing the amount of noxious substance stimulating the sub-mucosal nerves (32, 33).

### 2b. Analgesics

Pain management is an important part in the management of BPS, however it is not sufficient and other avenues of treatment should be explored. In complicated cases, a multidisciplinary team approach to pain management may be required (24). Gabapentin, an epileptic drug used in combination with amitriptyline and NSAIDs has shown considerable promise in reducing the OAB symptoms after 4 weeks of treatments. Large scale studies are however needed to verify these results (34).

### 2c. Antidepressants

Amitriptyline is recommended by the American Urological Association for its mast cell stabilising effect (24). However, evidence to support this is mainly from single site clinical trials and case reports. A multicentre, randomised control trial carried out by *Foster et al.* showed that there was no significant improvement in symptoms of BPS sufferers when treated with amitriptyline. However, they conclude that if a daily dose of 50 mg or greater can be achieved, then amitriptyline may be of benefit (35).

### 2d. H<sup>2</sup>-receptor antagonist

In a pilot study, *Seshadri et al.* found encouraging results with the use of cimetidine in the treatment of BPS. Using the H<sup>2</sup>-antagonists (300 mg BD orally); 66% of patients experienced symptom relief while 44% reported a complete and sustained response (36).

### 2e. Antihistamines

Hydroxyzine, a mast cell stabilizer seems and thus may play a role in mediating the inflammatory processes observed in PBS/IC. However the only reported study reporting hydroxyzine as a treatment for IC is an open label, non-consecutive case series. Given the multifactorial aetiology of PBS/IC, patients with bladder mastocytosis seemed to benefit more from the treatment (37).

## INTRAVASCULAR

### Tanezumab

Mast cell degranulation is a proposed aetiology for BPS. In the study by *Evans et al.* the degranulation of mast cells resulted in the release pro-inflammatory agents, one of which is the neurotrophin NGF. NGF is involved in the generation of pain in tissue injury and inflammation (38). Tanezumab is a proposed drug that is administered intravenously and is composed of anti-NGF antibodies and thus it prevents interaction with pain receptors on afferent neurones. The results showed that patients that took tanezumab were 7 times more likely to have a 50% or greater reduction in pain compared to the placebo arm. They also observed a significant reduction in urgency episodes.

## INTRAVESICAL THERAPY

### 3a. Dimethylsulfoxide

Dimethylsulfoxide is an anti-inflammatory, analgesic and muscle relaxant (39). It was approved to treat BPS since 1977 and is the most commonly prescribed intra-vesical therapy. It results in symptom improvement in 50% of patients with BPS (33).

### 3b. Heparin

Heparin acts by replacing the damaged GAG layer and therefore restores the urothelial barrier. It is used alone or in combination with PPS and can provide immediate symptom relief (33, 39).

### 3c. Liposomes

A study carried out by *Lee et al.* concluded that intravesical administration of liposomes once a week for one month resulted in 50% improvement with the effect being maintained for 2 months. It was concluded that liposomes help maintain the urothelial barrier. The study also concluded that the use of intravesical liposomes, injected once a week for 4 weeks could achieve either a similar or better effect compared to oral pentosan polysulfate. They suggested that more frequent treatment may improve clinical outcome. However, they further large-scale studies, with placebo controls, are required to fully evaluate the effect of intravesical liposomes (32).

### 3d. Bacillus Calmette-Guerin (BCG)

BCG works on the basis of an autoimmune aetiology therefore acting via an immunological mechanism (39). *Peters et al.* showed in a long-term follow up of patients treated with BCG that 89% continued to have excellent response when evaluating 24 to 33 months after treatment was initiated (40).

### 3e Hyaluronic acid and Chondroitin sulphate

Intravesical hyaluronic acid (GAG) mono therapy or in combination with sodium chondroitin sulphate (Synthetic GAG) offers effective symptom improvement and long-term efficacy in the treatment of BPS (41). *Nickel et al.* demonstrated in their RCT that sodium chondroitin offers safe and effective treatment leading to

a greater reduction in ICSI (*Interstitial Cystitis Symptom Index*) and VAS (*Visual Analogue Score*) when compared with controls. However, it must be made clear that replacement therapy should only be effective in patients with IC/BPS and GAG abnormalities or deficiencies. The uncertain aetiology of BPS/IC therefore requires a multi-modal approach and monotherapy with the above agents is therefore not advocated (42).

## SURGICAL

### 4a. Botulinum toxin

*Pinto et al.* used the noxious relieving effects of botulinum toxin as pain relief in BPS patients (43). Their study investigated the effect of trigonal botulinum toxin injections and established that the treatment was both safe and effective. A pilot study by *Gottsch et al.* showed that periurethral injections of botulinum toxin however did not effectively treat the pain symptoms of BPS (44). Botox should be considered when other intra-vesical therapies have failed.

### 4b. Hydrodistension

As explained by *Aihara et al.*, hydro-distension has an unknown mechanism of action but it has been shown in animal studies to damage the sub-mucosal nerve plexus forming the basis of its therapeutic use. They reported that hydro-distension was therapeutically effective in 71% of patients after one month but the affect diminished over time and only 37% of patients reported improvement at 6 months. In conclusion, therapeutic use of hydro-distension has a poor long term efficacy (45).

### 4c. Transurethral resection – coagulation of Hunners lesions

Hunner first described the lesion that could be resected to relieve symptoms. Cystoscopic ablation of 'Hunners lesions' can result in temporary improvement in symptoms and the procedure could be repeated if symptoms recurred (29, 30).

### 4d. Sacral Neuromodulation

Sacral neuromodulation is a minimally invasive procedure in which the S3 sacral nerve is stimulated by a mild electrical current generated via a pulse generator. Several studies have demonstrated it to be effective in the management of refractory PBS with good long-term outcomes. The main reported adverse effects of this treatment apart from the risks of bleeding or infection relate to lead displacement, device malfunction and early replacement which have cost implications (46).

### 4e. Cystoplasty

Enterocystoplasty is a popular technique when BPS is refractory to conservative therapies. The basis for the treatment is to enlarge the bladder and provide symptom relief. Trigone sparing techniques allow for reduced complications by avoiding ureteral reflux. It has also been found that ileocecal bowel segments offer better results. *Ophoven et al.* concluded that enterocystoplasty remains a

valuable surgical intervention with 15 of the 18 patients reporting excellent therapeutic results (47).

#### 4f. Urinary diversion

The most common surgical treatment for BPS is urinary diversion with the formation of an ileal conduit (25). This is the most invasive option and being irreversible requires strict selection criteria and careful patient evaluation. Rossberger *et al.* found that 94% of patients with Hunner-type disease reported complete resolution of their symptoms (48). It was also found that the treatment for those with Hunner-type disease is far more unpredictable and this should be factored in when urinary diversion is being contemplated. Furthermore, before contemplating irreversible intervention, patients must be made clear that the pain may not disappear even after a urinary diversion.

#### CONCLUSIONS

This review shows the complexity behind the aetiology of bladder pain syndrome. This tangled web of hypothesis creates confusion in the diagnosis and its subsequent management. The importance of research particularly pertaining to the aetiology of BPS has been highlighted. This should provide physicians with a common understanding of the syndrome so that diagnosis is established early and an effective management plan tailored to the patient needs are devised.

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