

# Painful bladder syndrome

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Painful bladder syndrome is a debilitating condition that should be considered in women with bladder symptoms and pelvic pain. After exclusion of other causes of bladder pain, a variety of conservative, pharmacological and surgical treatments are available.

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**P**ainful bladder syndrome (PBS) is a chronic bladder disorder wherein patients present with persistent or recurrent suprapubic pain and pressure in the bladder and surrounding pelvic region. Patients also often have a frequent and urgent need to urinate. The term is often used interchangeably with interstitial cystitis. The classic feature is a painful desire to void that is relieved by urination. The pain can be relentless, forcing the patient to the toilet sometimes more than 20 times daily. In general, patients do not have incontinence, as the bladder is never full.

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The urgent and frequent need to urinate can prevent patients from working, travelling, shopping or simply visiting friends. Patients often make lifestyle changes because of their embarrassment and physical discomfort, leading to social isolation. Nocturia is another feature of PBS, where the painful desire to void wakes the patient from sleep often two to five times per night. The consequent sleep deprivation can be exhausting and have a psychological impact ranging from frustration to depression. Patients may experience pain during or, more often, after sexual intercourse. Women may also have vaginal and vulval pain, and symptoms may worsen during menstruation. Overall, PBS can affect patients psychologically, physically and sexually.

Although the symptoms can resemble those of a urinary tract infection (UTI), a bacterial infection is rarely identified. By definition, a diagnosis of recurrent UTI rules out a diagnosis of PBS. Results of physical examination may be unremarkable but tenderness of the anterior vaginal wall, which corresponds to the base of the bladder, is often present.

## EPIDEMIOLOGY

PBS occurs mainly in women (more than 80% of cases) but is uncommon, with prevalence rates estimated at 0.8 to 2.7%,

**TABLE 1. CONDITIONS EASILY CONFUSED WITH PAINFUL BLADDER SYNDROME AND INVESTIGATIONS TO DIAGNOSE OR EXCLUDE\***

Condition	Investigations
Carcinoma, carcinoma in situ	Cystoscopy and biopsy
Infection with: <ul style="list-style-type: none"> <li>• common intestinal bacteria</li> <li>• <i>Candida</i> spp., <i>Chlamydia trachomatis</i>, <i>Corynebacterium urealyticum</i>, <i>Mycoplasma hominis</i>, <i>Mycoplasma genitalium</i>, <i>Ureaplasma urealyticum</i></li> <li>• <i>Mycobacterium tuberculosis</i></li> <li>• herpes simplex virus, human papillomavirus</li> </ul>	Routine bacterial culture Special culture  Dipstick; if 'sterile' pyuria, specific culture for <i>M. tuberculosis</i> Physical examination
Radiation, chemotherapy (including immunotherapy with cyclophosphamide), anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder neck obstruction	Flowmetry and ultrasound
Neurogenic outlet obstruction	Medical history, flowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or haematuria (upper urinary tract imaging such as CT or IVP)
Urethral diverticulum, urogenital prolapse, endometriosis, vaginal candidiasis	Medical history and physical examination
Cervical, uterine or ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured on ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA test
Benign prostatic obstruction	Flowmetry, pressure-flow studies
Chronic prostatitis (bacterial or nonbacterial)	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination; nerve block may prove diagnosis
Pelvic floor muscle-related pain	Medical history, physical examination

ABBREVIATIONS: IVP = intravenous pyelogram; PSA = prostate-specific antigen.

\*Adapted from van de Merwe JP, et al. Eur Urol 2008; 53: 60-67.<sup>2</sup>

depending on the definition used.<sup>1</sup> It is found extremely rarely in children, although many women give a history of longstanding problems dating to childhood or adolescence.

## DIAGNOSIS

For a diagnosis of PBS, doctors must first rule out other conditions that can cause bladder pain (Table 1).<sup>2</sup> There is no single definitive test to identify PBS, a clinical syndrome; however, there are many investigations that are useful.

### What the GP can do

**Urinalysis and urine microscopy and culture** are useful to rule out infection. Dipstick urinalysis is cost effective for many urinary tract conditions but not for PBS; culture of a formal midstream urine specimen is essential. Empirical treatment for 'possible cystitis' in patients with PBS only delays diagnosis of this rare condition.

**A voiding chart** kept by the patient can document frequency and nocturia. A typical example of a voiding chart in a woman with PBS appears in Table 2. This shows that the patient voided 14 times daily, with two to three episodes of nocturia. Bladder volumes were very small (20 to 100 mL).

**An ultrasound measurement of postvoid residual urine volume** is useful to screen for incomplete bladder emptying. This is a different condition to PBS, possibly caused by a urethral stricture.

**A pelvic ultrasound examination** can screen for a pelvic mass.

**Referral** to a urogynaecologist or urologist allows further diagnostic testing.

### What the specialist can do

**Cystoscopy and cystodistension** Cystoscopy with bladder distension under general anaesthesia is the main diagnostic test for PBS. This involves:

- hydrodistension of the bladder to assess its maximum capacity under anaesthesia. Often in PBS, there is a reduced bladder capacity of 400 to 600 mL (normal capacity under

- anaesthesia, 800 to 1000 mL)
- retention of the fluid in the bladder for three minutes to stretch the bladder wall. This may have some symptomatic benefit by disrupting the subepithelial nerves
- refill of the bladder with a smaller volume to allow inspection of the bladder wall.

Findings at cystoscopy with cystodistension in patients with PBS are as follows.

**Glomerulations** appear as pinpoint petechial haemorrhages after distension of the bladder (Figure 1). They often coexist with cascade or waterfall haemorrhages from engorged capillaries. Petechiae may also be seen in patients with other bladder conditions and in those who have had radiotherapy or chemotherapy and are thus not absolutely specific to PBS. Mucosal splitting is typical of PBS (Figure 2).

**Hunner's lesions** appear as inflammatory patches that crack and bleed after hydrodistension (Figure 3a). These are a feature of classic PBS. Previously known as Hunner's ulcers, these lesions are not true ulcers but typically appear as circumscribed reddened mucosal areas with small vessels that radiate towards a central scar with a fibrin deposit. This ruptures on distension with petechial oozing.

Classic Hunner-type PBS responds well in the short term to treatments such as diathermy (Figure 3b).

### Biopsy

We recommend undertaking a biopsy, with an emphasis on detrusor muscle sampling, during cystoscopy. However, the role of biopsy in diagnosing PBS is controversial, and biopsy is considered optional in the algorithm of the International Consultation on Incontinence and American Urological Association.<sup>3</sup> Biopsy is also important to rule out other pathology.

Samples of the bladder wall that include detrusor muscle are examined for an increase in mast cells, which are not found in detrusor muscle from healthy patients.

**TABLE 2. EXAMPLE OF A VOIDING CHART**

Date chart recorded: 12/6/14

Bladder chart – day 2

Time	Amount and type of fluid in	Time	Amount of urine passed	Comments (e.g. leakage, urge, pain, burning)
		6:05	75 mL	
		8:05	50 mL	
8:25	200 mL water	9:07	75 mL	
8:55	200 mL milk coffee	9:35	100 mL	
		9:55	100 mL	
		11:00	100 mL	Leaking
		12:50	50 mL	Pressing
13:50	200 mL apple juice	16:00	100 mL	
15:54	200 mL cola	17:55	60 mL	
17:40	3 swallows of cola	18:55	50 mL	
		20:30	50 mL	
		21:15	50 mL	
		21:55	25 mL	
		22:30	20 mL	
		00:40	50 mL	
		02:05	20 mL	

Mast cell counts are often higher in patients with PBS than in those with other bladder diseases (Figure 4). In the past, a mast cell count greater than 28 cells/mm<sup>2</sup> was considered diagnostic of PBS. This threshold is now controversial but is still a useful rule of thumb.

PBS can be classified as:

- classic inflammatory PBS with Hunner's lesions or
- nonlesion PBS.

It is estimated that only 10 to 15% of patients with PBS develop Hunner's lesions.

### Urodynamic studies

Urodynamic studies can be performed in patients with PBS but are often quite painful and are usually not indicated as the patients generally do not have incontinence. If performed, urodynamic studies will show a reduced bladder capacity but generally no

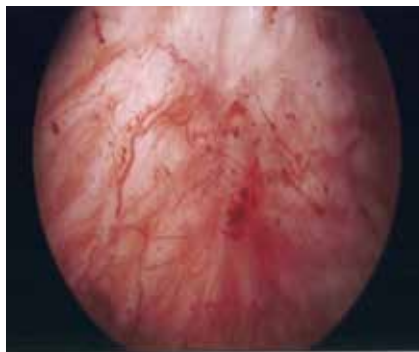


Figure 1. Petechial haemorrhages, (glomerulations) seen at refill cystoscopy.

evidence of systolic pattern detrusor over-activity (a small number of patients will have poor compliance) or incontinence. Often there is evidence of poor voiding, presumably caused by pelvic pain.

### AETIOLOGICAL THEORIES

There are two main theories about the aetiology of PBS.

**Defective epithelial barrier theory.** This theory proposes that the bladder epithelium is denuded of its protective glycosaminoglycan layer for reasons that are not understood. The increased permeability allows urine solutes such as potassium, urea and other chemicals to penetrate the bladder lamina propria, triggering nerve depolarisation. This leads to increased pain perception, resulting in frequency and urgency. It may be a form of autoimmune reaction. This theory is supported by the finding that PBS often coexists with

vulvar vestibulitis (20%) and Sjögren's syndrome (variable).

**Detrusor mastocytosis theory.** Mast cells appear degranulated or activated. They release histamine, which leads to increased vasculature, neurogenic inflammation and increased substance P. This causes pain, swelling, scarring and interferes with healing. This theory is supported by the observation that mast cells carry high-affinity oestrogen receptors and that PBS is often worse around the time of the menses.

The aetiology of PBS is probably multifactorial. There is documented interaction between mast cells, neurogenic inflammation, autoimmunity, psychological factors and other chronic pain conditions.

Some comorbidities seem to occur more often in patients with PBS, including irritable bowel syndrome, fibromyalgia, migraine, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, depression, anxiety and allergy/hypersensitivity. The reasons for these associations are still unclear.

### TREATMENT

There is no absolute cure for PBS, and each patient's treatment needs to be individualised according to their response. Because the cause of PBS is unknown, most treatments are aimed at relieving symptoms and providing patient education and support. Treatment should focus on pain management and dealing with the symptoms of urgency and frequency.



Figure 2. Cystoscopy showing splitting of the mucosal lining of the bladder.

### Dietary modification and an oxalate-free diet

Bladder symptoms are exacerbated in some patients by foods and drinks that contain oxalate (oxalic acid), especially certain fruits, acidic foods such as citrus, vinegar and tomatoes, and food and drinks containing caffeine or alcohol. Carbonated drinks as well as highly spiced foods can also cause discomfort. The oxalate content of selected fruit is shown in Box 1. Further information on dietary modifications to treat PBS can be obtained from the US Vulvar Pain Foundation ([www.thevpfoundation.org](http://www.thevpfoundation.org)).

### Imipramine or amitriptyline

Imipramine or amitriptyline may be prescribed while the patient awaits specialist assessment or cystoscopy. A starting dose of 25 mg or even 10 mg is titrated slowly to 50 to 75 mg over a few weeks if tolerated. The effect is greatest on night-time symptoms. A quarter of patients cannot tolerate this treatment because of sedation.

### Behavioural changes, stress reduction and relaxation therapy

PBS flares can be exacerbated by physical and emotional stress, exercise, sexual intercourse and travel. Professional counselling, relaxation therapies, meditation, yoga, gentle stretching exercises and mindfulness training can often be of benefit.



Figures 3a and b. a (left). Hunner's lesion seen on cystoscopy, showing a deep fissure in the bladder wall. b (right). Hunner's lesion after diathermy.

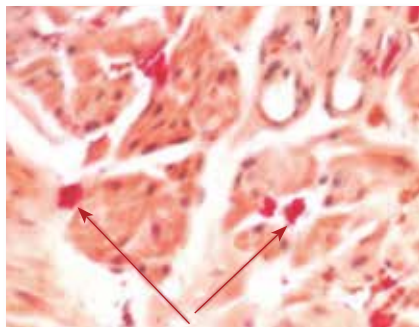


Figure 4. Mast cell infiltration of the muscle wall of the bladder. Mast cells (arrowed) are stained red (para-rosanilin stain).

### Bladder instillation with dimethyl sulfoxide

One of the most commonly used drugs for bladder instillation is dimethyl sulfoxide (DMSO). It is believed to have anti-inflammatory and analgesic properties and relaxes the bladder muscles. The patient is catheterised by a nurse, and approximately 50 mL DMSO is instilled into the bladder. The patient retains it for at least 20 minutes so that it is absorbed into the urothelium. The treatment is repeated weekly for six to 12 weeks; patients often begin to experience relief after a few treatments. A randomised crossover trial revealed a benefit in 70% of patients.<sup>4</sup> A common side effect is a garlic-like smell of the breath but it is otherwise well tolerated. Some patients go on to a maintenance regimen of DMSO instillation monthly or as required.

Bladder instillations of a cocktail of DMSO, heparin, bicarbonate, hydrocortisone and bupivacaine or various combinations of these have also been described with variable success rates.

### Oral drugs

Pentosan polysulfate sodium is thought to protect the bladder from the irritant elements of urine and to re-establish the protective glycosaminoglycan layer. A randomised controlled trial found it to be effective in one-third of patients.<sup>5</sup> This

drug is very expensive in Australia, costing approximately \$650 per course. Treatment is for at least six months, and usually no effect is seen until three months.

Aspirin and ibuprofen inhibit the production of prostaglandins that stimulate inflammation. They also relieve pain but can have the side effect of gastric irritation.

### Transcutaneous electrical nerve stimulation

In transcutaneous electrical nerve stimulation (TENS), mild electrical pulses are transmitted by placing electrode pads on the suprapubic region or lower back. TENS is often used as supplemental pain control. It is believed to block pain signals to the brain and also to increase the natural release of endorphins. No randomised controlled trials have been performed of TENS in patients with PBS.

### Bladder training

Bladder training is more successful in patients whose dominant symptoms are urgency and frequency rather than pain. The aim is to increase the time between voids, thereby reducing frequency and increasing bladder capacity. Bladder training is less successful in patients with severe pain and is of no benefit in those with a very low bladder capacity under anaesthesia (less than 100 mL, suggesting a fibrosed bladder).

### Surgery

Surgery is a last option for PBS treatment and not to be taken lightly. Botulinum toxin injections at cystoscopy have been used for PBS. However, an Australian randomised controlled trial found that botulinum toxin injections helped only 25% of women. Each treatment costs between \$450 and \$900 and its effects last for six to nine months.

Sacral neuromodulation has been described for PBS but many centres have only limited experience of this. Published

### 1. OXALATE CONTENT OF SELECTED FRUIT

#### Low-oxalate content

Apples, peeled  
Avocado  
Cherries, bing and sour  
Cranberries, canned  
Grapes  
Mangoes  
Melons  
Nectarines

#### Medium-oxalate content

Apples, whole  
Apricots  
Grapefruit  
Oranges  
Peaches  
Pears  
Plums

#### High-oxalate content

Blackberries  
Blueberries  
Figs, dried  
Raspberries  
Redcurrants  
Rhubarb  
Strawberries  
Tangerines

results are variable but a trial of this approach is worth considering before major urological surgery.

Major urological surgery includes bladder augmentation (clam cystoplasty), partial cystectomy or complete cystectomy with urinary diversion. Major surgery has been more successful in patients with a low-capacity bladder and a normal psychological assessment. Phantom pain has been described to continue after surgery.

### CONCLUSION

PBS can be a debilitating condition that needs to be considered as a possible diagnosis in women experiencing bladder symptoms and pelvic pain.

## 2. USEFUL WEBSITES FOR DOCTORS AND PATIENTS ON PAINFUL BLADDER SYNDROME

- International Painful Bladder Foundation (<http://painful-bladder.org>)
- National Kidney and Urologic Diseases Information Clearinghouse (<http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis>)
- The Vulvar Pain Foundation (<http://www.thevpfoundation.org>)
- American Urological Association (<http://www.auanet.org/education/guidelines/ic-bladder-pain-syndrome.cfm>)

Appropriate referral and management will expedite the patient's treatment. However, PBS is an uncommon condition so it is imperative that other pathology is ruled out before a diagnosis of PBS is made. Some useful resources on PBS are listed in Box 2. **MT**

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