The challenge of bladder pain syndrome

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Bladder pain syndrome is a debilitating condition that can severely impact on a patient's quality of life. In this article, the authors describe how to tackle the diagnostic and management challenges it presents.

Bladder pain syndrome (BPS), also referred to as interstitial cystitis (IC), is a chronic and debilitating condition. It presents with lower urinary tract symptoms in the form of urinary frequency, urgency, nocturia, and suprapubic and pelvic pain. The severity of the symptoms varies from person to person. It is diagnosed after ruling out other conditions that may have similar symptoms (*ie* it is a diagnosis of exclusion) (Box 1).

The estimated prevalence is reported to be around 300 per 100 000 women and 30–60 per 100 000 men.[1] BPS mainly affects adult females; however, it can occur at any age. The female to male ratio is >5:1.

Patients with BPS commonly suffer from other associated conditions such as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia rheumatica, vulvodynia, allergies and autoimmune disease, *eg* Sjogren's syndrome.[2] It can co-exist with overactive bladder syndrome (OAB). Patients may suffer from associated sexual dysfunction, such as painful ejaculation in males and dyspareunia in females, leading to some patients avoiding sexual intimacy. As a result, patients with BPS are more likely to develop anxiety or depressive disorders, and have relationship breakdowns.[3]

Box 1. Conditions that might manifest with symptoms similar to BPS (for exclusion)

- Urinary tract infection (bacteriuria)
- Radiation, tuberculous- or cyclophosphamide-related cystitis
- Bladder tumours
- Bladder or lower ureteric stone
- Uterine, cervical, vaginal or urethral cancer
- Vaginitis
- Active herpes
- Overactive bladder
- Endometriosis
- Urethral diverticulum

AETIOLOGICAL FACTORS

The exact cause of BPS is not yet fully understood; however, it is likely to have multifactorial causes (Table 1). Numerous reports have shown that BPS is a disorder of the glycosaminoglycan (GAG) layer of the bladder urothelium. The GAG layer is a mucopolysaccharide that has hydrophobic properties. Alterations in this layer lead to the urothelium being exposed to urinary toxic agents, causing irritation of the submucosal layers of the bladder. Part of the treatment of BPS is aimed at replacing this layer with GAG analogue therapies. It is also thought that in patients with BPS, the nerves (c-fibres) in the bladder become ultra-sensitive to pain and changes in pressure.

Another aetiological theory is the accumulation of bioactive antiproliferative factor (APF) in urine, capable of altering the architecture of urothelial cells, leading to epithelial thinning and denudation. Both are

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characteristic of BPS. APF is found in the urine of 95% of BPS patients (versus 9% of controls).

In many patients, there is no clear explanation as to why or how the symptoms of BPS initially develop, but it is not uncommon for patients to have an initial symptomatic bacterial urinary tract infection (UTI), followed by persisting symptoms of cystitis, even after the infection has been successfully treated.

DIAGNOSIS

Clinical history

Common presenting symptoms include urinary frequency, urgency, nocturia, suprapubic or bladder pain on bladder distension (typically relieved by bladder emptying), and urethral discomfort or burning. The pain may improve for a period of days to months and then recur (symptom flare), or may be present constantly. Be alert for red-flag symptoms and signs that would prompt early referral to secondary care, including haematuria, abdominal mass, recurrent UTI and suprapubic/loin pain. Include a thorough gynaecological history in women with pelvic pain to assess whether there is an underlying gynaecological cause. Dysmenorrhoea, dyspareunia or cyclical exacerbation of pain may indicate a hormonally driven problem, such as endometriosis, which would require referral to gynaecology for further investigation (such as diagnostic laparoscopy).

Patients may report that they suffer exacerbation of BPS symptoms after consuming certain foods or drinks (*eg* acidic foods or drinks, fruit juices, fizzy drinks, caffeinated drinks, alcohol, spicy foods), during stressful times, or after activities such as exercise and sexual intercourse. Any triggers should be recognised and avoided where practical.

Clinical examination

Abdominal examination commonly elicits suprapubic tenderness. Pelvic examination (female) may reveal tenderness in the vagina and around the bladder. External genitalia and digital rectal examination (male) may reveal scrotal and penile tenderness.

Causative theories of BPS	Mechanism
Urine toxins	Leads to irritation and inflammation
Aberrant activation of sensory nerves, *eg* c-fibres	Causes release of neuropeptides, resulting in neurogenic inflammation
Defective glycosaminoglycan (GAG)	Allows urine to leak past the luminal surface, leading to inflammation
Increased sympathetic activity	May increase mast cell activation and exacerbate pain
Mast cells	Release histamine causing pain, hyperaemia and fibrosis
Antiproliferative factor (APF)	Denudation and thinning of urothelium
Bladder autoimmune response	Inflammation and fibrosis

Table 1. Causative theories and their proposed mechanisms for development of BPS

Questionnaires

The O'Leary-Sant Symptom Index (or Interstitial Cystitis Index) is a validated symptom score questionnaire that is useful in assessing baseline symptoms and the later effectiveness of therapies to help guide management.

Investigation in primary or secondary care

There is no simple, single test that can definitively diagnose BPS. The aim is to rule out other conditions:

- Urine dipstick +/– mid-stream urine for microscopy culture and sensitivity. This will rule out any active UTI, non-visible haematuria or sterile pyuria.
- If available, a frequency volume chart or bladder diary can be very useful in objectively assessing the patient's urinary frequency, fluid intake habits, total urine output and any urinary incontinence. It is common to see high frequency of voids, day and night, with low voided volumes.
- Imaging (such as ultrasound) can be considered if there is a clinical indication (*ie* patient reports associated loin pain, pelvic pain).

Further investigation in secondary care

Cystoscopy is used as both a diagnostic and therapeutic tool, and can also be utilised to rule out bladder pathology and to investigate any haematuria. Bladder distention (cystodistention) is performed at the time of cystoscopy under general anaesthesia. The bladder is then re-inspected for glomerulations (pinpoint areas of bleeding), which if present are considered to be a diagnostic sign of BPS (Figure 1). Around 5–10% of patients will have a breach of the bladder urothelium, termed a 'Hunner's ulcer'. This is a distinctive erythematous urothelial patch with central scarring and is considered pathognomonic of BPS. On bladder filling, the lesion ruptures and there is 'waterfall' bleeding (Figure 1). Hunner's lesions can be resected by a loop resectoscope, diathermised or lasered,[4] all of which can provide symptom benefit. A bladder biopsy may be performed to rule out other bladder pathologies if suspected, but is not required to confirm the diagnosis.

A urodynamic test can be used to assess any associated voiding dysfunction and OAB in selected patients. It is not always successful, as the patient may not be able to tolerate filling of the bladder for the test.

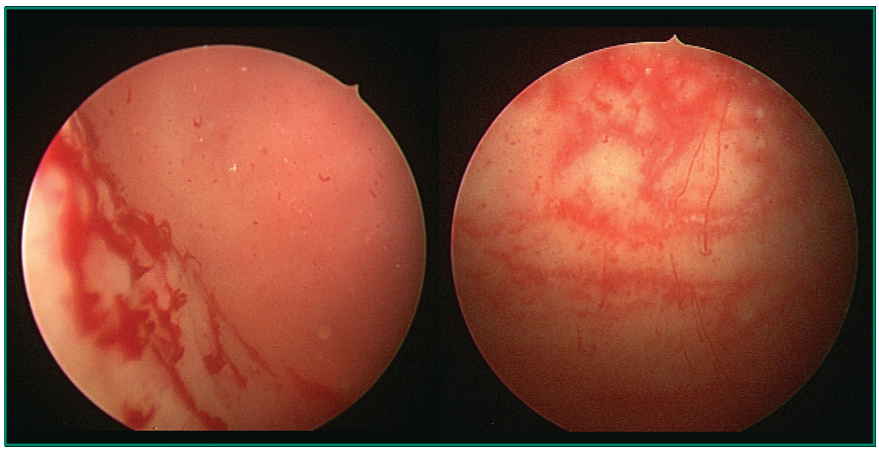

Figure 1. Pinpoint areas of bleeding (glomerulations) seen after cystodistention are diagnostic of bladder pain syndrome (left). A Hunner's ulcer with 'waterfall' bleeding may also be seen (right)

MANAGEMENT IN PRIMARY OR SECONDARY CARE

The principles of management encompass several components. The patient's expectations need to be managed carefully: it is important to explain that the aim is for improvement in symptoms and quality of life, but that cure may not be possible. A multimodal (and multidisciplinary) approach is required, as patients often need a combination of conservative and medical therapies to control symptoms.

When trying medication, ensure that one drug is tried at the optimal dose. If it works, continue the treatment; if it does not work, try an alternative drug option (see below). If it improves symptoms partially (by ≥50%), continue that treatment and add in another treatment.

Pain relief should be addressed early. Simple forms of analgesia are preferred to opiates and stronger drugs. Input from pain team specialists can be sought at any point in the management pathway, but generally after simple measures have been tried and failed.

Avoiding stimuli

In every patient, certain dietary or lifestyle triggers will exacerbate their symptoms and can lead to a symptom flare. Patients usually become familiar with their triggering factors, and will be able to identify and avoid them in order to prevent a flare. A food diary can be helpful in identifying these, and a controlled elimination diet can be tried, being careful that patients do not exclude too many things at once or make their diets too restrictive or unhealthy.

Pelvic floor relaxation with a physiotherapist

BPS is associated with increased muscle tone in the pelvis, perineum and lower back. Relaxation techniques and pelvic floor physiotherapy lead to decreased muscle tightness, including the muscles and tissues of the vagina or rectum, lower abdomen, hips, thighs, groins and lower back. The physiotherapist should be trained in pelvic soft tissue manipulation and rehabilitation. Weiss *et al* reported that 70% of BPS patients who were treated with manual physical therapy to the pelvic floor tissues for 12 to 15 visits experienced moderate to marked improvement in their symptoms.[5]

Psychological support

BPS is a distressing condition, and symptoms can be made worse by stress or anxiety. The condition itself can lead to a decline in mental wellbeing, and early support and counselling can be very beneficial.

Oral medications

Amitriptyline — A first-line drug treatment. It is a tricyclic antidepressant, mainly used to treat chronic neuropathic pain. In low doses it reduces pain perception, and has anticholinergic and antihistamine effects. Start at a low dose (10mg) and titrate up according to efficacy (unless side-effects limit its use). If drowsiness is a problem, nortriptyline is an alternative.[6]

Gabapentin and pregabalin — Originally used in epilepsy, these drugs are also used as adjunctive therapy in chronic neuropathic pain. They can be used as an alternative to amitriptyline, or as an adjuvant.

Antihistamines — Drugs such as hydroxyzine (H_1-antagonist) have been used to treat BPS with variable results.[7] Cimetidine (H_2-antagonist) has also been used.[8]

Pentosan polysulfate sodium (Elmiron) — An oral, synthetic GAG analogue that acts by repairing the protective layer of the bladder in patients with BPS. It is effective in alleviating symptoms in some patients with BPS, although it rarely causes the symptoms to completely subside. It can take three to six months of treatment before a benefit is seen. Side-effects are usually mild and include alopecia, gastrointestinal symptoms and deranged liver function tests.[6] It is used widely in the USA and Europe, but is not licensed in the UK.

Bladder calming medication — Consider anticholinergic drugs or the beta$_3$-agonist mirabegron for patients with concomitant OAB.

Bladder instillations

Intravesical therapy is considered as an adjuvant to oral medication, or if patients have failed to gain benefit from or have been unable to tolerate oral drugs. Many therapies are GAG analogues (chondroitin sulfate, hyaluronic acid, heparin sulfate) and are used to replenish the bladder lining, make it more robust and reduce the risk of leak of noxious urinary components. They can be used as monotherapy, in combination with other GAG analogues, or in combination with alkalinised lignocaine. There is no standardised protocol

for their use, but regimens generally incorporate induction treatment (bladder instillation via an in-and-out catheter once per week for four to six weeks), followed by maintenance therapy if successful (once per month for four to six months). Sodium hyaluronate (Cystistat, Hyacyst) is available on FP10 prescription, and potentially could be administered locally or self-administered by patients who are able to perform intermittent self-catheterisation.

Sodium hyaluronate — One study reports complete bladder symptom remission in 50% of cases at five-year follow up, and symptom recurrence improvement with maintenance therapy in 41.7%.[9]

Chondroitin sulfate (Uracyst, Gepan) — A meta-analysis by Thakkinstian *et al* has shown a global response rate of 43% in the chondroitin sulfate group when compared to placebo.[10]

Pentosan polysulfate (PPS) — Most effective when combined with oral PPS; however, not readily available in the UK.

Dimethylsulfoxide (DMSO) — An FDA-approved drug to treat BPS, but it remains unlicensed in the UK. It has anti-inflammatory, analgesic, and muscle-relaxing properties. A large systematic review of 1470 patients from 21 randomised controlled trials reported a modest benefit, with a relative risk of 1.78, for patient-reported improvement in symptoms.[11]

Sodium hyaluronate and chondroitin sulfate (iAluRil) — Giberti *et al* reported a statistically significant improvement in interstitial cystitis symptom index score (ICSI) post-treatment in 20 patients treated with this combination therapy.[12]

Alkalinised lignocaine (with bicarbonate) — A randomised controlled trial of 102 patients by Nickel *et al* reported 30% of patients experienced significant improvement in their symptoms after completing a five-day course of treatment.[13]

Lignocaine, heparin and sodium bicarbonate (Parson's 'cocktail') — The combination of these three instillations into the bladder reduces the nerve sensitivity of the bladder and helps to repair the lining of the urothelium. In a study by Parsons *et al,* about 80% of patients had reduced pain for at least four hours after one instillation of the combination treatment. In addition, some patients experienced reduced pain for days or weeks after bladder instillations.[14] In another study by Nomiya *et al,* a 60% and 76.6% improvement in symptoms were reported respectively at the fourth and twelfth instillations in 32 patients. The effect of treatment was maintained for six months.[15]

SURGICAL OPTIONS

Surgery is considered a third- or fourth-line option. Hydrodistension of the bladder has been shown to temporarily improve symptoms and pain by 56%, but only lasting for a mean duration of two months.[16] Resection, fulguration or laser of Hunner's ulcer can produce symptom relief initially in around 90%, sustained in 40% at three years (although patients may need repeat treatments and bladder perforation is a risk).[17] In combination with hydrodistention, this treatment can improve symptoms for around 28 months.[18]

Cystoscopy and injection of botulinum toxin A (BTX-A) into the bladder is reserved as a fourth-line option. BTX-A works by inhibition of acetylcholine release from the presynaptic efferent nerves at the neuromuscular junction in the detrusor muscle. It also regulates the sensory nerve function by blocking neurotransmitter release and reducing receptor expression in the urothelium. Recent studies have additionally shown an anti-inflammatory effect and reduction of substance P in the urine following intradetrusor BTX-A injection.[19,20]

Sacral nerve stimulation (SNS) is not widely available. It involves placing a lead into sacral foramen S3, connected to an implantable neurostimulator under the skin just above the sacrum. The electrical stimulation modulates the sacral nerves that innervate the bladder, bowels, urinary, anal sphincters and pelvic floor muscles. This impulse interrupts signals from the brain that trigger pain, urgency and frequency. The treatment is performed in two stages. Stage 1 is a trial (temporary) period lasting for a few days to a week. If the trial improves the symptoms, the patient will go on to have a permanent SNS implant. Small studies have shown that SNS improves bladder pain and urinary symptoms in patients with BPS.[21] Potential complications of SNS include the need for a subsequent surgery to reposition, remove or replace the wire or the battery, infection, bleeding and pain.

CYCLOSPORIN A

This is a fifth-line therapy for BPS, and is rarely used in the UK due to the risk of side-effects. It works by dampening down the immune response to the bladder in BPS by decreasing epidermal growth factor (EGF) levels in the urine. In a study by Sairanen *et al*, the response rate to cyclosporin A is about 72%.[22]

RECONSTRUCTIVE SURGERY

Reconstructive surgery is considered for intractable BPS that has failed all other treatments. Surgery does not guarantee to resolve the patient's pain issues. Results are better in patients with ulcer-type BPS disease. Urinary diversion, with or without cystectomy (*ie* ileal conduit formation), aims to improve symptoms by diverting urine away from the bladder.

CONCLUSIONS

BPS is a debilitating chronic condition that mainly, but not exclusively, affects females. It usually has a significant impact on patient's quality of life. BPS can be difficult to diagnose and is typically a diagnosis of exclusion. Patients with recurrent cystitis-like symptoms and negative urine cultures may be on the spectrum of BPS. It is essential to exclude other pathologies that may have similar clinical presentation at the outset. It is also important to treat reversible causes first, before embarking on more

invasive and time-consuming treatments. Patients with BPS can have either constant or intermittent pain issues, which need to be addressed at all stages of their care pathway. In certain difficult cases, a multidisciplinary and multimodal approach with the involvement of various teams – such as the pain team, clinical psychologist, psychiatrist, general practitioner and physiotherapist – is needed. A combination of oral and other therapies is the mainstay of treatment. A referral to secondary care for further investigation should be sought in patients who develop red-flag symptoms or if they have failed first- and second-line therapies.

Declaration of interests: *none declared.*

KEY POINTS

- **Bladder pain syndrome is a debilitating chronic condition**
- **It can be difficult to diagnose and is typically a diagnosis of exclusion**
- **Treat reversible causes first, before embarking on more invasive and time-consuming treatments**
- **In difficult cases, a multidisciplinary and multimodal approach is required**
- **A combination of oral and other therapies is the mainstay of treatment**
- **Refer patients to secondary care for further investigation if they develop red-flag symptoms or if they have failed first- and second-line therapies**

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