Diagnosis and treatment of painful bladder syndrome

Sharon Holroyd

Interstitial cystitis or painful bladder syndrome (IC/PBS) is a chronic condition presenting with symptoms including pain, urinary urgency and urinary frequency. IC/PBS is often poorly diagnosed and many patients may have seen multiple healthcare professionals over a period of years and undergone a variety of unsuccessful treatments. The lack of a definitive definition of IC/PBS and diagnosis of its aetiology, cause and successful treatment contributes to a poor quality of life for many patients. This article looks at the main symptoms, diagnostic techniques and treatments for the IC/PBS. The author outlines how comprehensive history-taking, physical examination and appropriate clinical tests all help community nurses to arrive at an appropriate and timely diagnosis, which, when combined with individualised treatment plans, can offer patients effective relief of their symptoms.

KEYWORDS: Continence ■ Painful bladder ■ Diagnosis ■ Quality of life

Painful bladder syndrome (also often known as interstitial cystitis and referred to below as IC/PBS) has been described as a debilitating and chronic condition that is often difficult to diagnose accurately (Davis et al, 2015). It is estimated that around 400,000 people in the UK experience IC/PBS and it predominantly occurs in females (Nickel et al, 2010; Cashley et al, 2012). There are some clinicians who doubt the validity or existence of the condition (Warren, 2014) and its management is a challenge due to lack of consensus on what the term actually means (Ghosh and Imoh-Ita, 2016).

This article explores current theories on the aetiology, diagnosis and management of IC/PBS, identifying issues around timely and accurate diagnosis, the effects on the quality of life of those with the condition, and the efficacy of treatments.

FUNCTION OF THE BLADDER

Urine can only be effectively stored in the bladder if the urethral pressure remains higher than the internal bladder pressure. To maintain continence, a sustained substantive contraction of the pelvic floor, urethral wall and external sphincter increases and maintains a higher urethral pressure in comparison to the intravesical pressure.

A ‘compliant’ bladder operates when the detrusor muscle actively relaxes during the filling stage of the micturition cycle, allowing the bladder to stretch without increasing the internal pressure. The parasympathetic nervous system inhibits detrusor contraction until the individual is ready to pass urine.

Increased abdominal pressure in a healthy person during coughing, laughing or sneezing etc is equally distributed throughout the urethra and bladder to ensure pressures are maintained and the pelvic floor supports the bladder, effectively preventing leakage.

During the filling stage of the micturition cycle, receptors within the detrusor are stimulated to send messages to the sacral cord via afferent nerve pathways. Motor efferent nerves then transmit signals back to the detrusor muscle, initiating relaxation while maintaining a contracted external sphincter. This mechanism allows stretching and filling of the bladder.

The sensation of wanting the toilet intensifies as the bladder fills until the voiding phase where the spinal sacral nerve receptors (S2-S4) are activated, initiating simultaneous sphincter relaxation and bladder contraction to expel urine. This mechanism is susceptible to muscle fatigue and cannot be sustained indefinitely. Any urine remaining when the mechanism reverses is retained in the bladder until the next time urination is initiated.

IC/PBS

The presentation of IC/PBS was first described in the 19th century by Gross (1876), while Skene (1878) went on to describe a chronic inflammatory lesion of the wall of the bladder. Later, Hunner (1915) detailed the case histories of eight females presenting with urgency, frequency, nocturia...
The science — physiology of the bladder

The function of the bladder is to store urine until effective micturition is initiated in a socially acceptable time and place. An empty bladder sits low in the pelvis and is generally a triangular shape until it starts to fill and becomes more oval in appearance. The bladder is capable of distending to accommodate large volumes of urine, although it is accepted that in adults the normal filling capacity is achieved between 400–600mls before urination takes place.

The bladder itself consists of three layers:

- The outer layer: consists of connective tissue covered with a layer of peritoneum (serous membrane) and is highly vascular and innervated (having a dense supply of nerve endings)
- The middle layer: a mix of smooth muscle fibres and elastic tissue that are tightly intertwined into three layers known as the detrusor muscle. This layer enables the bladder to contract and expel urine
- The third and innermost layer: known as the mucosa, this layer is lined with transitional epithelium, which is capable of stretching as the bladder fills.

The mucosa is six or seven cells thick and is partly formed by umbrella cells that are in direct contact with urine. As the bladder empties, the walls contract into rugae, or wrinkles, creating the potential for pockets of urine to be trapped. As the bladder empties, the walls contract into rugae, or wrinkles, creating the potential for pockets of urine to be trapped.

A triangle-shaped base of the bladder (the trigone), is found behind the symphysis pubis (a joint in the pubic bone) and is the least mobile part of the bladder's structure, preventing stretching of the urethra or backflow of urine into the ureters. In males, the prostatic ligaments offer further stabilisation. The trigone contains three openings: two ureteric orifices are located on the posterior bladder wall and are the entry points for urine travelling down from the kidneys. Spiral smooth muscle fibres become elongated as the ureters approach the bladder and the Waldeyer’s sheath encases the lower ureter in fibromuscular tissue as it enters the bladder wall. The lowest bladder opening is the internal urethral orifice, which facilitates urine exiting the bladder and body. The trigone is less elastic than the mucosal lining and during filling, storage and emptying undergoes relatively little movement.

and suprapubic pain alongside multiple visible bleeding areas on the bladder wall identified during cystoscopy (medical procedure used to examine the inside of the bladder using an instrument called a cystoscope). These lesions were later referred to as ‘Hunner’s ulcer’, which for a long time was the definitive symptom used to diagnose IC/PBS.

However, current figures show that only 10–15% of cases exhibit these lesions/ulcers (Gupta et al, 2015), so it is arguable that the condition has traditionally been misdiagnosed, with the similar symptoms meaning that patients often undergo several courses of antibiotic treatments for bacterial infection before the actual diagnosis of IC/PBS is established (McDermott, 2009; Fiander, 2013). The author would agree with this analysis, as in her clinical experience it has been common to see patients who have accessed several services and treatments over many years without correct diagnosis.

Current definitions of IC/PBS

Symptoms of IC/PBS include an unpleasant sensation featuring pain, a feeling of pressure and discomfort in the bladder associated with lower urinary tract symptoms (LUTS), but with no evidence of bacterial infection or other identifiable causes. It is widely acknowledged that before attributing a diagnosis of IC/PBS, the symptoms should have been present for over six weeks (Dasgupta and Tincello, 2011; Hanno et al, 2011; Fiander, 2013; ).

However, the author would question the use of ‘unpleasant’ above as it could indicate that the intensity of pain is not as severe as that described by some patients. The International Continence Society (ICS) (Abrams et al, 2002) defines IC/PBS as a complaint of suprapubic pain related to bladder filling accompanied by other symptoms (see below), which, it could be argued, is a more objective description.

Long-term symptoms reported by patients include pelvic and/or perineal pain, pain during sexual intercourse, nocturia, and urinary frequency and urgency. The associated pelvic pain is further defined in the European Urology Association guidelines (Engeler et al, 2014) as suprapubic pain sometimes radiating to the groin, rectum, sacrum and genitalia.

Symptoms may be aggravated by some food and drink but is temporarily relieved with voiding of the bladder. On physical examination, a thinning of the epithelial lining of the bladder can be determined, and in some cases, ulceration of the bladder lining is also present (You et al, 2012).

A healthy bladder is protected by the sterile urine ‘flushing’ through the system and the mucous glycosaminoglycans (GAG) layer, a layer of protein and sugar molecules that coat the bladder and provides a protective shield against irritants.
and damage, and prevents bacteria adhering to the bladder urothelium (Dyer and Twiss, 2014; Hurst et al, 2015).

Some researchers hypothesise that IC/PBS is caused by a faulty GAG layer mechanism, often referred to as a ‘leaky’ bladder (Generali and Cada, 2013), suggesting that the normally healthy impermeable membrane has somehow been damaged or underdeveloped, allowing irritants in the urine to permeate the bladder wall, leading to pain and irritation (You et al, 2012; Hurst et al, 2015; Flores-Carreras et al, 2015).

**Diagnosis**

Diagnosis of IC/PBS is complicated and often unreliable as the exact causes have never been identified or agreed (Gupta et al, 2015; Davis et al, 2015). The European Study for the classification of IC/PBS described inclusive criteria for diagnosing this complex condition (van de Merwe et al, 2008):

- **Grade 0**: normal mucosa
- **Grade I**: petechiae (small spots caused by bleeding) in at least two quadrants of the bladder
- **Grade II**: large submucosal bleeding (ecchymosis)
- **Grade III**: diffuse global mucosal bleeding
- **Grade IV**: mucosal disruption, with or without bleeding/oedema.

The American Urology Association (AUA) (Hanno et al, 2011) also provided guidance on improving the early detection and accurate diagnosis of IC/PBS, including:

- Basic assessment should include a careful history, physical examination, and laboratory examination to document symptoms and signs that characterise IC/BPS and exclude other disorders that could be the cause of symptoms.
- Baseline voiding symptoms and pain levels to measure subsequent treatment effects.
- Cystoscopy and/or urodynamics should be considered when the diagnosis is in doubt; these tests are not necessary for making the diagnosis in uncomplicated presentations.

**Urodynamic tests**

Urodynamics is an established bladder investigation that aims to replicate symptoms by first asking the patient to empty their bladder while a machine measures the urine flow rate; the bladder is then refilled with a catheter over a period of minutes, while the abdominal pressures are also measured using a rectal catheter; the result demonstrates/eliminates any issues with the patient’s detrusor function or bladder capacity and the presence of any stress leakage.

Elliott and Payne (2012) highlight that urodynamic tests should be carried out to eliminate any other causes for the symptoms of IC/PBS, as overactive bladder (OAB) can have a similar profile, for example a standard definition of OAB would also include detrusor overactivity (symptoms of urgency, frequency and on occasion leakage caused by involuntary and unpredictable contractions of the detrusor muscle in the bladder) with frequency- and urgency-associated symptoms. OAB can react positively to antimuscarinics, antispasmodics or anticholinergics (Kuo and Kuo, 2012).

The accepted urodynamic presentation for IC/PBS is pain without detrusor overactivity (Elliott and Payne, 2012). Urodynamic testing can be an intolerable diagnostic test for some patients due to the severity of the pain experienced on filling their bladder. Also, detrusor overactivity is not always demonstrable with urodynamic tests so other diagnostic techniques should be considered, such as symptom profile, reaction or lack of to pharmacological agents or visual diagnosis from cystoscopy.

Historically, the presence of Hunner’s ulcers identified through cystoscopy was the preferred way of diagnosing IC; similarly a diagnosis of IC/PBS was often made using cystoscopy when a patient presented with all of the previously named IC/PBS symptoms, but no ulcers. However, in recent years, several studies have demonstrated the difficulty in differentiating some IC/PBS symptoms from other urological or gynaecological conditions such as OAB (Elliott and Payne, 2012; Vij et al, 2012). Currently, it is thought that the role of cystoscopy is less diagnostic, being primarily used to exclude other diseases or causes for the symptoms described by the patient.

Potassium chloride sensitivity testing (PST) was at one time described as a ‘gold standard’ test for IC/PBS diagnosis (Parsons et al, 2002). This involved instilling a solution of potassium chloride directly into the bladder via a urinary catheter and monitoring the patient’s response and perception of pain during the procedure. The test proved too painful for many patients, however, and has now been widely acknowledged as a poor indicator, with many studies showing a lack of substantive data to prove the validity of such a test (Hanno et al, 2015).

There is no universally accepted ‘gold standard’ test for the diagnosis...
of IC/PBS as many of the current interventional diagnostics available are intolerable for patients due to an exacerbation of their pain. In many cases, the diagnosis is made after eliminating other possible causes without using an invasive procedure/test.

TREATMENT

Treatment options for IC/PBS remain varied due to the wide array of symptoms reported by patients and the variety of severity described in each case (Dyer and Twiss, 2014). In the opinion of many experts, non-invasive treatment is the first-line choice (Hanno et al, 2011; Giannantoni et al, 2012; Engeler et al, 2014). These measures include:

- Bladder retraining with dietary modifications
- Timed voiding
- Pelvic floor therapy.

Bladder retraining and dietary modifications

It is widely acknowledged that certain irritants such as caffeine, carbonated drinks, alcohol, nicotine artificial sweeteners and spicy foods may exacerbate symptoms of IC/PBS in as many as 90% of patients (Shorter et al, 2007; Friedlander et al, 2012), although many studies were questionnaire-based and therefore subjective.

One particular placebo-controlled study was unable to find an association between exacerbation of symptoms and specific foods (Fisher et al, 1993), and in the author’s opinion, dietary irritants vary between patients and need to be tailored to individual circumstances.

Timed voiding

Timed voiding is a method of retraining the bladder using a schedule based on how much a normal healthy bladder should hold (approximately 500mls) and how many times a day a healthy bladder should empty (4–8 times within 24 hours). This can be an effective way of normalising bladder function in many patients, even if they have no sensation of bladder filling as voiding can be prompted at set times of the day.

Pelvic floor therapy

Pelvic floor physiotherapy can be useful in treating several urological and gynaecological conditions. It is important to understand the underlying cause of the symptoms to ensure the correct therapeutic approach is adopted. In many functional disorders, pelvic floor exercises are aimed at strengthening muscles that affect continence and reducing or inhibiting detrusor contractions to help with urgency.

It has been highlighted, however, that concentrating on strengthening exercises in the initial treatment of IC/PBS may worsen the symptoms as structured periods of exercise aimed at strengthening the urinary sphincters and supporting muscles may create a trigger that causes increased pain for the IC/PBS patient due to the hypersensitivity of the GAG layer of the bladder (Elliott and Payne, 2012). Instead, the recommendation is to focus on relaxing tight muscles, restoration of muscle length and identifying/massaging trigger points, with some evidence suggesting an 83% improvement in symptoms (Weiss, 2001).

In the author’s opinion, the obvious downside to pelvic floor exercises lies in the variation in teaching techniques. Structured pelvic floor exercises are a specialist area of therapy and should be delivered by appropriately experienced professionals with examination and review to ensure efficacy.

Pharmacology

Pharmacological treatments include anticholinergic medications, which are an obvious choice to manage urge symptoms in up to 75% of patients, however, while this class of drugs is successful in many OAB patients (Abrams and Andersson, 2007; Nabi et al, 2006), it has little effect in patient with IC/PBS and is not recommended for use in the EAU or AUA guidelines (Engeler et al, 2014; Hanno et al, 2015). Pain is a primary and consistent symptom reported by many patients experiencing IC/PBS, but evidence suggests that the pain responds poorly to popular analgesia (Fiander, 2013).

Opiates have shown some success, but as the condition is chronic and may require long-term management, it is advisable to consider the side effects of any analgesia, including a risk of dependency (Engeler et al, 2014). Amitriptyline may also have limited use, although it is associated with drowsiness and in their study Foster et al (2010) suggested that no significant improvement in pain symptoms was achieved at a lower dose. It is therefore recommended as a second-line therapy for IC/PBS (Hanno et al, 2011).

Cimetidine has been used to treat IC/PBS as it inhibits the H2 receptors affecting the T-cells. As patients with IC/PBS cystitis have been shown to have significantly increased concentrations of lymphocytes, T cells and blood vessels in the mucosa of the bladder, using cimetidine twice a day at a dose of 400mg can relieve nocturia and suprapubic pain (Thilagarajah et al, 1998).

Hydroxyzine is an H1 receptor antagonist useful in treating allergies and as many IC/PBS patients have allergy profiles (Koziol et al, 1993), Theoharides and Sant (1997) found that the use of hydroxyzine may offer improvement in up to 58% of patients.

Intravesical therapies

Intravesical therapies (where the drugs are delivered directly into the bladder through a catheter) are currently the most popular treatment for IC/PBS in the UK. Typically, intravesical instillations are given via a urethral catheter once a week for a period of 4–12 weeks depending on effect. Patients often return for repeat courses over several years.

Dimethy sulfoxide (DMSO) has analgesic and anti-inflammatory actions and has been used since the 1980s for the successful management of IC/PBS symptoms, with response rates improving in up to 90% of patients who reported general symptom relief (Parkin et al, 1997).

Sodium hyaluronate is used to temporarily repair the damaged GAG layer seen in IC/PBS and studies have shown improvement in symptoms in up to 75% of patients.
CONTINENCE

gradually increasing with subsequent instillations (Daha et al, 2005; Kallestrup et al, 2005; Ahmad et al, 2008).

Another drug, chondroitin sulfate is also used to repair the GAG layer in the bladder and improve the symptoms associated with IC/PBS. Downey et al (2015) and Steinhoff et al (2012) have published studies on the efficacy of chondroitin sulfate compared to other intravesical options, concluding that the drug is effective in the short-term management of IC/PBS and is a relatively cheaper option in comparison to other preparations. However, it should be noted that these studies all had a low number of participants and are therefore not indicative of the whole population of people with IC/PBS.

Many studies report positive outcomes and improvement in quality of life for IC/PBS patients following intravesical instillations (Arance et al, 2013; Lai et al, 2013). Matsuoka et al (2012) performed a systematic review of the efficacy of various intravesical treatments and concluded that there are few clinical trials with high levels of evidence to evaluate effectively. In the UK, some intravesical treatments are now available on FP10 and therefore accessible in a community setting, with some patients learning to self-administer. It is the author’s conclusion that this treatment has a valuable contribution to the successful treatment and management of symptoms in IC/PBS.

Sacro-neuromodulation
Sacro-neuromodulation (SNS) was first initiated in 2000 as a treatment for IC/PBS and involves electrical stimulation of the sacral (S3) nerve to block afferent bladder activity and has been very successful in the treatment of OAB symptoms (Siddiqui et al, 2010). Studies have suggested that when used for IC/PBS, three-quarters of patients reported a significant improvement in their symptoms during the percutaneous SNS testing phase and were considered for a permanent implant (Chai et al, 2000; Maher et al, 2001).

It has been reported, however, that posterior tibial nerve stimulation (PTNS) (where neurostimulator electrodes are inserted into the peripheral nerve), and which is often used as an alternative to SNS, was not successful in the treatment of IC/PBS (Zhao et al, 2008). SNS and PTNS are only offered at a few centres across the UK and PTNS can be labour-intensive, requiring a lot of commitment from the patient as it requires up to 12 half-hour weekly appointments.

Similarly, SNS is a specialised option available only in a few tertiary referral centres; it is costly at up to £20,000 for bilateral implants and has had issues with funding and long waiting lists. The trial phase can be difficult for patients as it involves temporary wires being held in place primarily by a large occlusive dressing, which requires the patient to refrain from bathing/showering the area for up to three weeks while the trial is active. Patients also have to keep a diary of their symptoms and activity and if there is a significant improvement in symptoms, they may then be considered for a permanent single or bilateral implant. The waiting time for this can be several months to a year, meaning this method of treatment is not always available to every patient.

CONCLUSION
IC/PBS is a chronic, complex and poorly diagnosed condition presenting many challenges for patients and clinicians. Many patients with this condition have seen multiple healthcare professionals over a period of many years and may have tried a variety of unsuccessful treatments. If the lack of a definitive definition of IC/PBS, diagnosis of its aetiology, nor successful treatment can contribute to a poor quality of life for many patients, often likened to that of a patient with end-stage renal failure (Chung et al, 2015).

Despite widespread consensus that damage to the bladder’s GAG layer is a primary cause of IC/PBS symptoms, many of the studies available are based on low participant numbers and lack the substantive quality data to establish an absolute cause as well as an effective treatment for IC/PBS. Further clinical trials and larger participant volume studies are required to fully understand this condition.

Pain is a primary symptom of IC/PBS, but it is accepted that there are many triggers for the pain experienced by sufferers. For community nurses, comprehensive history taking, physical examination and appropriate clinical tests all help to arrive at an appropriate and timely diagnosis, which, when combined with individualised treatment plans, can offer patients long-term effective relief of their symptoms. Increased knowledge and consensus around IC/PBS is needed, however, before patients’ experiences become more positive.

REFERENCES


Downey A, Hennessy DB, Curry D, Cartwright C, Downey P, Pahuja A


