Review Painful bladder syndrome and interstitial cystitis

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Key content:
• Painful bladder syndrome is a chronic disabling condition that mainly affects women.
• The aetiology is uncertain, but is almost certainly multi-factorial and presents as a triad of pain, urinary urgency and frequency.
• The most common diagnosis made is interstitial cystitis. Diagnosis is based on history and examination and supplemented by clinical investigation.

Learning objectives:
• To be able to identify the clinical features of interstitial cystitis and arrange appropriate diagnostic tests.
• To know how to manage interstitial cystitis using non-pharmacological, dietary and behavioural treatment, as well as pharmacological and surgical therapy.

Ethical issues:
• How much information should women be given about possible adverse effects?

Keywords: interstitial cystitis / painful bladder syndrome / pelvic pain / urinary frequency / urinary urgency

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Introduction

Painful bladder syndrome (PBS) is categorised by suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency in the absence of proven urinary tract infection or other pathology. The International Continence Society believes this to be a preferable term to interstitial cystitis. In the past the two terminologies have been used interchangeably. Painful bladder syndrome (Table 1) encompasses a much broader range of causes that need to be excluded, such as carcinoma in situ and endometriosis (Figure 1).

There is considerable overlap between the overactive bladder syndrome (OAB), the urethral pain syndrome (urethral syndrome) and PBS. Whereas the principal complaint of women with OAB is urgency, in women with PBS it is predominantly pain related to bladder filling (Figure 2). Women with urethral pain syndrome, on the other hand, complain of pain on voiding.

The term PBS, therefore, includes cases with painful urinary symptoms that may not meet the strictest definition of interstitial cystitis, for example, radiation cystitis and cyclophosphamide cystitis. The term interstitial cystitis is used alone when describing cases that meet all of the interstitial cystitis criteria established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (Box 1) and is a diagnosis of exclusion.

The aim of this review is to summarise the presentation, investigation and management of women with interstitial cystitis.

Interstitial cystitis

Interstitial cystitis is a chronic inflammatory disorder of the bladder and one of the causes of PBS first described by Hunner in 1915. It results in consistently low quality-of-life scores, is notoriously difficult to manage and can cause considerable morbidity.

Women between the ages of 40 and 60 years are most commonly affected. The condition occurs far more frequently in Caucasians and there is a 9:1 female predominance. Up to 50% of women experience spontaneous remissions unrelated to treatment, with a duration ranging from 1 to 80 months. Reported prevalence rates for this condition vary widely as there is no universally accepted definition.

Aetiology

The pathophysiology of interstitial cystitis remains elusive and many theories have been formulated. A detailed discussion of the aetiology is outside the scope of this article.

Bladder wall dysfunction and GAG layer deficiency

Dysfunctional lower urinary tract epithelium is said to be characterised by damage to the glycosaminoglycans (GAG) layer. This can lead to increased permeability to potassium, which then permeates the bladder musculature, triggering imperative urgency and bladder contractions. Mast cell activation is considered to be a result of GAG layer deficiency: this provokes a neurogenic inflammation with overexpression of neurotransmitters. This remains controversial and, as yet, unconfirmed by electron microscopy.

Differential diagnosis of PBS

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Table 1

Differential diagnosis of painful bladder syndrome and methods of investigation
Autoimmune system disorders
Disorders of the immune system are suspected as being causative because of the association with certain HLA groups, allergies and autoimmune processes.5,6

Hypoxia
Vascular, hormonal or toxic factors leading to bladder wall hypoxia may affect the GAG layer.7 A reduced blood flow in the suburothelial layers (but not deeper layers) has been seen in women with interstitial cystitis.

Visceral hypersensitivity theory
Interstitial cystitis has been described as visceral neuropathic pain, a hypersensitive state that is secondary to a site of irritation located in the urinary bladder.8 This may explain the association with other visceral hypersensitivity disorders such as irritable bowel syndrome9 and fibromyalgia.10

Clinical features
Pelvic pain, urgency and urinary frequency are essential to support a diagnosis of interstitial cystitis.11 Pain typically occurs in the pelvic area and can manifest in the bladder, vagina, urethra, rectum or perineum. It is chronic and urinary tract infection is absent. It can be sharp in nature but there can also be feelings of pressure or burning. It can also be related to sexual intercourse. However, the characteristic feature is the relationship of pain to bladder filling and relief during voiding. Pain during voiding, on the other hand, is more suggestive of urinary tract infection, vulval or vaginal disorders or the urethral pain syndrome and can occasionally be caused by urethral diverticula.

Investigation and assessment
There have been three major conferences recently to try and establish a consensus on the diagnosis of interstitial cystitis.12–14 The diagnostic consensus reached from these meetings is presented in Box 2.

Pelvic examination
Pelvic examination is of limited value in making a positive diagnosis of interstitial cystitis. The bladder can occasionally be tender on palpation but the examination is helpful in excluding other conditions that can cause similar symptoms.
Physical examination should include a vaginal examination with pain mapping of the vulval region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor and pelvic organs.

Pain mapping of the vulva requires the exclusion of vulvar/vestibular diseases by the touch test (using a wet cotton stick or fingertip). This consists of the palpation of six randomly ordered vestibular sites with a cotton swab.\textsuperscript{13}

**Voiding diary**

This is an important tool in the investigation of lower urinary tract symptoms. For a voiding diary to have value it must be completed correctly. A 3-day diary has been suggested as optimal.\textsuperscript{16} It is usual to see women with interstitial cystitis having frequent, small volume voids.

**Urine testing**

Urinalysis is usually normal in interstitial cystitis. Haematuria can be present but other causes should be excluded. Urine culture is essential to exclude simple urinary tract infection. Culture and sensitivity should be done for atypical infections such as *Ureaplasma urealyticum*, *Mycoplasma hominis* or *Chlamydia trachomatis*. Urine cytology is recommended if haematuria is present or where risk factors for bladder cancer are identified (smoking, age above 50 years, family history or occupational exposure to certain industrial chemicals such as aromatic amines).\textsuperscript{17}

**Questionnaires and symptom scales**

To date there are three published questionnaires for use in interstitial cystitis: the University of Wisconsin Interstitial Cystitis Scale,\textsuperscript{18} the O’Leary–Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index\textsuperscript{19} and the Pelvic Pain and Urgency/Frequency (PUF) Scale.\textsuperscript{20}

The general consensus of an expert panel in Kyoto was that none of the scales could be used for diagnosis, although they can be valuable in monitoring the progress of treatment outcomes.\textsuperscript{21}

**Urine markers**

Urine markers show promise in the assessment and diagnosis of interstitial cystitis. Certain markers are significantly increased in interstitial cystitis, including antiproliferative factor, epidermal growth factor, insulin-like growth factor (IGF) binding protein-3, interleukin (IL)-6 and nitric oxide.\textsuperscript{22} Antiproliferative factor is the most likely candidate to become a diagnostic test, with the least overlap between interstitial cystitis and control groups.\textsuperscript{23} However, none of these markers are routinely used for the diagnosis of interstitial cystitis. Research is under way to test their usefulness in clinical practice.

**Urodynamics**

Urodynamics is used to rule out alternative pathology such as obstructed voiding or detrusor overactivity, rather than positively diagnose interstitial cystitis. Hypersensitivity during filling cystometry, a small bladder capacity, reduced maximal flow rate and abnormal flow pattern have been observed in women with interstitial cystitis. These findings are not specific and can also be encountered women without interstitial cystitis.\textsuperscript{24} Interestingly, 14% of patients with interstitial cystitis have abnormal urodynamics.\textsuperscript{25}
cystitis have evidence of detrusor overactivity on subtracted cystometry.\textsuperscript{24}

\textbf{Potassium sensitivity testing}  
This test involves a comparison of pain and urgency sensation after consecutive instillation into the bladder of 40 ml of water and 40 ml of 40 mEq/100 ml potassium chloride for 5 minutes each. A positive test results in an increase in pain with potassium chloride. Potassium sensitivity testing does not correlate to bladder capacity or cystoscopic findings, hence is of limited value in the diagnosis of interstitial cystitis.\textsuperscript{25} It is not part of the routine assessment of painful bladder symptoms in the UK and attempts to modify the test so that it is more comfortable for women are under way.\textsuperscript{26}

\textbf{Cystoscopy}  
In 1915 Hunner described the ulcers, consisting of glomerulations and small, discrete purple haemorrhages of the bladder mucosa, that are often found in women with interstitial cystitis. However, women with interstitial cystitis can have a normal appearance to the urothelium. The purpose of cystoscopy in the investigation of bladder pain is the exclusion of local, intravesical abnormalities (Figure 3).

The decision for cystoscopy is frequently based on the presence or absence of risk factors for bladder cancer. One percent of women with interstitial cystitis in a tertiary unit in the US were eventually diagnosed with transitional cell carcinoma of the bladder\textsuperscript{17} and some authors advocate cystoscopy as a mandatory investigation.\textsuperscript{27}

\textbf{Management}  
Management of women with interstitial cystitis (Box 3) remains a therapeutic dilemma. A total of 183 different types of therapies have been recorded, suggesting that there is no simple solution.\textsuperscript{29} Management begins with initial assessment, acknowledging and validating pain and setting expectations.\textsuperscript{30} Single drug therapy is sufficient for most women, but multi-modal therapy can be appropriate for those with severe or longstanding disease. In most studies involving placebo controlled trials there has been a demonstrable benefit in the placebo arm.

\textbf{Non-pharmacological treatments}  
A major part of the management of women with interstitial cystitis is behavioural and non-pharmacological. Strategies such as physical therapy, avoidance of flare inducing foods (such as those with high acidity or a high potassium content. See Table 2), bladder training and stress management techniques can supplement pharmacological treatment and improve clinical response.\textsuperscript{31}

\textbf{Pharmacological treatments}  
Attempting to address all aspects of pain management is beyond the scope of this review. The current pharmacological options available specifically for managing interstitial cystitis pain are outlined here, including some new developments. Pharmacotherapy in interstitial cystitis is based on four principles:

- controlling a dysfunctional urothelium by restoring the mucus/GAG layer with GAG or GAG-like drugs
- inhibiting neurological activity
- suppression of allergies
- pain control.
Spices

- Rosemary, thyme, oregano, basil, marjoram, fennel
- sage, dill, mixed herbs

Sweets

- White chocolate, frozen yogurt
- Apples, apricots, avocados, bananas, cantaloupes, melons
- Beets, broccoli, Brussels sprouts, chives, carrots, onions, cucumber, cauliflower, leeks
- Sausage, dill, mixed herbs

Beverages

- Bottled water, red bush tea, pear juice
- Alcoholic beverages (including beer and wine), carbonated drinks such as sodas, coffee or tea, fruit juices, especially citrus or cranberry
- Rye and sourdough

Breads

- White bread, rice bread/cakes, millet, buckwheat, matzo, plain pita
- Canned, cured, processed or smoked meats and fish, anchovies, caviar, chicken livers, corned beef and meat that contain nitrates or nitrites
- Onions and tomatoes

Grains

- Refined, rice, plain pasta
- Fava beans, lima beans, soy beans, tofu
- Almonds, cashews, peanuts

Fats

- Butter, margarine, vegetable oils
- L-arginine
- Nutmeg, cinnamon, ginger

Sauces, fish and poultry

- Soups made with allowed vegetables
- Cream cheese, cottage cheese, ricotta, milk in capsule form, usually in doses of 100–200 mg, 3 times a day; it is best to take them with meals. It is not currently licensed in the UK. It can be obtained in most health food shops and some pharmacies and it can also be taken in conjunction with standard medical treatments for interstitial cystitis.

Cheese/dairy

- Almonds, cashews, peanuts
- Fava beans, lima beans, soy beans, tofu
- Almonds (other than cantaloupes), blueberries and peaches

Vegetables

- Purple cabbage, brussels sprouts, carrots, broccoli, cauliflower, okra (lady’s fingers), celery, cucumber, cauliflower, leeks
- Green peas, kidney beans, lima beans, navy beans, soy beans
- Brown sugar, honey, maple syrup

Beans

- Purple cabbage, brussels sprouts, carrots, broccoli, cauliflower, okra (lady’s fingers), celery, cucumber, cauliflower, leeks
- Grapes, kiwi, olives, oranges, pears, pineapple, plums, prunes
- Raisins, dried figs, dates

Sodium pentosanpolysulfate (Elmiron®)

- This acts by substituting a defective glycosaminoglycan layer and inhibiting complement reactions in inflammatory processes. It is the only oral agent used to treat interstitial cystitis that has been rigorously investigated in double blind trials. It takes time for the drug to work. Some response usually occurs within 4 weeks but treatment should be continued for a minimum of 3 months. It is not currently available in the UK. It temporarily replaces the deficient GAG layer on the bladder wall, helping to relieve the pain, frequency and urgency of interstitial cystitis. For the first 4 weeks of treatment, patients with interstitial cystitis receive one instillation each week. After that, treatments are usually given once a month until the symptoms resolve.

Oral medication

Antihistamines

- Histamine is an enzyme that causes an increase in the internal dimensions of the blood vessels. Antihistamines have been shown to be useful for the symptomatic treatment of interstitial cystitis, especially in women with documented allergies or evidence of bladder mast cell activation, perhaps by preventing the release of histamines that cause inflammation. In the immediate term it can improve nocturia. Sufferers of interstitial cystitis should normally see an improvement within 6–8 weeks of continuous use.

Cimetidine

- More commonly used for healing stomach ulcers, this drug has also been found to be effective at controlling some symptoms of interstitial cystitis.

Amitriptyline

- Amitriptyline is frequently used in pain management. Anecdotal experiences with the tricyclic class of antidepressants suggest that amitriptyline can be an effective treatment for bladder pain. It can also be taken in conjunction with standard medical treatments for interstitial cystitis.

Prelief

- Prelief® (AkPharma, Pleasantville, NJ) contains calcium glycerophosphate, a food-grade mineral classified as a dietary supplement, which can be used with acidic foods and beverages to make eating more comfortable.

Drugs used for bladder instillation

Hyaluronic acid

- Hyaluronic acid (Cystistat, Bioniche Life Sciences Inc, Belleville, Ontario) is licensed for use in the UK. It temporarily replaces the deficient GAG layer on the bladder wall, helping to relieve the pain, frequency and urgency of interstitial cystitis. For the first 4 weeks of treatment, patients with interstitial cystitis receive one instillation each week. After that, treatments are usually given once a month until the symptoms resolve.
Response time will vary; however, women who do not notice an early improvement should not be discouraged, as five or six instillations can be necessary before symptoms begin to resolve. Treatment can be repeated if symptoms return.

**Chondroitin sulphate**

Chondroitin sulphate (Uracyst,® Stellar Pharmaceuticals Inc, London, Ontario) recently became available in the UK. One study using chondroitin sulphate showed 67% of patients responding favourably.75 The mechanism proposed for the action of hyaluronic acid and chondroitin sulphate is coating of damaged bladder.75

**Dimethyl sulfoxide (DMSO)**

Dimethyl sulfoxide is not licensed in the UK for use in interstitial cystitis. It reduces inflammation by acting as an antioxidant, a scavenger of the free radicals that gather at the site of injury, and by stabilising membranes, which slows or stops leakage from injured cells and which may be useful in restoring the GAG layer. The treatment is usually given for 6–8 weeks at fortnightly intervals. A catheter is placed into the bladder and the DMSO solution is held in place for up to 15 minutes. Some women can find this painful. The solution is then voided. No significant adverse effects of DMSO have been noted, although approximately 20% of women complain of a garlic halitosis. In our experience it is these women who have the best response.

**Intravesical heparin**

Heparin is a glycosaminoglycan which can afford protection to the urothelium and which reduces the relapse rate. It is better tolerated than DMSO and does not produce garlic halitosis. It is not associated with coagulation anomalies when administered intravesically and has a response rate of up to 56% of patients.81

**Hydrodistension**

Cystoscopy with hydrodistension is the most commonly performed intervention in women with interstitial cystitis. Hydrodistension is thought to work by disrupting the neuronal pathways of the bladder, thereby disrupting pain transmission. Treatment efficiency ranges from 12–70%.82 84 The benefits are, however, short lived and it can cause ischaemia, damage84 and even bladder rupture4 and is not recommended in our unit. During hydrodistension, the infusion height should be approximately 80 cm above the symphysis pubis, using a dripping chamber until the flow stops and around the ulcers.

When maximum capacity is reached, distension is maintained for 3 minutes and the bladder emptied and refilled to around one-third of the maximum for visualisation of haemorrhage and possible biopsy, which should be performed to include detrusor muscle.

**Surgery**

Reconstructive surgery is considered where other treatments have failed and symptom severity is such that the woman’s quality of life is seriously affected. Surgery is invasive and irreversible and there is no guarantee that the symptoms will improve. Some can, in fact, become worse. Potential complications from surgical procedures also need to be considered. Options available include partial cystectomy, augmentation cystoplasty and urinary diversion with or without cystectomy. Other less invasive surgical options include endoscopic resection or fulguration of bladder ulcers and local injection of hydrocortisone, saline and heparin in and around the ulcers.

**Conclusion**

The clinical diagnosis of interstitial cystitis is based on identifying symptom criteria and excluding organic disease with diagnostic evaluation. Clinicians should feel secure with the diagnosis of interstitial cystitis, if made properly, because it is rarely associated with other explanations for symptoms. An integrated diagnostic and treatment approach first requires an effective physician–patient relationship. A careful history will also identify the need for diagnostic studies and treatments, depending on the nature and severity of the predominant symptoms and the degree and extent of influencing psychosocial and other factors.

The fact that definite structural or biochemical abnormalities for these disorders cannot be detected with conventional diagnostic techniques does not rule out the possibility that neurobiological alterations will eventually be identified to explain fully the symptoms of most functional disorders. As with other chronic illnesses, a multi-component model that involves physiologic, affective, cognitive, and behavioural factors can be formulated for PBS. Instituting a multidisciplinary approach using non-pharmacological and pharmacological therapeutic modalities may result in the most effective outcome.

Hopefully, future studies will enhance our understanding of this condition and lead to newer, more effective treatments.

**References**


