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Treatment Approaches for Painful Bladder Syndrome/Interstitial Cystitis

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Contents

Abstract

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a disease of unknown aetiology, characterised by severe pressure and pain in the bladder area or lower pelvis that is frequently or typically relieved by voiding, along with urgency or frequency of urination in the absence of urinary tract infections. PBS/IC occurs primarily in women, is increasingly recognised in young adults, and may affect as many as 0.1–1% of adult women. PBS/IC is often comorbid with allergies, endometriosis, fibromyalgia, irritable bowel syndrome and panic syndrome, all of which are worsened by stress. As a result, patients may visit as many as five physicians, including family practitioners, internists, gynaecologists, urologists and pain specialists, leading to confusion and frustration. There is no curative treatment; intravesical dimethyl sulfoxide, as well as oral amitriptyline, pentosan polysulfate and hydroxyzine have variable results, with success more likely when these drugs are given together. Pilot clinical trials suggest that the flavonoid quercetin may be helpful. Lack of early diagnosis and treatment can affect outcomes and leads to the development of hyperalgesia/allodynia.

1. Presentation

Painful bladder syndrome/interstitial cystitis (PBS/IC), as it has recently been named by the International Continence Society[1] and the International Interstitial Cystitis Association,[2] is a painful disease occurring mainly in women.[3] There is no curative therapy.[4] Early recognition of PBS/IC is very important because symptoms are disabling and affect quality of life. PBS/IC is a diagnosis of exclusion characterised by >6 months of pain, pressure or discomfort involving the lower abdomen, and specifically the bladder, that is relieved by voiding, along with urgency and frequency of urination, in the absence of a urinary tract infection (UTI).[3] Pain can be severe and is commonly suprapubic. Urgency and frequency of urination are less frequent in men with PBS/IC, who may also present with type III prostatitis, also known as abacterial prostatitis or chronic prostatitis.[5] There are subtle differences in the definition and diagnosis of PBS/IC between the US and the EU, with cystoscopy under spinal or general anaesthesia, along with urodynamics, still acknowledged in Europe,[6] but downplayed in the US.[2,7] A subject of great contention is what constitutes 'bladder pain' or 'pain of bladder origin'[8] as compared with 'chronic pelvic pain' (CPP).[9] There are approximately 9 million individuals with CPP in the US, but an increasing number of reports indicate that the bladder is an important origin for such pain.[10-14] Some large multicentre studies have identified the bladder as the major cause of CPP.[10-14] It was suggested at the 2006 The National Institute of Diabetes and Digestive and Kidney Diseases

(NIDDK) symposium that PBS/IC be renamed 'bladder pain syndrome'.[15] The pain sometimes persists after bladder removal, indicating a neuropathic component, such as that of phantom limb pain, as is also suggested by the hypersensitivity to somatic stimuli seen in >50% of patients with PBS/IC.[16] As a result of all this, patients may visit as many as five physicians, including family practitioners, internists, gynaecologists, and urologists and pain specialists, leading to confusion and frustration.

Symptoms can be assessed using the validated one-page O'Leary-Sant Symptom and Problem Index, which consists of two sets of four questions and results in a possible score of between 0 and 36, the latter reflecting worst symptom severity.[17] The results obtained with this index correlate highly with the University of Wisconsin Symptom Instrument (UWI).[18] Both the O'Leary-Sant Symptom and Problem Index and the UWI were sensitive to subject improvement over time as measured by the Global Response Assessment.[19] The Pelvic Pain and Urgency/Frequency (PUF) Symptom scale also assesses sexual dysfunction.[20]

Family linkage studies have shown that PBS/IC is associated with stress and panic disorder.[21,22] Precipitating factors include beverages containing biogenic amines[23] and caffeine,[24] as well as smoking.[25] Patients tend to avoid spicy or 'acid' foods; however, a prospective, double-blind, randomised, crossover study evaluating the effect of raising urine pH on pain sensation of PBS/IC patients showed no benefit from this practice.[26]

Patients with PBS/IC have a higher incidence of other comorbid diseases, such as prostatitis, endometriosis, pelvic pain syndrome, vulvodynia and anxiety, compared with the general population.[27-31] Allergies, asthma and/or atopic dermatitis occur in >50% of patients with PBS/IC;[32] in fact, in one study of 34 patients with PBS/IC (aged 20–39 years), 86% had complications of allergic diseases.[33] Irritable bowel syndrome (IBS)[34] and endometriosis[12] are also common. In one prospective multicentre study of 197 patients presenting with pelvic pain, 84% had concurrent urological symptoms that were consistent with PBS/IC.[14] In another study of 178 women with pelvic pain, who presented with bladder base tenderness, 65% of patients had both PBS/IC and endometriosis.[12] The prevalence of vulvodynia may also be underestimated;[35] in one study of 64 patients undergoing laparoscopy for CPP, 20% had documented vulvar pain.[10] Patients with PBS/IC who had Hunner's ulcers had a 33–100 times higher prevalence of inflammatory bowel disease (IBD) than the general population[32] and a 30 times higher chance of having systemic lupus erythematosus (SLE).[30] Sjögren's syndrome, chronic fatigue syndrome, fibromyalgia, migraines, rheumatoid arthritis and multiple chemical sensitivities may also be present.[30-32]

2. Prevalence

Early estimates used the National Institutes of Health/NIDDK (NIH/NIDDK) research criteria that were established to select a rather homogeneous population for clinical studies; these included Hunner's ulcers, or any two of (i) pain on bladder filling that is relieved by emptying; (ii) pain (suprapubic, pelvic, urethral, vaginal or perineal); or (iii) glomerulations on endoscopy (upon hydrodistension with spinal or general anaesthesia).[36] However, the fact that over 60% of patients possibly having PBS/IC do not fit these criteria prompted expansion of the definition of PBS/IC.[6,37] The population-based Nurses Health Study II estimated the prevalence of PBS/IC as being 55 per 100 000 individuals.[38] The prevalence in a managed-care setting was later reported to be 190 per 100 000 women and 41 per 100 000 men. In a subsequent population-based study in Finland, which has a more homogeneous population than the US, the prevalence of clinically confirmed PBS/IC in women was estimated at 230 per 100 000.[39] Recent results obtained in an office setting in the US reported that the rate of probable cases of PBS/IC determined using the O'Leary-Sant Problem and Symptom index was 575 per 100 000 individuals, but increased to 12 600 per 100 000 when using the PUF scale.[40]

PBS/IC has been reported in adolescents[41,42] and children.[42,43] There have also been case reports of children who presented with vulvar vestibulitis syndrome (VVS)[44] or SLE in addition to PBS/IC.[45] PBS/IC can develop at an age where most health providers may not be familiar with this condition, the cystoscopic appearance of which may not initially include glomerulations.[46]

In response to a mail-in questionnaire, 3.7% of persons indicated that they had family members with confirmed or suspected PBS/IC,[47] with the prevalence of PBS/IC in first degree relatives of patients with PBS/IC reported to be 17 times higher than in the general population[47] In a study of twin pairs, five of eight monozygotic twin pairs had confirmed or suspected PBS/IC compared with 0 of 26 dizygotic twin pairs.[48] Recent family linkage studies showed a strong association of PBS/IC with panic disorder, which has been localised to chromosome 13q.[49]

3. Diagnosis

Diagnostic evaluation often varies among urologists or urogynaecologists and between different centres; this problem has led to some conflicting findings.[36,50,51]

The diagnosis of PBS/IC continues to be symptom-driven; a diagnosis is made by exclusion and is based on a comprehensive history that includes >6 months of suprapubic pain, pressure and discomfort related to bladder filling, as well as urinary frequency and urgency in the absence of UTIs or other pathology.[52] A thorough history and physical examination is particularly critical and should differentiate PBS/IC from other conditions that may have similar symptoms, such as endometriosis.[53] The medical history should inquire into recurrent UTIs, pelvic surgery, spinal cord trauma, and CNS or autoimmune diseases. A voiding diary and the O'Leary-Sant, Wisconsin or PUF indices are helpful for follow-up, but not for diagnosis. Physical examination should address high-tone pelvic floor muscles, and the Kaufman Q-tip touch sensitivity test might help screen for the presence of VVS.[54]

3.1 Noninvasive

Urine culture and sensitivity tests are negative in PBS/IC. If haematuria is present, urine cytology, renal ultrasound, pelvic CT and cystoscopy with or without biopsies should be performed.

There are no specific blood or urine markers of PBS/IC available for use in diagnosis. Levels of the histamine metabolite, methylhistamine,[55] and the unique mast cell protease, tryptase,[56] were increased in 24-hour urine samples from patients with PBS/IC who met NIDDK criteria, but the sample was too small to calculate the specificity or sensitivity of the results. Urine interleukin (IL)-6[57] levels were only elevated in newly diagnosed patients.[57,58]

Increased urine levels of an antiproliferative factor (APF) in patients with PBS/IC lead to decreased *in vitro* proliferation of bladder epithelial cells that distinguishes PBS/IC from other urological disorders.[59] The urine APF level can also apparently distinguish PBS/IC from chronic pelvic pain syndrome in men.[60] In a recent study that included 38 Chinese patients with PBS/IC and Hunner's ulcers (classic type), 26 patients with PBS/IC but without Hunner's ulcers, 10 control individuals without bladder disease, 10 patients with bacterial cystitis and 10 patients with bladder cancer, urine APF levels were higher and heparin-binding epidermal growth factor-like growth factor levels were lower ($p < 0.0001$) in patients with PBS/IC than in individuals in the other groups, but the 'classic' type could not be distinguished from the common type.[61] APF was recently identified as a frizzled-8 surface sialoglycopeptide.[62] Gene expression patterns of epithelial cells from the bladders of patients with PBS/IC and normal epithelial cells treated with APF showed a differential expression of genes that was consistent with a less proliferative phenotype than in normal untreated epithelial cells.[61,63] APF appears to be the most promising marker for PBS/IC, but this needs to be validated and the results need to be independently reproduced.

3.2 Invasive

The requirement for cystoscopy and hydrodistension under general or spinal anaesthesia mandated by the NIDDK research criteria is now considered too restrictive;[51] yet it remains the most common procedure performed in patients with PBS/IC[6] and may be necessary to exclude other pathologies, to look for the presence of urothelial petechiae (glomerulations), and to measure bladder capacity. However, glomerulations have also been observed in the bladders of normal women undergoing tubal ligation.[64] In a recent retrospective study of 84 patients with PBS/IC (68 women and 16 men), hydrodistension was performed in 47, but provided little diagnostic benefit beyond that provided by the medical history and physical examination.[7] Nevertheless, European urologists still view cystoscopy with bladder hydrodistension important, if not mandatory, because they consider that bladder glomerulations and/or ulcers constitute the best diagnostic criteria.[2,6] In a recent prospective study of 12 newly diagnosed women with PBS/IC who had not previously received treatment for this condition, there was strong correlation between pain and cystoscopic findings of bladder inflammation.[65] Classic PBS/IC is characterised by bladder ulcers (Hunner's ulcers)[3] and may define a subset of patients with PBS/IC with a greater degree of bladder inflammation, but the proportion of patients classified as being in this subset varies considerably (5–15%) among urologists.[66] Classic PBS/IC may also be differentiated from disease without ulcers by the presence of elevated urinary nitric oxide levels.[67]

Urodynamic studies remain controversial, but may be beneficial in evaluating bladder dysfunction, especially in male patients with PBS/IC.[68] Assessment of maximum bladder capacity is performed using different methodologies, with procedures using water, an 0.9% sodium chloride solution, a potassium chloride 0.2 mol/L solution or an isotonic glycine solution,[50] making comparisons between studies difficult. Standardisation of procedures of evaluation should, therefore, be in order,[6,50] especially since sterile water could damage fragile urothelium because of its hypotonicity.

Biopsy with histopathology may be necessary to exclude neoplasms and eosinophilic or tuberculous cystitis. A count of tryptase-positive bladder mast cells could be useful in potentially identifying a subpopulation of patients with PBS/IC who may respond to certain drugs, such as hydroxyzine (see section 5.6.1).[69]

Intravesical administration of concentrated (0.4 mol/L) potassium chloride (the potassium sensitivity test), during which neuronal depolarisation of exposed bladder sensory nerve endings elicits pain that is scored by the patient, has been proposed for use in PBS/IC diagnosis.[20,70] However, both the sensitivity and the specificity of this test are approximately 75% and potassium chloride needs to be followed by lidocaine to mitigate the bladder pain on which it is based. The International IC Consultation in Rome recommended that this test not be used for diagnostic purposes because of its low prognostic value.[2]

4. Pathogenesis

The precise cause of PBS/IC is unknown. However, several aetiological, but not mutually exclusive, theories have been proposed, although they continue to remain somewhat speculative and controversial to some urologists.

4.1 Infections

In a retrospective study of 45 women with PBS/IC, the most common previous diagnoses were UTIs in 19 patients, gynaecological indications in 14 patients and urethra-related conditions in 6 patients.[71] No bacterial or viral DNA, including that of *Helicobacter pylori*,[72] *Gardnerella vaginalis*[73] and *Chlamydia trachomatis*, as well as adenovirus, cytomegalovirus, herpes simplex I and II and all types of papillomavirus,[74] has been detected by reverse transcriptase-polymerase chain reaction. One report of the presence of some unknown strain of Gram-negative bacteria in the bladder tissue of 29% of patients with PBS/IC based on amplification of a 16S rRNA fragment [75] was later dismissed as a sampling artefact.[76]

4.2 Bladder Lining

The protective bladder lining, composed primarily of the glycosaminoglycans (GAG), chondroitin sulfate and sodium hyaluronate, may be damaged in PBS/IC (figure 1).[77,78] According to this theory, noxious urine substances might penetrate the urothelium and activate sensory nerve endings and/or inflammatory cells. Increased urinary levels of chondroitin sulfate and sodium hyaluronate have been reported in some patients with PBS/IC,[79,80] along with decreased levels of the mucosal glycoprotein, GP1.[81] In a recent study of 37 patients with PBS/IC who met the NIDDK criteria, urine uronate and sulfated GAG levels were increased in patients with severe disease, irrespective of whether they had glomerulations, when compared with 14 control individuals without PBS/IC ($p < 0.001$; 80% specificity and 88% sensitivity for uronate; 69% specificity and 92% sensitivity for sulfated GAG).[82] In a more recent study, urine hyaluronic acid levels were found to be 3–4 times higher in patients with PBS/IC who scored >50% on the O'Leary-Sant index than in control individuals without PBS/IC. The sensitivity of urine uronate and hyaluronic acid measurements to indicate PBS/IC severity was 83%.[83] However, such increases in urine uronate and hyaluronic acid levels may be due to elevated production and not to damaged GAGs. It remains to be shown if any defect in the bladder lining present in patients with PBS/IC is the cause or effect of the disease.[84] For instance, transvesical absorption of ^{99m}technetium was not different between patients with PBS/IC and control individuals,[84] and ultrastructural studies of the urothelium of patients with PBS/IC did not indicate damage to GAGs.[85] Nevertheless, it has recently been reported that *in vitro* addition of APF to confluent monolayers of human bladder epithelial cells disrupted tight junctions and permitted increased ^{3}H-inulin flux.[86]

4.3 Bladder Inflammation

No known autoimmune markers have been reported to be associated with PBS/IC. However, variable bladder inflammation[87] and increased expres-

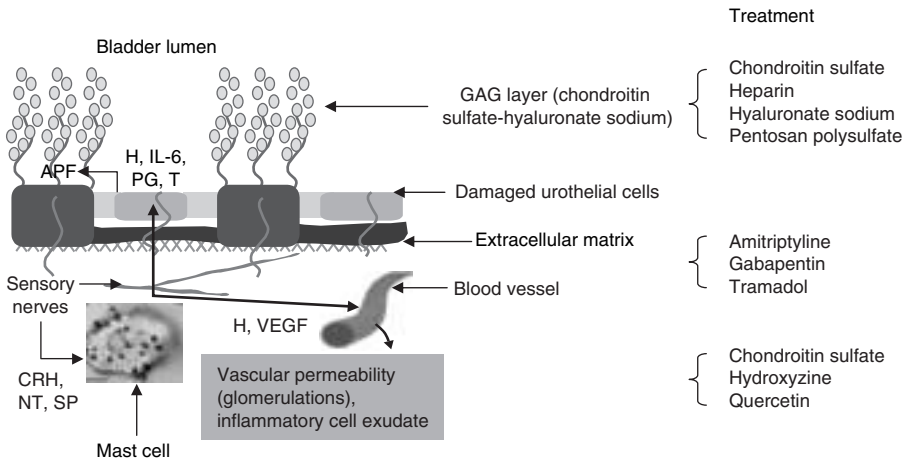

Fig. 1. Diagrammatic representation of the key processes involved in the pathogenesis of painful bladder syndrome/interstitial cystitis and corresponding medications that may target them. The urothelium and associated glycosaminoglycan (GAG) layer may be damaged, leading to production of antiproliferative factor (APF), which affects adjacent urothelial cells, and possibly allows other noxious molecules to reach the suburothelium. There, sensory nerves are activated and stimulate mast cells (one rat mast cell shown with Nomarski optics at 400× magnification) through corticotropin-releasing hormone (CRH), neurotensin (NT) or substance P (SP) to secrete small (arrow head in the inset image points to extruded secretory granules) histamine (H) and vascular endothelial growth factor (VEGF), which increase vascular permeability (e.g. glomerulations) and induce inflammatory cell exudate; prostaglandins (PGs), interleukin (IL)-6, tumour necrosis factor and tryptase (T) induce neurogenic inflammation.

sion of intercellular adhesion molecules[88,89] have been reported. A small number of newly diagnosed patients with PBS/IC have elevated urine levels of IL-6,[57,58,90] which appear to be associated with the age at symptom onset and the severity of bladder inflammation.[87] Levels of APF, heparin-binding epidermal growth factor and insulin-like growth factor binding protein-3 were also increased in 24-hour urine samples from patients with PBS/IC.[91]

An increased number of activated bladder mast cells has repeatedly been reported in patients with PBS/IC and this topic has been reviewed extensively.[92] One study has indicated there are twice as many mast cells in the urothelium of patients with PBS/IC and ten times more in the detrusor, as compared with numbers in controls.[93] Moreover, >70% of bladder mast cells are activated, as determined by electron microscopy, in patients with PBS/IC, compared with <10% in control individuals.[28,92] Multivariant analysis of results obtained from 204 patients who provided bladder biopsy samples in the Interstitial Cystitis Data Base (ICDB) showed that the presence of tryptase-positive mast cells in the lamina propria was the only pathological finding that was statistically correlated with any symptom; this finding showed a statistically significant correlation with the symptom of nocturia ($p = 0.048$).[94] Increased numbers of activated mast cells were also reported in the bladder and colon of a patient with both PBS/IC and IBS.[95] Moreover, unaffected intestine used for bladder diversion in two patients with PBS/IC became infiltrated with mast cells, but this occurrence could be either pathogenetic or epigenetic.[96] Levels of the mast cell growth factor, stem cell factor (SCF), were shown to be increased in bladder biopsies from patients with PBS/IC.[93,97] Moreover, monocyte chemoattractant protein-1, a strong chemoattractant for mast cells,[98] can be produced by human detrusor muscle cells,[99] which also release IL-6 and soluble SCF.[100] Bladder myocyte pathophysiology should be explored further because these cells may be the source of additional cytokines.[101]

Mast cells have been implicated in immunity[102] and inflammatory disorders[103] by their secretion of many vasoactive, inflammatory and nociceptive mediators:[103,104] including histamine, kinins and proteases, such as tryptase (preformed), as well as cytokines, leukotrienes, prostaglandins, nitric oxide and vascular endothelial growth factor (VEGF) [newly synthesised]. VEGF can be selectively released from activated mast cells[105] and is overexpressed in the bladders of 68% of patients with PBS/IC.[106] Tryptase may cause microvascular leakage[107] and stimulate protease-activated receptors, leading to widespread inflammation and neuronal hyperexcitability.[103] Mast cell-derived tumour necrosis factor (TNF) could also mediate urothelial inflammation.[108] Moreover, TNF was recently shown to promote trafficking of mast cells from the proximal detrusor to the lamina propria of the bladder in neurogenic cystitis in mice.[109] Increased expression of mRNA for substance P was also reported in bladder biopsies from patients with PBS/IC.[110]

The cat is the only animal that has so far been found to have a disease that resembles PBS/IC (feline 'IC' [FIC]), except that unlike PBS/IC, FIC occurs almost equally in female and male cats.[111] It presents with many of the clinical features of PBS/IC, including increased bladder mast cell counts[112] and high affinity binding sites for substance P.[113] In addition, cats with FIC had elevated corticotropin-releasing hormone (CRH) levels, which may also characterise a subset of patients with PBS/IC who have other comorbid conditions,[114] all of which appear to be worsened by stress.[103] Other animal models of inflammatory cystitis have also been used.[115] These include autoimmune cystitis,[116] antigen-induced cystitis,[117,118] cyclophosphamide-induced cystitis[119] and CNS-induced neurogenic cystitis[120] or peripheral neurogenic cystitis,[109] all of which are associated with bladder mast cell activation. The most useful and reproducible model is probably the experimental cystitis induced by intravesical administration of bacterial lipopolysaccharide.[121] Functional neuroimmune networks in the bladder may explain sensory neuronal hyperreactivity leading to neuropathic pain in PBS/IC.[122] In patients with PBS/IC, mast cells have been seen

to be located perivascularly, and close to an increased number of substance P-containing nerve endings.[95,123]

4.4 Neuroimmune Interactions

Antidromic stimulation of the lumbosacral dorsal roots has been shown to induce vascular permeability in the rat urinary bladder, an effect that was reduced by capsaicin administration, which implicates sensory neuropeptides in this process.[124] A number of recent reports have linked stressors to the worsening of symptoms of PBS/IC.[21,125]

Restraint stress in rodents has been shown to induce bladder mast cell activation,[126] increase urine histamine and IL-6 levels [127] and also to result in loosening of the urothelial tight junctions.[128,129] CRH, released from the sensory ganglia in response to stress[130,131] has proinflammatory actions,[103,132] apparently through the activation of mast cells.[133] In fact, intravesical administration of CRH leads to increased VEGF release from mouse bladder explants.[134] CRH can also lower the micturition threshold.[135]

The purinergic pathway also appears to be upregulated in the bladders of patients with PBS/IC;[136] the pituitary adenylate cyclase-activating polypeptide is also upregulated in mouse cystitis and this has been shown to increase the amplitude of bladder muscle contractions.[137]

5. Therapeutic Interventions

There is no curative therapy for PBS/IC.[4,138-140] Clinical trials to date, including those by the NIDDK-sponsored PBS/IC Clinical Research Network, have used adult patients with varying durations and severities of symptoms, making it difficult to draw definitive conclusions. The clinical trials reviewed below were selected either because of their double-blind or multicentre nature or because they were testing a new approach not reported previously and the results were statistically significant. The placebo response and level of significance are reported, when available, even though many of these studies are very small and the results should be considered suggestive rather than conclusive.

The most common interventions for PBS/IC compiled by the ICDB in 2000 were bladder hydrodistension, intravesical heparin and oral amitriptyline[139] (table I). Additional benefit may be derived from the concurrent use of pentosan polysulfate with amitriptyline or hydroxyzine (see sections 5.8.1 and 5.6.1, respectively). Only intravesical dimethyl sulfoxide (DMSO) and oral pentosan polysulfate have been approved, only in the US, for use in PBS/IC. The oral formulation com-

Table I. Oral agents commonly used for the treatment of painful bladder syndrome/interstitial cystitis

Agent	Dose regimen	Class	Adverse effects	References
Cyproheptadine[a]	24mg at bedtime	Histamine and serotonin receptor antagonist	Sedation, weight gain	138
Hydroxyzine[bc]	50–75mg at bedtime	Histamine-H1 receptor antagonist, anxiolytic	Sedation, fatigue (overcome on daily use)	69,141-143
Montelukast	20mg at bedtime	Leukotriene receptor antagonist	NA	144
Pentosan polysulfate	100mg tid	Synthetic mucosal GAG component	Hair loss, gastrointestinal upset, potential bleeding	141,145,146
Chondroitin sulfate	300mg tid	Urothelial GAG component	NA	147,148
Sodium hyaluronate[d]	300mg tid	Proteoglycan, urothelial GAG component	NA	88,149,150
Quercetin[d]	300mg tid	Anti-inflammatory mast-cell inhibitor	NA	147,148

a Preferred for patients with irritable bowel syndrome or children/adolescents.

b Preferably administered at bedtime with a patient self-titration protocol.

c Increase gradually starting at 10–25mg over 1 month to overcome sedation.

d Formulated together, along with glucosamine, chondroitin sulfate, sodium hyaluronate and rutin (rutoside).

GAG = glycosaminoglycans; **NA** = not applicable; **tid** = three times daily.

bining chondroitin sulfate, glucosamine, sodium hyaluronate, quercetin and rutin (rutoside) is available as a dietary supplement.[136]

5.1 Hydrodistension

Hydrodistension under epidural anaesthesia performed for 30 minutes on 2 consecutive days was shown to reduce symptoms in about 70% of 52 patients with PBS/IC meeting the NIDDK criteria who were studied for up to 3 months.[151] This procedure could be repeated weekly for 4–6 times, but the lack of understanding of how or why it might be helpful makes it controversial, since only 5 of the 52 patients were classified as 'good' responders and this improvement was short lived.[7]

5.2 Intravesical Dimethyl Sulfoxide

DMSO (50% intravesical solution) is approved by the US FDA and in Europe for use in patients with PBS/IC. A 'controlled', crossover trial of 30 women and 3 men with PBS/IC treated with DMSO (50%) administered every 2 weeks for two sessions of four treatments each reported that 53% of treated patients assessed subjectively showed marked improvement in symptoms, compared with 18% of placebo recipients;[152] however, it is hard to imagine how this study was controlled, as DMSO treatment is typically associated with exhalation that has a very strong garlic-like odour. A series of six instillations apparently resulted in symptom reduction in 28 patients with PBS/IC and in 13 patients with classic PBS/IC, and follow-up telephone interviews reported a "residual treatment effect" that lasted 16–72 months.[153] In another open-label study, 25 patients were treated with DMSO, methylprednisolone and heparin sulfate every week for 6 weeks; 23 of 25 patients went into 'remission' for 8 months.[154]

The effect of different concentrations of DMSO on the compliance and contractility of bladder muscle strips was studied; it was shown that solutions of concentrations of ≥30% irreversibly abolished contractions and altered compliance, calling into question the current practice of using a 50% DMSO solution.[155]

5.3 Bladder Mucosal 'Protectors'

5.3.1 Pentosan Polysulfate

Pentosan polysulfate is the only orally administered drug approved (under the Orphan Disease Act) in the US for treatment of PBS/IC (table I); it is a branched polysaccharide that was originally synthesised as a heparin substitute, that presumably 'replenishes' the GAG layer[145] (figure 1). One study of pentosan polysulfate (300 mg/day) with a duration of 3 years showed that it had twice the effect of placebo for reducing pain, but the reduction of pain in the placebo group was unusually low (18%).[3,4] A randomised, double-blind, multicentre, dose-ranging (300, 600 or 900 mg/day) study (32 months) of 380 PBS/IC patients with >6 months of symptoms and a positive cystoscopic examination reported that 45–50% of all patients were classified as responders (≥50% improvement on the Patient's Overall Rating of Improvement of Symptoms [PORIS]), irrespective of the dose;[146] however, this study was not designed to assess efficacy and was not placebo-controlled. In a recent NIH-sponsored randomised, placebo-controlled, double-blind, multicentre 3-month clinical trial in 136 patients, pentosan polysulfate (300 mg/day) had no better effect than placebo.[141] It is interesting that it has recently been shown that only 6% of pentosan polysulfate is excreted in the urine, indicating that it is very poorly absorbed.[156]

5.3.2 Heparin

Intravesical administration of heparin 40 000U with either 1% lidocaine 80mg or 2% lidocaine 160mg and 8.4% sodium bicarbonate was used in patients with newly diagnosed PBS/IC. Following one 20-minute instillation, 35 of 47 patients in the 1% lidocaine arm and 33 of 35 patients in the 2% lidocaine arm reported 50% or better improvement in PORIS.[157] Heparin may act as a substitute for the GAG layer or may be useful because it has been reported to inhibit mast cells[158,159] and acute inflammation.[160]

One study[161] also examined the concurrent administration of oral pentosan polysulfate (300 mg/day) and subcutaneous heparin (3 × 5000 IU/day for

2 days, followed by 2 × 5000 IU/day for 12 days and 5000 IU/day 'maintenance' for 3 months in 41 PBS/IC patients classified as 'responders' to pentosan polysulfate compared with 17 patients randomly receiving pentosan polysulfate). The primary endpoint was a change in overall wellbeing, measured using the Global Response Assessment; at 3 months, 24% of patients receiving combination therapy were considered responders compared with none in the group receiving pentosan polysulfate alone.

5.3.3 Sodium Hyaluronate

Intravesical sodium hyaluronate, which is approved in Canada but not the US, (0.04% weekly for 4 weeks, then monthly for a further 2 months) was used in a prospective uncontrolled study and was reported to reduce PBS/IC symptoms by 50–70% after 20 weeks of treatment.[88,149] In a recent uncontrolled study of 20 patients with PBS/IC who received similar treatment, 65% 'responded' to therapy with pain reduction and to a lesser extent a reduction in urinary frequency.[150] This benefit may be explained by results obtained from experiments in rodents where intravesical sodium hyaluronate promoted urothelial healing in acid-induced cystitis.[162,163] However, one large multicentre trial that was supported by the pharmaceutical company marketing intravesical sodium hyaluronate and that administered an 0.4% sodium hyaluronate solution (10 times higher than what is currently available in Canada) showed no benefit when compared with placebo; these studies have not been published (results available from www.ichelp.org). A dietary supplement is available in the US that contains both sodium hyaluronate and chondroitin sulfate along with the natural flavonoid quercetin (see section 5.6.4).

5.3.4 Chondroitin Sulfate

An open-label study of chondroitin sulfate used 40mL of 0.2% chondroitin sulfate solution instilled intravesically once per week for 4 weeks and then once per month for 12 months; 13 of 18 patients were followed up for 1 year and 46% showed a 'good' responses on quality of life, pain and voiding indices.[164]

5.4 Anti-Inflammatory Agents

5.4.1 NSAIDs

There have not been any clinical studies of the effects of monotherapy with NSAIDs in patients with PBS/IC. One study investigated the efficacy of combination treatment with oral doxepin (75mg once daily) and piroxicam (40mg once daily) in 37 patients with PBS/IC. After 8 weeks of treatment, 81% of patients were almost symptom free, but symptoms returned after treatment cessation in most patients.[165]

5.4.2 Corticosteroids

Use of prednisone 25mg daily for 2 months in 14 patients with classic PBS/IC resulted in a 22% ($p < 0.02$) reduction in the O'Leary-Sant index and 69% ($p < 0.001$) improvement in pain control.[166]

5.4.3 Ciclosporin

Ciclosporin (cyclosporin), a well known immunosuppressive agent, inhibits the calcium-dependent phosphatase calcineurin, thereby inhibiting the dephosphorylation of a transcription factor required for the IL-2-mediated activation of T cells.[167] Ciclosporin also inhibits allergic conditions and mast cell activation.[167] In one open-label study in 11 patients with intractable PBS/IC, ciclosporin treatment for up to 6 months (initial single dose of 2.5–5.0 mg/kg orally, followed by an oral maintenance dose of 1.5–3.0 mg/kg daily) reduced micturition, urinary frequency and bladder pain significantly in most patients;[168] however, symptoms recurred in most patients after treatment cessation. Another study of ciclosporin treatment for 1 year reported a 50% reduction in the number of voidings over 24 hours and no pain in 20 of 23 patients with PBS/IC who had not responded to multiple other treatments.[169] A more recent study[170] randomised 64 patients with PBS/IC that met the NIDDK criteria to either ciclosporin 1.5 mg/kg twice daily or pentosan polysulfate 100mg three times daily for 6 months; the clinical response rate, as determined using the Global Response Assessment, was 75% for ciclosporin, compared with 19% for pentosan polysulfate ($p < 0.001$).

5.4.4 Methotrexate

Methotrexate is a well known folic acid synthesis inhibitor commonly used for the treatment of certain malignancies, rheumatoid arthritis (RA) and psoriasis. Administration of oral methotrexate 10 mg/week in nine women with refractory PBS/IC was associated with a significant subjective reduction ($p = 0.047$) in pain in approximately 45% of patients at 6 months, but no reduction in urinary frequency or the voided volume.[171]

5.4.5 Infliximab and Etanercept

Inhibition of TNF action has proven useful for the treatment of certain inflammatory conditions, such as RA.[172] Etanercept is a soluble human TNF receptor that has been approved for subcutaneous administration in the treatment of RA, while infliximab is a chimeric human/mouse TNF-blocking monoclonal antibody that has been approved for intravenous administration in the treatment of RA and IBD. Neither etanercept nor infliximab has so far been used in PBS/IC, but they may reasonably be tried in patients with severe bladder inflammation. Adverse effects include headache and increased susceptibility to pulmonary infections.[172]

5.4.6 Imatinib

Imatinib was the first inhibitor of protein kinases, including c-kit, and was rationally designed for the treatment of chronic myeloid leukaemia.[173] Imatinib has also been used for the treatment of systemic mastocytosis[174] and IBD.[175] C-kit is a receptor important for proliferation of a number of different cells, including mast cells.[97] C-kit-positive cells are present in various tissues including the normal bladder, and mast cells in the bladders of patients with PBS/IC have been reported to overexpress c-kit.[97] The c-kit ligand SCF is also chemotactic for mast cells,[176] and mast cells can also secrete SCF, indicating that this factor could have autocrine actions.[177] C-kit mutations have been identified in patients with systemic mastocytosis.[178] It would, therefore, be reasonable to, at least, investigate the effect of imatinib in those patients with PBS/IC who have increased numbers of bladder mast cells.

5.4.7 Nanocrystalline Silver

Silver is known to have antimicrobial and anti-inflammatory actions, and has been shown to reduce TNF levels in an experimental model of allergic dermatitis.[179] In a recent study of experimental bladder inflammation in rodents, nanocrystalline silver inhibited histamine and TNF release into the urine and in bladder explants.[180]

5.5 Immunomodulators

The potential of some immunomodulators for the treatment of PBS/IC has been reviewed recently.[140]

5.5.1 Interleukin-10

IL-10 is a regulatory cytokine produced mostly by type 2 helper T cells (T_h2), that was originally termed 'cytokine synthesis inhibiting factor' because of its ability to inhibit the production of T_h1 cytokines from antigen- or mitogen-activated mononuclear cells.[181] Human recombinant IL-10 is currently being tested in the treatment of RA, psoriasis and IBD;[181,182] the use of gelatine microspheres containing IL-10 has been more encouraging.[182] However, IL-10 inhibits long-term IL-6 production as well as TNF release, but not preformed mediator release, from rat peritoneal mast cells,[183] and does not inhibit tryptase and IL-6 release from human leukaemic mast cells.[184] Surprisingly, IL-10 exerts some immunostimulatory effects on B cells and cytotoxic T cells, possibly when administered at higher concentrations and with a longer duration of treatment.[184] Consequently, the use of IL-10 alone may not be an appropriate therapy in patients with a history of allergies or bladder mastocytosis.

5.5.2 Bacillus Calmette-Guérin

Intravesical bacillus Calmette-Guérin (BCG) was initially reported to have some benefit in patients with PBS/IC;[185] however, a subsequent double-blind, placebo-controlled trial in 248 patients who met the NIDDK research criteria for PBS/IC and were randomised to 6 weekly instillations of BCG showed that Global Response Assessment rate at 34 weeks was 21% for BCG compared with 12% of patients for placebo ($p = 0.062$).[186]

5.5.3 Suplatast Tosilate

Suplatast tosilate is an immunomodulator capable of inhibiting the production of T_h2 cytokines, especially IL-4 and IL-13.[187] In an open-label clinical study of 1 year's duration performed in 14 women, oral suplatast tosilate (300 mg/day) significantly increased bladder capacity and reduced the symptoms of PBS/IC.[188] There were no significant adverse effects. A recent study of experimental bladder inflammation reported that suplatast tosilate could decrease urine histamine levels and TNF secretion in bladder explants without having any direct effect on mast cells.[180] A large international, multicentre trial is currently underway to assess the therapeutic potential of this compound.

5.6 Allergy-Related Products

Typical histamine-1 receptor antagonists do no appear to have any benefit in PBS/IC.

5.6.1 Hydroxyzine

Hydroxyzine is used by many urologists as a first-line treatment, but needs to be titrated slowly to 50–75mg administered at bedtime and it requires 3–4 months to show an effect.[69,142] Any beneficial effect of hydroxyzine may be due to its anxiolytic, sedative, anticholinergic and mast cell inhibitory properties, along with its ability to reduce neurogenic bladder inflammation[189] (figure 1). Hydroxyzine may best benefit patients with allergies and bladder mastocytosis. It may be more effective when used in combination with other agents. Hydroxyzine (titrated, as tolerated, to 50 mg/day) was compared with placebo and pentosan polysulfate (300 mg/day); neither drug was effective when used alone, but their combination was associated with a 40% response rate compared with 31% with placebo (still not a statistically significant difference).[141] It should be noted, however, that this study was not sufficiently powered and few patients reached the desired hydroxyzine dosage of 75 mg/day.

5.6.2 Omalizumab

A recent case report described that following treatment with subcutaneous omalizumab, a recombinant DNA-derived humanised IgG1 monoclonal anti-IgE antibody, in one female patient with asthma and allergic rhinitis, concurrent bladder symptoms of increased urinary frequency, urgency and pelvic pain also subdided.[190]

5.6.3 Montelukast

Montelukast is a leukotriene D (LTD_4)-receptor antagonist that is administered once daily for the maintenance treatment of mild to moderate asthma. In one open-label study using montelukast 20 mg/day for 3 months in ten women with PBS/IC (diagnosed as per NIDDK criteria and with at least 28 mast cells/mm^2 detrusor muscle tissue), patients were observed to have significantly reduced urinary frequency, nocturia and pain.[138,144]

5.6.4 Quercetin

Quercetin is a flavonol member of the flavonoid family, commonly found in plants and seeds.[191] Quercetin has antiallergic and anti-inflammatory actions, which include blocking the secretion of histamine, tryptase, IL-6, IL-8 and TNFα from normal human mast cells.[192] Quercetin inhibits the proliferation of and secretion from all mast cells,[191,193] especially mucosal mast cells that are not affected by sodium cromoglicate (cromolyn sodium).[194] A quercetin-containing formulation (equivalent to 500mg of quercetin twice daily for 4 weeks) administered to 20 patients in an open-label clinical trial was reported (the journal has since ceased publication) to improve PBS/IC;[195] however, this preparation is a proprietary formulation with multiple ingredients, the amounts purity and sources of which have not been disclosed. Proper disclosure of the contents and their source and purity should be an absolute requirement for all dietary supplements.[196] Quercetin has synergistic effects when combined with the mucosal GAG components sodium hyaluronate, which also reduces bladder inflammation,[127] and chondroitin sulfate, which also inhibits mast cells.[148,196,197] An open-label study in 39 female patients with PBS/IC who received six capsules, each containing a formulation composed of quercetin (150mg), its natural glycoside, rutin (150mg), glucosamine sulfate, chondroitin sulfate (130mg) and sodium hyaluronate (40mg), per day for 6 months showed statistically significant symp-

tom reduction as assessed using the O'Leary-Sant index.[147] This preparation achieved higher oral absorption compared with quercetin or chondroitin sulfate administered separately because quercetin is very lipophilic and chondroitin sulfate is highly anionic with of large molecular weight, limiting their oral absorption in powder form to <10%.[148] A larger open-label study of 263 female patients for 1 year showed that, using the Global Response Assessment, the symptoms were reduced by 51.2% ($p = 0.0001$).[148]

5.7 Hormone Modulators

Probably the least well studied aspect of PBS/IC is the involvement of sex hormones. Many women with PBS/IC experience symptom exacerbation during sexual intercourse and in association with their menstrual cycle.[28,198,199] In a recent study performed in seven patients with PBS/IC and eight healthy control individuals, perimenstrual worsening of micturition frequency and pain was observed in the cystometrograms of patients with PBS/IC.[198]

5.7.1 Leuprorelin and Tamoxifen

In 15 female patients with irritable bladder symptoms and pelvic pain without endometriosis, symptoms improved in 8 of 9 treated with leuprorelin (leuprolide acetate) and in 5 of 6 treated with oral contraceptives.[199] The estrogen receptor antagonist tamoxifen was shown to significantly increase the mean maximum bladder volume by over 70% in a rat chemical cystitis model.[200]

5.8 Pain Modulators

Patients with PBS/IC could benefit from referral to pain specialists and it is recommended that physicians treating such patients follow well established pain management guidelines as provided by the WHO, the American Pain Society and the International Society for the Study of Pain.[201]

5.8.1 Amitriptyline

The tricyclic antidepressant amitriptyline is commonly used for the treatment of PBS/IC at dosages 12.5–125 mg/day, as tolerated[4,139] (table II). In an open-label study, amitriptyline (initially 25mg administered at bedtime, increasing to 75mg) was administered over a 3-week period to 25 patients in whom treatment with hydrodistension and intravesical DMSO had failed.[202] Twenty patients tolerated the protocol for 3 weeks and of these, five patients found no benefit; the rest reported approximately 50% reductions in pain and daytime urinary frequency, but no change in nocturia. A recent ran-

Table II. Pain modulators for the treatment of painful bladder syndrome/interstitial cystitis

Agent	Dose regimen	Class	Adverse effects	References
Amitriptyline[a]	12.5–125 mg/day at bedtime	Antidepressant	Dry mouth, sedation, weight gain	202-204
Doxepin[b]	50–75mg od	Antidepressant	Sedation, weight gain	165
Belladonna + opium suppositories	1–3 suppositories od	Anticholinergic + opioid	Retention	205
Fentanyl patch	50–100 μg/h	Opioid analgesic	Dizziness, nausea and vomiting	205
Gabapentin[c]	200–400mg PO qid	Antepileptic	Sedation, nausea and vomiting	206
Pregabalin	50–200mg PO tid	Antiepileptic	Dizziness, sedation	207
Morphine[d]	30–90mg IM od	Opioid analgesic	Constipation, nausea and vomiting, addiction	143,206
Tramadol[e]	75–100mg PO od	Opioid[f]	Nausea	

a Preferably administered at bedtime with a patient self-titration protocol.

b Could be given with piroxicam (40mg od).

c Treatment together with morphine was shown to have superior benefit to either agent administered alone.[206]

d Together with hydroxyzine was shown to result in increased analgesia.[143]

e Also available with paracetamol (acetaminophen) [tramadol 37.5mg/paracetamol 325mg bid].

f Not addictive.[138]

IM = intramuscular; **od** = once daily; **PO** = oral; **qid** = four times daily; **tid** = three times daily.

domised, double-blind, placebo-controlled clinical trial of amitriptyline in 44 women and 6 men with PBS/IC that used a self-titration protocol (up to 100 mg/day at bedtime for 4 months) reported significant improvements in all symptoms.[203] Long-term follow-up of 60 patients treated with a mean amitriptyline dosage of 55 mg/day for 19 ± 12.5 months was associated with a response rate of 64% using the Global Response Assessment. However, there was a dropout rate of 31% (29 patients) after 6 weeks of treatment at a mean dosage of 70 mg/day, primarily because of a lack of response to treatment.[204] Amitriptyline is associated with dry mouth and significant weight gain; it should be administered following a patient self-titration protocol with intake preferably limited to ingestion at bedtime.[204]

Drugs similar to amitriptyline, such as doxepin, may also be used. Cyproheptadine may be used in patients with both PBS/IC and IBS (table II). Newer specific serotonin reuptake inhibitors do not appear to be useful, but no formal study has been conducted thus far.

5.8.2 Gabapentin and Pregabalin

The antiepileptic drug gabapentin, at dosages up to 1600 mg/day, could be used to treat PBS/IC; the combination of this agent with morphine was recently shown to achieve better analgesia for neuropathic pain than either agent administered alone.[206] Pregabalin, a newer anticonvulsant used for neuropathic pain, may also be helpful, but requires multiple daily dosages (50–200mg three times daily) and is associated with a high frequency of dizziness.[207]

5.8.3 Tramadol

Tramadol, an opioid with low addiction potential,[138] which is also available in combination with paracetamol (acetaminophen) [37.5/325mg twice daily], may also be used for the treatment of PBS/IC (table II). However, there have not been any formal trials.

5.8.4 Morphine, Fentanyl and Belladonna in Combination with Opium

Belladonna plus opium suppositories or morphine and related drugs can be used for the treatment of patients with PBS/IC, depending on the severity of the pain, but there have not been any definitive studies of these modalities.[205] Severe pain may require the use of transdermal fentanyl patches. Belladonna plus opium suppositories may cause urinary retention (table II). Morphine together with hydroxyzine also produce better analgesia with fewer adverse effects than opioids used alone[143] (table II).

5.8.5 Dextroamfetamine

Two female patients with PBS/IC refractory to other medications were treated with dextroamfetamine 20 mg/day without any other treatment; all pain and urinary urgency was evidently gone within 1 week.[208]

5.8.6 Resiniferatoxin

Resiniferatoxin is a capsaicin analogue more potent than capsacicin that activates afferent sensory c-fibres and subsequently desensitises them.[209] A randomised, placebo-controlled study of intravesical administration of resiniferatoxin (single 10 nmol/L dose) or saline in 18 patients with PBS/IC-like symptoms reported significantly decreased urinary frequency, nocturia and pain 30 days later in resiniferatoxin compared with placebo recipients.[209] However, a subsequent company-sponsored multicentre, double-blind study in 163 PBS/IC patients randomised to receive ≤0.01 mmol/L failed to show any benefit using Global Response Assessment.[210]

5.8.7 Botulinum Toxin

Botulinum toxin-A injections (100–200U) to the trigone, external sphincter or bladder base (35 men and 75 women) resulted in decrease incontinence in 67% measured at 7 and 30 days.[211] However, another study in eight women and two men with refractory PBS/IC, using suburothelial injections of botulinum toxin-A (100U), resulted in limited improvements in urinary frequency and pain in only two patients.[212] In a pilot study of 12 women and 2 men with PBS/IC, patients received 200U of botulinum toxin-A injected into the trigone and bladder floor; 85% of patients reported subjective improvement and bladder cystometric capacity was significantly increased at 1 and 3 months follow-up.[213]

5.9 Other Therapies Evaluated as Treatments for Painful Bladder Syndrome/ Interstitial Cystitis

5.9.1 Arginine

A randomised, double-blind trial of oral arginine 1500 mg/day performed in patients with PBS/IC (27 of 53 patients received arginine, while 26 of 53 received placebo) showed an improved global response in 48% of patients receiving the intervention, as compared with 24% of placebo recipients ($p = 0.05$); however, an intent-to-treat analysis showed no statistically significant difference in response between the two groups.[214]

5.9.2 Cimetidine

The histamine-1 receptor antagonist cimetidine was reported to decrease the median symptom score in 34 patients with PBS/IC, but no histological changes were apparent in the bladder mucosa of these patients.[215]

6. Conclusions

PBS/IC appears to affect many more, and younger, patients than previously suspected, with a possible prevalence of 0.1–1% of all adult women.[40] It is associated with severe disability, poor quality of life and substantial costs.[27] PBS/IC may be the cause of pain in many patients with CPP and is also associated with other comorbid disorders that share pathophysiologies involving bladder mast cell and sensory nerve activation. Diagnosis is still challenging and effective treatment options are few, causing frustration to both physicians and patients. Clinical trials should look 'outside the square' and test therapeutic modalities that may not necessarily be favoured by current trends that have been plagued by biases for over 10 years. Moreover, trials do not necessarily have to be multicentre, as meta-analysis of multiple small trials has proven as useful as analysis of individual larger ones.[216]

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Dr TC Theoharides has been awarded Patents No. US 5,994,357; US 6,635,625; US 6,641,806; US 6,689,748; US No. 6,984,667 and European Patent Office No. 1365777 and is awaiting a decision on US patent 10/811,839 for Painful Bladder Syndrome/Interstitial Cystitis and related inflammatory disorders. Dr TC Theoharides owns stock in Algonot, LLC (Sarasota, FL).

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