Interstitial Cystitis: An Unsolved Enigma

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Painful bladder syndrome/interstitial cystitis (PBS/IC) is a chronic disease of unknown etiology characterized by vague bladder pain and nonspecific urinary symptoms, such as urgency and frequency. Although it was initially considered to be a rare condition, its prevalence has significantly increased, possibly because of different definitions used and greater physician awareness. Because of the multiple diagnostic criteria used, there is significant variation in its prevalence. In addition, there is often a delay in the diagnosis of PBS/IC. It affects predominantly women of middle age, and it significantly decreases quality of life. Diagnosis of PBS/IC is mainly a diagnosis of exclusion; there are no characteristic symptoms or pathognomonic findings. Therefore, it is important to rule out diseases that have a similar clinical picture (i.e., urinary infections, bladder carcinoma) but definite therapies and worse prognosis if left untreated. PBS/IC management suffers from lack of evidence; many therapies are empiric or based on small studies and case series. Treatment includes supportive therapies (psychosocial, behavioral, physical), oral treatments, and intravesical treatments, whereas other more invasive treatments such as electric neuromodulation and reconstructive surgery are reserved for refractory cases. Physicians should always keep in mind the diagnosis of PBS/IC in patients presenting with chronic urinary symptoms after excluding other more common diseases.


Pathophysiology

Although PBS/IC underlying pathophysiology is incompletely understood, it involves primarily urothelial permeability changes, along with mast cell activation and neurogenic inflammation (14) (Figure 1). In PBS/IC, damage of the protective bladder lining leads to impaired urothelial cell barrier function. Consequently, urinary solutes penetrate the epithe-
Table 1. National Institute for Diabetes and Diseases of the Kidney criteria

For PBS/IC diagnosis to be made, patients should have:
1. Bladder pain or urinary urgency
2. Glomerulations or Hunner’s ulcers on cystoscopy/hydrodistention
3. None of the following:
   - Awake cystometric capacity >350 ml using a fill rate of 30-100 ml/min,
   - Absence of intense urge to void at 100 ml gas or 150 ml liquid,
   - Involuntary detrusor contractions on cystometry,
   - Urinary frequency <8 voids/d,
   - Absence of nocturia,
   - Duration of symptoms <9 mo,
   - Age <18 yr,
   - Cystitis (bacterial, chemical, post-irradiation), prostatitis, vulvitis (herpes) or vaginitis,
   - Cancer (bladder, uterine, cervical, vaginal or urethral),
   - Bladder or lower ureteral calculi
   - Urethral diverticulum

Adapted from Reference 107.

PBS/IC pathophysiology: patients not only have increased number of mast cells but also a centrally (23). However, it is undetermined whether the neurogenic upregulation occurring both peripherally and centrally (23). It is now known that it can appear later in the progress of the disease (2).

PBS/IC may present with flares lasting for several days and remissions. Beverages containing biogenic amines, caffeine, smoking, stress, allergies, and sexual activity are considered precipitating factors (20,29). In addition, women report exacerbation of symptoms during the premenstrual week (29). Pain is associated with sexual activity, leading to severe sexual dysfunction and poor quality of life (30); dyspareunia is a common finding in PBS/IC patients. In addition, women with PBS/IC have significantly more hysterectomies and other pelvic surgeries in comparison with age-matched controls (31); most of them are done before PBS/IC diagnosis. However, it is unclear whether these operations were performed because of pelvic pain related to undiagnosed PBS/IC or the surgery itself contributed to chronic pelvic pain.

Several systemic and autoimmune conditions are more frequent in PBS/IC patients than the general population (32): irritable bowel syndrome and systemic lupus erythematosus are many folds more frequent in PBS/IC patients. In addition, the increased prevalence of Sjögren disease, rheumatoid arthritis, and the presence of autoantibodies in PBS/IC patients provide a possible background for an autoimmune underlying pathophysiologic mechanism (33). Therefore, PBS/IC is often considered a manifestation of a systemic disorder rather than a specific organ disorder (34). The correlation of PBS/IC with other unexplained physical symptoms and certain psychiatric conditions (35) along with the absence of pathognomonic findings may further support this theory.

Diagnosis

Because there are no definitive diagnostic tests, PBS/IC remains a diagnosis of exclusion; the diagnostic steps aim to rule out other diseases and overlapping syndromes.
History and Physical Examination

A thorough history and physical examination is particularly significant. Medical history should include history of symptoms (pain, nocturia, frequency, urgency), urinary infections, pelvic surgeries, central nervous system, or autoimmune diseases. Symptoms of PBS/IC typically worsen during the premenstrual week in contrast with endometriosis (36). In addition, because PBS/IC occurs in flares, it is often misdiagnosed as recurrent urinary tract infection (UTI) or prostatitis, with the resolution incorrectly attributed to antibiotic therapy and not to the disease’s natural pattern (37). There are no specific physical findings in PBS/IC patients. However, a careful pelvic examination is essential to rule out vaginitis, vulvar lesions, urethral diverticula, and pelvic floor dysfunction, whereas it may show anterior vaginal wall and bladder base tenderness in women with PBS/IC.

The O’Leary Sant symptom and problem index along with the pelvic pain and urgency/frequency symptom scale are the most commonly used surveys, which were developed for monitoring progress after treatment, but both have been used as screening tools as well (38–40). A voiding diary can be extremely helpful for documenting voiding volume and frequency, not only for screening reasons but also for monitoring response to treatment.

Laboratory Tests

There are no laboratory (urine or blood) tests that will identify PBS/IC. It is crucial, however, to rule out overlapping diseases. Urinalysis and urine culture are essential to exclude UTI. In presence of hematuria, and particularly in older patients with a history of smoking or with other risk factors for bladder malignancy, urine cytology is significant. Cystoscopy may be essential in severe cases of hematuria. In the quest for noninvasive techniques for PBS/IC diagnosis, many urinary biomarkers were tested: urinary histamine, tryptase, and others were found to be elevated in a subgroup of PBS/IC patients but they were not prospectively studied as a diagnostic tool. In addition, urine IL-6 levels were increased only in newly diagnosed patients (20), and whether it could be used as a diagnostic marker or as a predictor to response to treatment is still controversial (41). Recently, anti-proliferative factor (APF) was suggested as a candidate biomarker for PBS/IC diagnosis (42) because it was shown to have increased activity in the bladders of PBS/IC patients in comparison with asymptomatic controls. Using proteomic techniques and quantitative biomarker analysis, Canter et al. (43) reported that PBS/IC patients had decreased concentration of uromodulin, kininogen, and increased levels of inter-α-trypsin inhibitory heavy chain H4 in their urine; these substances could be used as biomarkers, but further studies are needed. Nitric oxide (NO), which is considered a nonspecific marker of inflammation (44), was tested in a recent study (45) as a possible diagnostic tool: NO levels in the bladder were shown to correlate with the degree of inflammation and with the response to treatment, but the limitation of this technique was that measurement of NO levels required catheterization.

Other Diagnostic Procedures

**Potassium Sensitivity Test.** In the potassium sensitivity test (PST), a potassium chloride solution and sterile water are instilled sequentially directly in the bladder; increased pain with the potassium solution is considered a positive test and indicates epithelial dysfunction. However, the PST has its limitations: patients with chronic UTIs, bladder outlet obstruction, or OAB may not respond to intravesical potassium (29). In addition, the PST has 75% sensitivity and specificity and is not recommended for diagnostic purposes because of its low prognostic value (20).

**Urodynamic Studies.** Urodynamic studies are optional, and their use remains rather controversial. Nevertheless, they can be helpful in excluding OAB and in evaluating bladder dysfunction, especially in male patients.

**Cystoscopy.** Whereas cystoscopy was initially considered mandatory for diagnosis (2,3,46), it is now performed at the physician’s discretion. In the United States, it is performed mainly when it is essential to rule out other pathology and particularly underlying malignancy; however, in Europe, it is...
considered to be important for diagnosis and for disease classification. In addition, it can be helpful in guiding treatment (e.g., patients with reduced bladder capacity are unlikely to benefit from oral pharmaceutical treatment). Hydrodistention of the bladder, which consists of filling the bladder (under general anesthesia) with normal saline or sterile water beyond its normal capacity, can also be performed during cystoscopy. With this technique, Hunner’s ulcers (patches) and glomerulations (pin-point petechial hemorrhage) can be more easily visualized. Glomerulations, once considered diagnostic of PBS/IC, can also be found in other bladder pathologies and in asymptomatic women (47). Hunner’s ulcers or Hunner’s lesions were originally described by Hunner (48) in 1915 and initially considered as pathognomonic for PBS/IC. They represent positive signs for PBS/IC and designate a specific type of the disease, not only cystoscopically, but also with reference to histology, response to therapy, and prognosis (49). This type was later defined as classic PBS/IC.

**Biopsy.** There are no specific findings in biopsies of patients with PBS/IC (47); therefore, biopsy in not essential for diagnosis. However, it is indicated in a patient with suspected PBS/IC, when specific bladder pathologies such as carcinoma, dysplasia, or tuberculosis must be excluded. In addition, biopsy findings can be useful in identifying subgroup of patients who are most likely to benefit from specific treatments: patients with mastocytosis or excessive eosinophils in bladder biopsy may be more effectively treated with antihistamines (50).

**Treatment**

Because of the absence of definitive diagnostic tests and standard clinical criteria, PBS/IC is a diagnosis of exclusion; as a result, the design of randomized controlled trials (RCTs) for its management is extremely difficult. Therefore, data regarding the efficacy of therapies are limited and often based on uncontrolled studies or case series. Although >180 different treatments have been tried in PBS/IC, data are still inconclusive; only pentosan polysulfate sodium (PPS) was found to be modestly beneficial (51). Three recent reviews focused on PBS/IC treatment (20,51,52), whereas a recent well-designed RCT gave promising results for therapy with intravesical alkanized lidocaine (53). Nevertheless, treatment of PBS/IC can be divided into supportive (nonspecific) management and to specific therapeutic modalities that target the suggested underlying pathophysiology.

**Supportive Therapies**

Supportive therapies include general measures that can alleviate symptoms or prevent exacerbations. Psychosocial support is significant because it is an essential part of any chronic pain treatment. Because depression is not uncommon in PBS/IC patients, referral to specialists is necessary if such a diagnosis is suspected. Other comorbid diseases that are common in PBS/IC patients (i.e., inflammatory bowel disease) should be diagnosed and treated aggressively. All factors associated with symptom exacerbation such as allergies, certain foods, and body position should be avoided.

Behavioral therapy can be effective in improving PBS/IC symptoms (54): avoidance of possible triggering factors or timed voiding protocol leading to increased bladder capacity are typical examples. Physical therapy by resolution of pain and trigger points (55) can improve quality of life.

**Specific Therapies**

It remains an important goal to properly select patients with PBS/IC for treatments based on individual patient characteristics. Currently, the most common stratification is based on presence/absence of visible ulcers on cystoscopy. This is a useful distinction because visible ulcers can be fulgurated (56). There are many indicators of bladder inflammation in PBS/IC (ulcers, NO, urine markers, bladder biopsy findings); however, it is unknown which of these are most predictive of treatment response (57). Specific therapies include intravesical, oral treatments, and other treatments, with the latter being used predominantly in refractory cases. Table 2 includes the most common PBS/IC treatments for which there is at least one RCT. Other treatments for which there are no RCTs conducted are shown in Table 3.

**Oral Treatments**

PPS is the only oral medication approved by the FDA for treatment of PBS/IC. The approved dose is 100 mg three times per day. Only trials for PPS-based therapy had enough numbers to allow pooled analysis of effect in a recent systematic review, where PPS was showed to be beneficial with a relative risk of 1.78 for patient-reported improvement in symptoms (95% confidence intervals, 1.34 to 2.35) (51). However, the well-designed NIDDK-supported trial (Interstitial Cystitis Clinical Trial Group) failed to provide evidence for the efficacy of PPS treatment in PBS/IC, although the study might be underpowered (58). In addition, increased doses of PPS (300 and 600 mg daily) have not been associated with greater efficacy but with more frequent adverse effects (59). PPS treatment within 6 mo after PBS/IC diagnosis is associated with greater efficacy in comparison with late treatment (60). However, administration for a prolonged period may be required before clinical response is noted, since oral treatment leads to low concentration in the bladder; it has been shown that only 6% of PPS is excreted in urine (61). The most commonly reported side effects include nausea, diarrhea, headache, and alopecia (62).

Although evidence is limited, hydroxyzine is considered by many urologists as a first-line treatment. Its anxiolytic and anti-cholinergic effect along with its ability to inhibit bladder inflammation may explain its efficacy (63). Dose starts at 25 mg daily, given at bedtime, and should be slowly titrated to 50 to 75 mg. Prolonged administration (3 to 4 mo) may be needed before any beneficial effect is shown; 40% of patients receiving hydroxyzine for more than 3 mo reported improvement in an open label study (64). However, the previously aforementioned NIDDK-supported trial in a accurately designed RCT failed to show the efficacy of hydroxyzine (58).

Amitriptyline, the oral tricyclic anti-depressant, is commonly used in PBS/IC treatment. Mechanism of action includes regulation of pain through modulation of neuronal dysfunction. The only placebo-RCT available showed amitriptyline to be
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Duration</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Van Ophoven (65)</td>
<td>2004</td>
<td>50</td>
<td>16 wk</td>
<td>Mean symptom score decreased ($P = 0.005$) Pain and urgency intensity improved ($P &lt; 0.001$)</td>
<td>Anticholinergic side effects in 92% in amitriptyline group</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Warren (75)</td>
<td>2000</td>
<td>50</td>
<td>18 wk</td>
<td>Improvement (no SS) in pain, urgency and overall in treatment group</td>
<td>Treatment group had more adverse effects ($P = 0.009$)</td>
</tr>
<tr>
<td>BCG intravesical</td>
<td>Peters (84)</td>
<td>1997</td>
<td>33</td>
<td>6 wk</td>
<td>60 vs. 27% (in control) reported at least moderate improvement ($P = 0.06$)</td>
<td>Similar adverse effects between groups</td>
</tr>
<tr>
<td>Peeker (82)</td>
<td>2000</td>
<td>21</td>
<td>12 wk</td>
<td>No improvement in BCG group</td>
<td>Decreased pain and urgency (only in classic PBS/IC) in DMSO group</td>
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<tr>
<td>Mayer (83)</td>
<td>2005</td>
<td>265</td>
<td>6 wk</td>
<td>Response rate 21% (BCG) vs. 12% (control) ($P = 0.062$), small symptom improvement of borderline SS</td>
<td>Adverse effects more common in BCG group without reaching SS</td>
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<tr>
<td>Cimetidine</td>
<td>Thilagarajah (72)</td>
<td>2001</td>
<td>36</td>
<td>12 wk</td>
<td>Symptoms improved ($P &lt; 0.001$) in treatment group. No histologic change.</td>
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<tr>
<td>Cyclosporine</td>
<td>Sairanen (70)</td>
<td>2005</td>
<td>64</td>
<td>24 wk</td>
<td>Response (based on GRA) 75% for Cya vs 19% for PPS ($P &lt; 0.001$)</td>
<td>More adverse effects in CyA group.</td>
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<tr>
<td>DMSO intravesically</td>
<td>Perez-Marrero (81)</td>
<td>1988</td>
<td>33</td>
<td>8 wk</td>
<td>Subjective improvement in 53% vs. 18% in placebo and objective improvement in 93% vs. 35 in placebo, $P &lt; 0.001$.</td>
<td>Placebo (saline) may not be appropriate because of effects of DMSO in smell and taste. DMSO was given twice weekly.</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Sant (58)</td>
<td>2003</td>
<td>121</td>
<td>24 wk</td>
<td>Response rate was 31% for hydroxyzine vs. 20% for not treated ($P = 0.26$) and 34% for PPS vs. 18% for no PPS group ($P = 0.064$)</td>
<td>Minor adverse events. No benefit provided for the majority of patients.</td>
</tr>
<tr>
<td>Treatment Study</td>
<td>Year</td>
<td>No. of Patients</td>
<td>Duration</td>
<td>Results</td>
<td>Comments</td>
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<tr>
<td>l-Arginine Korting (73)</td>
<td>1999</td>
<td>53</td>
<td>12 wk</td>
<td>Improvement in 29 vs. 8% in placebo ((P = 0.07)). Improve of GRA in 48 vs. 24% in placebo ((P = 0.05)). Decrease of pain ((P = 0.04))</td>
<td>Using an intention to treat approach, there were no differences between groups</td>
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<tr>
<td>Cartledge (74)</td>
<td>2000</td>
<td>16</td>
<td>4 wk</td>
<td>SS reduction in overall symptom score in l-arginine group, but not in other variables.</td>
<td>No SS difference between the response to l-arginine and placebo. Three patients withdrew because of side effects.</td>
<td></td>
</tr>
<tr>
<td>Lidocaine intravesically Nickel (53)</td>
<td>2008</td>
<td>102</td>
<td>5 days</td>
<td>Improvement in 30 vs. 9.6% in placebo ((P = 0.012)). The effect maintained beyond the end of treatment.</td>
<td>Peak serum lidocaine concentration was well below toxic level. No significant side effects.</td>
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<tr>
<td>Oxybutynin intravesically Barbalias (85)</td>
<td>2000</td>
<td>36</td>
<td>18 wk</td>
<td>SS improvement in all parameters in both oxybutynin and control group.</td>
<td>Improvement favored the oxybutynin group.</td>
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<tr>
<td>Oxygen hyperbaric Van Ophoven (108)</td>
<td>2006</td>
<td>21</td>
<td>36 wk</td>
<td>3/14 patients responded in hyperbaric oxygen vs. 0 in control ((P = 0.52)).</td>
<td>Responders had sustained improvement in symptoms.</td>
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<tr>
<td>PPS oral Holm-Bentzen (109)</td>
<td>1987</td>
<td>115</td>
<td>16 wk</td>
<td>No difference between pre- and post-trial values in PPS and placebo groups</td>
<td>Increase in bladder capacity in patients with anatomically verified PBS/IC</td>
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<tr>
<td>Parsons (110)</td>
<td>1987</td>
<td>75</td>
<td>16 wk</td>
<td>Subjective and objective improvement in all parameters in PPS group</td>
<td>Minor side effects</td>
<td></td>
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<tr>
<td>Mulholand (111)</td>
<td>1990</td>
<td>110</td>
<td>12 wk</td>
<td>Subjective improvement &gt;25% in 28% of PPS group vs. 13% placebo ((P = 0.03)). Objective improvement in 26% in PPS vs. 11% placebo ((P = 0.04))</td>
<td>Minor side effects</td>
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<tr>
<td>Parsons (112)</td>
<td>1993</td>
<td>148</td>
<td>12 wk</td>
<td>Improvement in 32 in PPS group vs. 16% placebo ((P = 0.01)). Reduced pain and urgency ((P = 0.04, P = 0.01)) in PPS group</td>
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<tr>
<td>Treatment Study</td>
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<td>Sant (58)</td>
<td>2003</td>
<td>121</td>
<td>18 wk</td>
<td>Response rate was 31% for hydroxyzine vs. 20% for not treated ($P = 0.26$) and 34% for PPS vs. 18% for no PPS group ($P = 0.064$)</td>
<td>Minor adverse events. No benefit provided for the majority of patients.</td>
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<tr>
<td>Sairanen (70)</td>
<td>2005</td>
<td>64</td>
<td>24 wk</td>
<td>Response (based on GRA) 75% for CyA vs. 19% for PPS ($P &lt; 0.001$)</td>
<td>More adverse effects in CyA group</td>
<td></td>
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<tr>
<td>Nickel (59)</td>
<td>2005</td>
<td>380</td>
<td>32 wk</td>
<td>Significant symptom improvement ($P &lt; 0.001$) for all doses</td>
<td>Response to treatment was not dose depended</td>
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<tr>
<td>PPS intravesical</td>
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<tr>
<td>Bade (113)</td>
<td>1997</td>
<td>20</td>
<td>12 wk</td>
<td>40% of patients in PPS group vs. 20% in placebo ($P = 0.33$). SS increase in capacity in PPS group ($P = 0.047$)</td>
<td>No important side effects</td>
<td></td>
</tr>
<tr>
<td>Davis (87)</td>
<td>2008</td>
<td>41</td>
<td>12 wk</td>
<td>Symptoms score was greater in PPS oral + intravesical group vs oral + placebo group ($P = 0.04$)</td>
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<tr>
<td>Resiniferatoxin intravesical</td>
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<tr>
<td>Lazzeri (114)</td>
<td>2000</td>
<td>18</td>
<td>Single application</td>
<td>In treatment group SS improvement in pain, frequency, nocturia and 30d and only in frequency at 3 mo. No improvement in placebo group.</td>
<td>4 patients in treatment group reported light warm or burning sensation during infusion</td>
<td></td>
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<tr>
<td>Chen (115)</td>
<td>2005</td>
<td>22</td>
<td>Single application</td>
<td></td>
<td>Pain during instillation in more than 80% of patients in treatment group</td>
<td></td>
</tr>
<tr>
<td>Payne (116)</td>
<td>2005</td>
<td>163</td>
<td>Single application</td>
<td>No improvement in symptom in treatment group at 12-wk follow-up</td>
<td>Dose-dependent increase in instillation pain</td>
<td></td>
</tr>
</tbody>
</table>

BCG, bacillus Calmette-Guerin; DMSO, dimethyl sulfoxide; PPS, sodium pentosanpolysulfate; GRA, Global Response Assessment; SS, statistically significant; CyA, cyclosporine.
<table>
<thead>
<tr>
<th>Treatment</th>
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<th>Year</th>
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<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum A</td>
<td>Kuo (117)</td>
<td>2005</td>
<td>10</td>
<td>Single therapy</td>
<td>Improvement in bladder capacity and pain score in only 2 patients</td>
<td>Patients had already failed conventional treatments</td>
</tr>
<tr>
<td></td>
<td>Giannantoni (118)</td>
<td>2006</td>
<td>12</td>
<td>Single therapy</td>
<td>Frequency, bladder capacity improved at 1 and 3 mo ($P &lt; 0.05$)</td>
<td>Patients had already failed conventional treatments</td>
</tr>
<tr>
<td></td>
<td>Giannantoni (119)</td>
<td>2008</td>
<td>15</td>
<td>Single therapy</td>
<td>Symptoms improved in 87% of patients at 3 mo, in 27% at 5 mo, and none at 12 mo. Short-term improvement (3 mo) with pain recurrence in all patients at 12 mo.</td>
<td>Short-term improvement with pain recurrence in all pts at 12 mo. Repeat injections may be required.</td>
</tr>
<tr>
<td>Chondroitin sulphate</td>
<td>Theoharides (120)</td>
<td>2005</td>
<td>37</td>
<td>24 wk</td>
<td>GAS, O'Leary symptom index significantly improved ($P &lt; 0.05$)</td>
<td>Oral therapy. Patients had already failed conventional treatments.</td>
</tr>
<tr>
<td></td>
<td>Steinhoff (121)</td>
<td>2002</td>
<td>18</td>
<td>48 wk</td>
<td>46% of patients had good, 15% fair, 31% partial response, and 1 did not respond</td>
<td>Patients had classic PBS/IC features and positive potassium test</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Soucy (77)</td>
<td>2005</td>
<td>14</td>
<td>72 wk</td>
<td>22% reduction in O'Leary index ($P &lt; 0.02$), 69% improvement in pain control ($P &lt; 0.001$)</td>
<td>Patients had Hunner's ulcers and failed conventional treatments. 64% of patients continued treatment at 16 mo.</td>
</tr>
<tr>
<td>Heparin</td>
<td>Van Ophoven (122)</td>
<td>2005</td>
<td>58</td>
<td>2 wk</td>
<td>10 responders at 3 mo and 9 responders at 6 mo in PPS + heparin SC vs. 0 in control (PPS alone)</td>
<td>Patients with less favorable PPS response had the greatest benefit. No placebo control.</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Porru (97)</td>
<td>2008</td>
<td>23</td>
<td>12 wk</td>
<td>Improvement in number of voiding and voiding volume</td>
<td>Hyaluronic acid was given intravesically along with chondroitine sulfate</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Moran (80)</td>
<td>1999</td>
<td>9</td>
<td>24 wk</td>
<td>Improvement in pain ($P = 0.047$), without signigicant change in voiding pattern. 44% of patients responded.</td>
<td>No significant side effects. Patients with refractory PBS/IC.</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Bouchelouche (123)</td>
<td>2001</td>
<td>10</td>
<td>12 wk</td>
<td>Pain, frequency, and nocturia significantly improved at 3 mo</td>
<td>No side effects reported. Patients had detrusor mastocytosis.</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Theoharides (120)</td>
<td>2005</td>
<td>37</td>
<td>24 wk</td>
<td>GAS and symptom index improved ($P &lt; 0.05$)</td>
<td>Cystoprotek was formulated with chondroitine and hyaluronate</td>
</tr>
<tr>
<td></td>
<td>Katske (124)</td>
<td>2001</td>
<td>22</td>
<td>4 wk</td>
<td>GAS and symptom index improved ($P &lt; 0.0001$)</td>
<td>No major side effects</td>
</tr>
<tr>
<td>Sulplatast tosilate</td>
<td>Ueda (125)</td>
<td>2000</td>
<td>14</td>
<td>48 wk</td>
<td>Bladder capacity and symptoms significantly improved</td>
<td>No major side effects</td>
</tr>
</tbody>
</table>

GAS, Global Assessment Scale; PPS, sodium pentosanpolysulfate; SS, statistically significant; CyA, cyclosporine.
effective with significant improvement of symptoms (65). However, there were no details regarding the use of active or inactive placebo. The median dose used was 75 mg/d (range, 15 to 150 mg/d). In addition, long-term follow-up (19.0 months) of patients treated with amitriptyline was correlated with a 64% response rate (66). It is noteworthy that there was a significant withdrawal of patients in this study because of nonresponse and anti-cholinergic side effects. Therefore, patients should start on the lowest possible dose (10 mg daily) and titrate up to the effective dose (66,67). Results (unpublished) presented by the Interstitial Cystitis Collaborative Research Network (IC-CRN) at the 2009 American Urological Association meeting showed lack of efficacy of amitriptyline.

Cyclosporine is a calcineurin inhibitor that may act in PBS/IC through inhibition of activation of T cells or mast cell activation. Data are limited, but it gave promising results in small open-label studies (68,69) and in a recent RCT, where patients treated with cyclosporine reported a higher treatment response in comparison with PPS treatment after 6 mo (70). In addition, the response correlated with a decrease in urinary epidermal growth factor concentration, whereas patients in the cyclosporine group had a tendency toward lower urinary IL-6 levels (71). However, symptoms may return after treatment cessation, and side effects are more common in the cyclosporine group.

Oral cimetidine was found to be very effective, with significant symptom improvement in the only RCT available (72). However, there was no apparent histologic change in the bladder mucosa after treatment, and the mechanism of symptom relief is rather undefined. l-Arginine is a substrate for NO synthase, and it was used in PBS/IC based on data that NO synthase activity is decreased in the urine of PBS/IC patients. Two recent RCTs reported limited efficacy with no or marginal improvement in the treatment group (Table 2) (73,74). Although some patients reported that use of antibiotics might decrease their symptoms, a recent RCT failed to show benefit from oral administration of antibiotics for 18 wk (75).

There are numerous other oral treatments, which have been used in PBS/IC, particularly in refractory cases, but data are scarce and based on small open label studies, sometimes of ambiguous design (Table 3); RCTs are urgently needed. Steroids were used in PBS/IC based on the hypothesis that ulcers signify underlying bladder inflammation (57,76); nevertheless, there is the caveat that normal bladders are rarely biopsied, so there are no well-established cut-points at which bladder inflammation is defined as abnormal. Data that steroids are effective in classic PBS/IC are extremely limited, and further well-designed studies are needed before steroid use can be widely recommended. Soucy and Gregoire (77) reported symptom improvement after corticosteroid use in 14 patients with refractory PBS/IC who failed conservative treatment.

Montelukast, a leukotriene receptor antagonist, which is used in asthma treatment, was also reported to reduce symptoms in 10 patients with detrusor mastocytosis (78). Nonsteroidal anti-inflammatory drugs have been used in a small open label study with 37 patients who reported symptom improvement (79); however, the anti-depressant agent doxepin was given simultaneously making difficult the evaluation of efficacy of each medication and in addition, symptoms recurred after the discontinuation of the treatment. Methotrexate was used in a study of 9 patients with refractory PBS/IC, with improvement in one half of them in pain control but not urinary frequency (80). The significant side effects of these medications should always be considered.

**Intravesical Therapies**

Intravesical treatments for PBS/IC were recently analyzed in a Cochrane review (52): only bacillus Calmette-Guerin (BCG) and oxybutynin seemed to be relatively well tolerated and gave the most promising results. However, it was repeatedly noted by the authors that the available evidence is extremely limited.

Dimethyl sulfoxide (DMSO) is the only intravesical medication approved by the FDA. The mechanism of action includes inhibition of mast cell activation with analgesic and inflammatory effects. Two rather small RCTs support its beneficial effect (81,82). However, the side effects of DMSO (garlic-like smell, taste) makes it almost impossible to perform a real placebo-controlled RCT. In addition, in these two early studies, DMSO was administered every 2 wk, whereas nowadays in common practice, DMSO is administered once weekly. Finally, in the crossover study by Peeker et al. (82), where DMSO could follow BCG treatment and vice versa, there was no clear washout period between treatments, making it difficult to determine which treatment was actually beneficial. Intravesical administration of BCG was initially shown to be beneficial in PBS/IC through an unknown immunologic mechanism; however, an RCT in 248 PBS/IC patients showed that BCG treatment was only slightly superior to placebo (83). In addition, in two other RCTs, the group receiving intravesical BCG had no or marginal improvement (82,84). Oxybutynin, which has an anti-cholinergic effect reducing bladder spasm, was shown to significantly increase bladder capacity and was correlated with reduced frequency and improved quality of life (85). In this RCT, 36 patients in both groups with PBS/IC had significant improvement favoring the oxybutynin group.

Because PBS/IC is associated with chronic pain produced by sensitized local bladder afferent nerves, a rational approach would be to install local anesthetic. Toward this direction, intravesical lidocaine have been used for many years but offered only superficial bladder anesthesia, because lidocaine cannot be converted to a lipid-soluble base form in the acidic bladder environment. However, when combined with bicarbonate, its absorption increases, giving promising results (86). A recent well-designed RCT showed that intravesical alkalized lidocaine is effective in a large proportion of PBS/IC patients not only for short-term relief, but it may also contribute to long-term downregulation of bladder sensory nerves (53). In addition, duration of treatment may enhance the clinical benefits without significant adverse effects or rebound effects such those associated with narcotics’ administration.

PPS has also been used intravesically based on the hypothesis that it replenishes the protective bladder lining composed primarily by glycosaminoglycans layer; additionally, only 6%
of PPS is excreted in urine when given orally (61). A recent RCT showed that combined therapy of intravesical and oral PPS led to two-fold reduction in the severity of PBS/IC symptoms compared with oral therapy alone (87).

Despite initial promising results, the effectiveness of resiniferatoxin and botulinum toxin type A (88) in the treatment of PBS/IC remains unknown. We recently showed that the results from available clinical trials including three RCTs (Table 2) regarding the efficacy of resiniferatoxin are rather inconclusive (89). Consistent with this, the aforementioned Cochrane review found no evidence of effect of resiniferatoxin for most outcomes; in addition, it reduced patient compliance by causing pain (52).

Several other intravesical treatments have been tried in PBS/IC patients, but data are limited, coming from small uncontrolled open-label studies. Heparin has been widely used intravesically for PBS/IC in combination with lidocaine and bicarbonate (86) as a substitute for bladder layer or as an inhibitor of inflammation (20). However, when used as monotherapy, it was not shown to provide any relief. Hydrodistention is mainly used for diagnosis, and it remains rather controversial whether it can also offer short-term relief (55); there is only a small open-label study that showed that adjuvant hydrodistention under epidural anesthesia can be effective in almost 70% of patients (90). Similarly, the use of intravesical hyaluronic acid in PBS/IC may be effective as shown in several open-label studies (91–96), but in a recent review, we concluded that it cannot be recommended because of the limited available data (97). A new open-label study, however, supports that the administration of intravesical hyaluronic acid plus chondroitin sulfate may represent a safe and efficacious method of treatment in PBS/IC (98) (Table 3).

**Other Treatments**

In cases of PBS/IC, which are refractory to oral and intravesical treatment, therapeutic options include transurethral resection of ulcers, reconstructive surgery, and neuromodulation. The cost-benefit ratio should always be considered before one of these invasive treatments is recommended.

Transurethral resection of ulcers in PBS/IC patients led to satisfactory response in 90% of patients with classic PBS/IC (99); the mechanism might involve the removal of the intramural nerve endings. However, this study was not randomized, and patients underwent hydrodistention before transurethral resection of ulcers. In addition, the patients of the study (classic PBS/IC) belong to a subgroup of PBS/IC patients that represent only 5% of PBS/IC patients.

Based on the hypothesis that PBS/IC symptoms may arise from a chronic simulation and pathologic upregulation of the pelvic nerves, sacral neuromodulation using an implantable neuroprosthetic device (which was shown to be effective in treating urgency and frequency) was reported to decrease narcotic requirements in refractory PBS/IC (100). Although results are rather promising, drawbacks of this technique include high cost, pain at the neurostimulator site, need for surgical revisions, and risk of infection. Because of the less invasive technique used and the technical improvements of the newer devices, complications rate of this technique is expected to decrease (101).

Reconstructive surgery for PBS/IC patients gave disappointing results in the past (102). In addition, a recent study (103) showed that medical therapy was perceived to be superior to invasive therapy in PBS/IC. Moreover, surgery was correlated with failure to resolve symptoms and several complications in patients with nonulcer PBS/IC. However, a good outcome was recently reported (104,105) in two studies of patients with classic PBS/IC who underwent reconstructive surgery after failure of various treatments including transurethral resections and intravesical installations. Nevertheless, reconstructive surgery should be reserved only for patients who fail conservative treatment and those with classic PBS/IC; these patients are likely to benefit most.

PBS/IC is chronic multifactorial disease of unclear etiology significantly affecting quality of life and increasing medical costs; average yearly cost per PBS/ICC patient is ~$4000 more than that for age-matched controls (106). Close follow-up of the patients is essential, because prolonged administration of medications may be needed before the alleviation of symptoms. Although lack of numerous RCTs regarding its management is obvious, we propose a treatment algorithm (Figure 2), based on the best available evidence and giving priority to the less toxic therapies, reserving the more invasive treatments and those with significant adverse effects for the refractory cases.

![Figure 2. Treatment algorithm for interstitial cystitis. BCG, bacillus Calmette-Guerin; PPS, pentosan polysulfate sodium; DMSO, dimethyl sulfoxide.](image-url)
because of the short duration of trials, the heterogeneity of disease, and the lack of evidence for its natural history. The NIDDK-sponsored trial (58) showed the feasibility of conducting a multicenter RCT in PBS/IC using uniform procedures and outcomes. It is crucial not only to recruit patients following specific inclusion criteria, but also to define objective outcome measures and to continue follow-up for a long period of time after intervention. The latter is essential in a disease with flares and remissions, which would otherwise make it almost impossible to attribute improvement to the intervention and not to disease fluctuation itself. In addition, there should be a consensus regarding objective standardized outcome measures (working or activity hours, physical or sexual activity, etc.): this is particularly significant to ensure that improvement is actually accomplished and that it is not the result of frequent subjective changes observed in patients with chronic disease. Intervention should follow the same protocol to allow a more accurate comparison between trials. Developing evidence-based therapies by conducting appropriately designed RCTs is essential for advancing to safe and effective interventions in patients with this chronic and debilitating disease.

Disclosures
None.

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