Multimodal Therapy for Painful Bladder Syndrome/Interstitial Cystitis

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Painful bladder syndrome (PBS)/interstitial cystitis (IC) has historically been viewed as a rare condition the symptoms and progression of which are difficult to control. While many treatment modalities have been used—183 different ones were recorded in the Interstitial Cystitis Data Base Study—the results of most have been disappointing, and no standard approach to the treatment of PBS/IC has been generally accepted.[1] The lack of well-designed, randomized, placebo-controlled trials of potential treatments has been a handicap in formulating an evidence-based management strategy. Because the exact cause of PBS/IC is unknown, no targeted cure has been developed, but recent experience demonstrates that symptoms can be controlled in the majority of patients.[2,3] A scientifically rational approach supports a multimodal strategy directed toward treatment of the 3 components considered key to the pathogenesis of IC: the dysfunctional bladder epithelium, associated allergies and neural upregulation.[4] The benefits of medication can be enhanced with nonpharmacologic approaches, such as dietary changes, physical therapy, and bladder retraining[5] (Figure 1).

Most patients who suffer from PBS/IC can now be simply and effectively treated.

Nonpharmacologic Therapy

Nonpharmacologic approaches are an important part of the multimodal approach that has been shown to be successful in the treatment of PBS/IC. Because symptoms can be exacerbated by certain foods, dietary modification is considered essential. Certain foods high in potassium and acid should be avoided, including citrus fruits, chocolate, caffeine, spices, alcohol, carbonated drinks, tomatoes, vinegar and artificial sweeteners, besides tobacco.[4,5]

When pelvic pain is associated with concomitant pelvic floor muscle tenderness and spasm, restoration of normal tone and function to the pelvic floor musculature can alleviate symptoms.[6] This is achieved with physical therapy and home exercises to realign the sacrum and ilium and by internal direct transrectal and transvaginal manual therapy of the pelvic floor muscles (Thiele massage).[6-8] Bladder training, especially when used in conjunction with biofeedback or behavioral modification, can improve urinary frequency by teaching patients to void at designated times, gradually increasing the time between voids. Warm sitz baths, heating pads and ice

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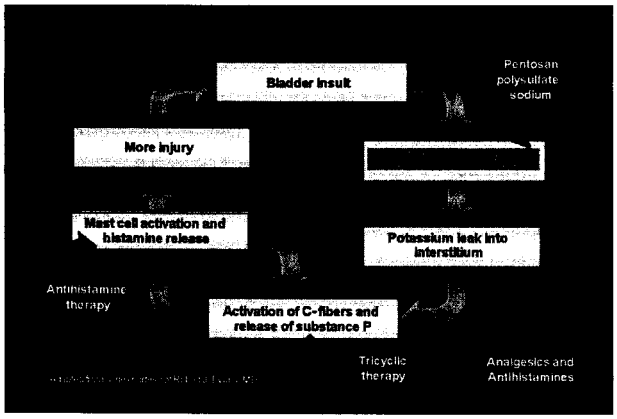

Figure 1 Etiology of IC and the rationale for multimodal therapy.

packs can provide short-term symptom relief.

Food and Drug Administration (FDA)–Approved Oral Agents for the Treatment of PBS/IC

To address what appears to be a fundamental cause of IC, a defective glycosaminoglycan (GAG) layer of the bladder epithelium, the cornerstone of treatment is pentosan polysulfate sodium (PPS), the only oral agent approved by the U.S. FDA for IC (Figure 2). With a molecular structure resembling the GAG layer of the urothelium, PPS appears to replenish the defective mucous layer and restore bladder integrity, thus acting as a buffer to control cell permeability and prevent irritating solutes from reaching epithelial cells.[5,9]

Treatment with PPS is a treatment approach recommended by a multidisciplinary panel convened in 2005.[10] PPS is currently the most effective treatment for PBS/IC and the most rigorously tested in clinical trials.[3] The approved dose is 300 mg/d (100 mg 3 times daily), although 200 mg twice daily (off-label dosage) is an evolving approach that appears equally effective and promotes greater patient compliance.

Symptomatic improvement with PPS (as compared to placebo) has been consistently demonstrated in clinical trials, which also revealed that treatment duration affects outcome. In 1 of the first studies of PPS, 38% of patients with moderate to severe IC achieved a >50% reduction in pain after just 3 months of monotherapy, as compared to 18% with placebo (Figure 3).[11] Other studies showed that overall relief of symptoms increased from approximately 50% at 12 weeks to almost 70% at 32 weeks with PPS, 300 mg/d.[11,12] An effect related to duration of treatment was also found in a 2,800-patient, open-label study in which 3 or more months of PPS treatment produced at least a moderate improvement over the baseline pain level for approximately half the patients, with a maximum benefit noted after 6–11 months.[13] Specialists have concluded that patients with early or mild disease may experience pain relief within 6–8 weeks, while the majority of patients, those with at least moderate PBS/IC, may require 6 months or so of PPS treatment.[5]

Patient education and support are critical in managing this complex but treatable disorder.

Clinicians must emphasize the need for realistic expectations for patients receiving oral PPS. While those with early-stage disease may gain symptom relief within a month, those with moderate or severe PBS/IC may require prolonged administration of the drug for repair of the urothelial dysfunction and palliation of symptoms. The longer the treatment duration, the greater the likelihood of response.[14] The majority of patients respond after 8–12 months of continuous therapy.[3,5,13,15]

PPS therapy may work to repair the underlying bladder defect as well as to improve the symptoms associated with PBS/IC. Clinical improvement with PPS treatment correlated with improved scores on the potassium sensitivity test (PST), an objective measure of potassium sensitivity and therefore disease, as shown in a large, multicenter study by Parsons et al.[9] The study evaluated 377 patients using PST before and after treatment with PPS (300, 600 or 900 mg/d [600 or 900 mg/d constitute off-label dosage]). Nearly 80% of the 198 patients completing the 32-week study had a positive PST at baseline, and 60% demonstrated significant improvements on the PST analog pain and urgency scales after treatment, regardless of the dosage administered. Patients with no clinical improvement generally demonstrated no change in their PST results. A majority of patients (71.4%) who completed the study had ≥50% improvement on the Patient Overall Rating of Improvement in Symptoms scale after PPS treatment.

The benefit of PPS for the treatment of IC was

Only oral drug approved for IC (1996)

Similar in chemistry/structure to GAG layer of the bladder

Action:
- Helps replenish defective GAG layer
- Coats the bladder epithelium

Dosage: 3 100-mg capsules per day

Course duration: at least 2–4 months: experts recommend for 6+ months

Well-tolerated agent with mild/transient adverse effects: diarrhea, nausea, rash, headache, reversible alopecia, rectal hemorrhage

Figure 2 Oral PPS.[5,17]

demonstrated in another recent study that evaluated PPS plus dietary modification vs. dietary intervention alone. Chung et al noted a 34% improvement in PBS/IC symptoms, based on the Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale, when patients received combination treatment,[16] which was nearly double the rate of improvement achieved with dietary intervention alone. The patients' mean PUF score improved from 15.01 at baseline to 9.87 after 6 months or more of combination therapy.[16]

PPS is well tolerated, with infrequent mild and transient side effects that can include minor gastrointestinal discomfort, alopecia (reversible upon treatment discontinuation) and headache. There is no effect on coagulation profiles and no known drug interactions. There may be slight liver function changes in approximately 1% of patients, generally without serious consequence.[17] Monitoring with liver function tests is required only in patients with risk factors for liver dysfunction.

Non-FDA-Approved Oral Agents

For enhanced symptom relief, oral PPS may be combined with other agents, including antihistamines, antidepressants, analgesics and occasionally anticholinergics (Figure 4).

Antihistamines

When mast cells are stimulated, histamine and other chemical mediators are released, leading to the inflammation and neural stimulation commonly thought to occur in IC. Antihistamines such as hydroxyzine can help prevent this cascade of events, and many specialists advocate the use of antihistamines in IC patients, especially those with a history of allergy.[3] In 1 controlled trial, there was a nonsignificant trend of greater improvement in global response assessment with either PPS alone or combination therapy (hydroxyzine plus PPS), although there were no treatment differences for a number of the secondary outcomes.[18]

Other means of suppressing the effects of mast cells may also be possible. Mast cells release leukotrienes, and the leukotriene receptor montelukast sodium was found, in 1 small, open-label study, to significantly improve urinary frequency and pain after 1 month of treatment.[19] Montelukast, 10 mg daily, added to antihistamines, may be especially helpful in patients with allergies or asthma.

Tricyclic Antidepressants (TCAs)

Antidepressants facilitate pain relief by inhibiting histamine secretion and decreasing norepinephrine and serotonin reuptake in the central and peripheral nervous systems. The TCA amitriptyline, at a dosage of 10–75 mg nightly, has been shown to relieve pain in half to two thirds of patients and to reduce nocturia and urinary frequency.[5,20,21] In 1 prospective, placebo-controlled trial, 50 patients meeting the National Institute for Diabetes, Digestive and Kidney Disease (NIDDK) criteria for PBS/IC received escalating doses of amitriptyline for 4 months and experienced significant decreases in pain and urgency intensity as well as urinary fre-

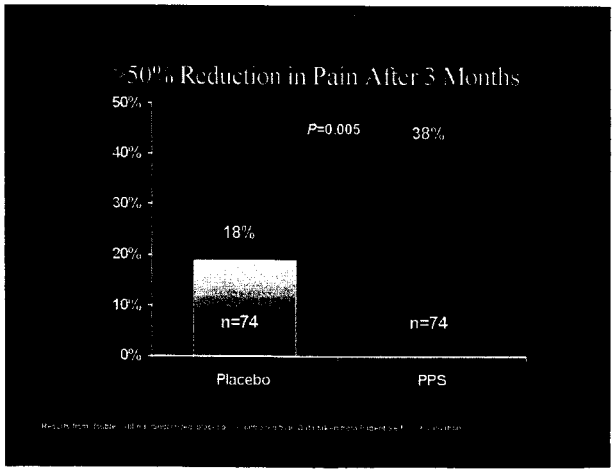

Figure 3 PPS effects on IC symptoms.[11]

Antihistamines
Analgesics
TCAs
Nonsteroidal antiinflammatory drugs
Opioids
Antiepileptics
Anticholinergics
Antibiotics

Figure 4 Adjunctive oral therapies for IC.

quency and functional bladder capacity.[21] However, 92% of the patients receiving amitriptyline reported side effects, especially dry mouth. In a separate study of 94 PBS/IC patients treated for a mean of 16 months, the same investigators reported a 64% treatment response and significant improvements in numerous symptoms, although 84% of patients experienced treatment-limiting side effects.[20] It is recommended that patients start treatment with amitriptyline at the lowest dosage and titrate up to achieve symptom relief, stopping short of the dose that provokes adverse events[5]; 25 mg at night is often all that is needed for most patients with mild or moderate disease.

Analgesics and Other Measures for Pain Relief

Since pain is a significant aspect of the PBS/IC process, aspirin and nonsteroidal antiinflammatory drugs can help relieve mild discomfort; however, they may release histamines, which can cause flares.[5] For severe symptoms suggestive of a neuropathic pain component, the long-acting opioids can be useful. Neuroleptics, such as gabapentin (100–3,200 mg/d) and topiramate (100–200 mg/d), may also help downregulate an overly stimulated spinal cord.[22,23] In a study of 21 patients with refractory genitourinary tract pain, 10 patients reported an improvement with gabapentin, 1,200 mg/d, including 5 of 8 patients with PBS/IC.[23] The newer neuroleptic pregabalin may prove to be at least as effective as gabapentin, with fewer side effects.

Short-term epidural anesthetic blockade may also provide temporary relief from severe pain. This approach, at least theoretically, downregulates the pain process and facilitates sleep, though the effects appear to be short lived. This approach was validated by Sukiennik et al, who found that urinary substance P levels initially increased and then fell in a series of 5 patients who achieved pain control with a 3-day epidural infusion.[24]

Adjunctive Treatment with Other Agents

A number of different agents, used off label, may serve as adjunctive treatment for PBS/IC, according to some reports[3,5]:

- Anticholinergics to decrease urinary frequency (especially for patients with concurrent overactive bladder), including oxybutynin chloride (10–30 mg or transdermal), tolterodine tartrate (4 mg) and hyoscyamine sulfate.[5]
- Polycitra-K crystals (Alza Corporation, San Francisco, California), one packet twice daily, or Urocit-K (Mission Pharmacal, San Antonio, Texas), 10 mEq twice daily, as a chelating agent in urine, although clinical data are lacking.[3]
- Estrogen cream in the hypoestrogenic woman; for women with menstrual flares, cycle suppression with continuous oral contraceptives or a gonadotropin-releasing hormone agonist may provide benefits.
- Skeletal muscle relaxants to help relax the pelvic floor and provide sedative and anxiolytic effects (diazepam, baclofen, cyclobenzaprine HCl, tizanidine and clonazepam).[5]

FDA-Approved Intravesical Instillations

On the basis of uncontrolled clinical trials, dimethyl sulfoxide (DMSO) was approved by the FDA in

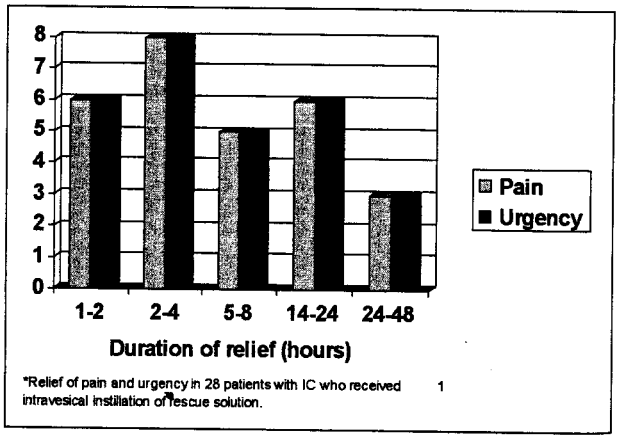

Figure 5 Duration of symptomatic relief* with intravesical rescue solution.[27] Reprinted from Urology, volume 65, CL Parsons, Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis, pages 45–48, Copyright 2005, with permission from Elsevier.

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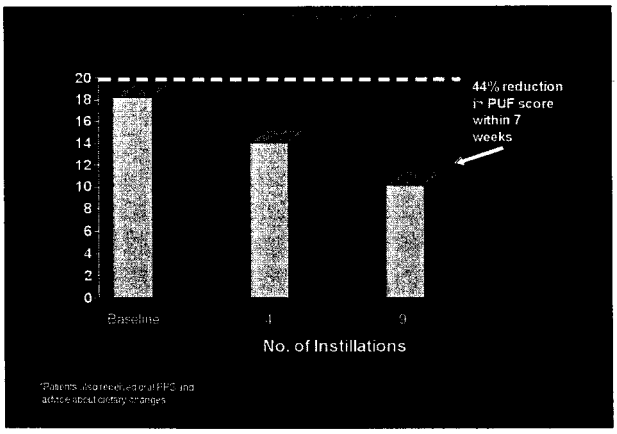

Figure 6 PPS intravesical instillation: symptom improvement in patients who received 9 treatments.*[28]

1977 for the treatment of PBS/IC, and its intravesical instillation became an established therapeutic approach before the advent of oral PPS therapy.[3] DMSO is an antiinflammatory analgesic that appears to stabilize mast cells. Its muscle-relaxing properties may prevent muscle contractions that can cause pain and urinary urgency/frequency. DMSO (packaged as 50 mL of a 50% aqueous solution) is administered intravesically in the clinician's office at 1- to 2-week intervals for 4–8 treatments, with maintenance therapy every 1–2 months as needed. Motivated patients can learn to self-catheterize at home. The instillation procedure involves passing DMSO into the bladder through a catheter, where it is retained for approximately 15 minutes before being expelled.

Clinical trials suggest that DMSO treatments afford at least moderate symptom relief and can also increase bladder capacity.[5,25] A recent study from Sweden in 28 treatment-resistant patients demonstrated an 87% response rate after 6 instillations, with a residual treatment effect lasting 16–72 months.[26] The most frequent side effect was a sensation of urethral irritation/pain in 48% after the first instillation, but this subsided in most patients with subsequent treatment. Despite some benefit, there is a movement away from using DMSO, mostly due to adverse effects of the drug, specifically a garliclike taste or odor on the breath or skin that lasts for up to 72 hours after treatment.[25]

Off-Label Intravesical Treatments

Intravesical solutions of heparin and hyaluronic acid can act as mucosal surface protectors in the bladder. Heparin is a normal component of the urothelium and appears to have beneficial antiadherence action that protects the bladder mucosa against bacterial invasion. Used intravesically, heparin has antiinflammatory benefits and surface protective actions and inhibits bladder scarring. Patients can be taught to self-instill heparin several times weekly until symptoms improve, with maintenance treatments thereafter.[5] Hyaluronic acid has properties similar to those of heparin and PPS, but its efficacy in PBS/IC has not been well established.[3]

Therapeutic Rescue Solutions

Since oral PPS treatment may not cause optimal benefits for several months, immediate palliation by another means is often necessary. An intravesical "rescue" solution can provide prompt relief, especially in patients with severe symptoms or longstanding disease.[3] This "jump start" approach is an emerging way to alleviate intermittent flares and to provide symptom relief to patients in distress before oral therapy can begin to resolve their symptoms. The suggested regimen is 10,000–40,000 units of heparin or PPS, 100–200 mg (dissolved in 8 mL of 1–2% lidocaine plus 3 mL 8.4% sodium bicarbonate [to enhance absorption of the lidocaine]).[4] In a recent study involving 82 newly diagnosed patients with severe symptoms, Parsons achieved significant symptom relief with this solution given 3 times weekly for 2 weeks (Figure 5).[27] Symptoms improved after only 1 instillation in 94% of subjects, and relief lasted at least 4 hours in 50% of patients; 80% reported significant sustained relief after 2

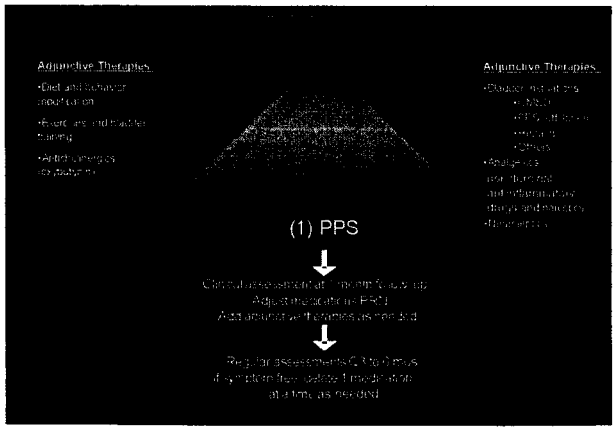

Figure 7 Summary: multimodal treatment for PBS/IC.

weeks of treatment.

Dell reported a 44% reduction in PUF scores within 7 weeks after 9 instillations of an intravesical solution consisting of 200 mg PPS (off-label use), 10 mL of 2% lidocaine and 3 mL of 8.4% sodium bicarbonate (Figure 6).[28] All patients were also given oral PPS, at 200 mg twice daily (off-label oral dosage).

Some clinicians recommend a solution of 10,000 units of heparin in 1 mL sterile water plus 8 mL of 2% lidocaine and 3 mL (8.4%) of sodium bicarbonate, to equal a total of 12 mL solution for infusion. The 12-mL solution is an adequate volume in an empty bladder.

Cystoscopy with Hydrodistention

Cystoscopy with hydrodistention of the bladder, with the patient under anesthesia, is not only a procedure to aid in diagnosis but has been shown to provide therapeutic benefit in patients with PBS/IC.[5,29] After an initial worsening, patients may experience symptomatic improvement with this modality, particularly those patients with less severe disease.[30]

Surgery

Surgical intervention is a last resort for patients diagnosed with PBS/IC. Bladder wall resection and laser therapy are typically reserved for patients suffering from gross inflammatory lesions of the bladder wall (Hunner's ulcer). Cystectomy with urinary diversion is used only when all other treatments have failed.[31] Augmentation cystoplasty is not recommended.

The current and preferred surgical intervention is sacral nerve root stimulation, which involves an implantable neuromodulator that is FDA-approved for the treatment of urinary frequency and urgency, urge incontinence and urinary retention. In a study of 25 refractory patients, Comiter found that 17 had an improvement (>50%) in frequency, nocturia, voided volume and average pain after a trial of sacral nerve stimulation.[32] After permanent implantation, 16 of the 17 patients (94%) maintained their improvement at 14 or more months. Less positive results, specifically a shorter duration of effect, were reported this year by Vaze et al.[33] Others have shown that sacral neuromodulation not only significantly reduces urinary frequency and pelvic pain but also normalizes the urinary markers antiproliferative factor and heparin-binding epidermal growth factor.[34]

Investigational Treatments for PBS/IC

A number of experimental approaches are under investigation for the treatment of PBS/IC. Bacillus Calmette-Guérin, used in the treatment of superficial bladder cancer, has shown some promise in preliminary trials, though the response rate in a recent, large study, of 265 patients with PBS/IC diagnosed by NIDDK criteria, was only 21% at week 34.[35] Agents that desensitize C-fibers through the vanilloid receptor are also under investigation, including capsaicin and an ultrapotent capsaicin analog, resiniferatoxin.[36,37] Italian investigators found that intravesical infusion of resiniferatoxin for 10 days via an in situ delivery system resulted in significant reductions in pain at 30 days and 3 months, without side effects.[37]

Botulinum toxin A is also showing promise in various types of lower urinary tract dysfunction and may provide benefit in PBS/IC.[38-40] Another experimental strategy involves using immunosuppressant agents to target the possible autoimmune component of PBS/IC. These include cyclosporine A, the oral prostaglandin E1 analog misoprostol and the new immunoregulator suplatast tosilate.[36,41]

Patient Education and Support

Along with appropriate treatment, patient education and counseling are critical components of IC management. Resource materials from the Interstitial Cystitis Association or Interstitial Cystitis Network, referral to support groups, and the help and understanding of physicians and nurses can facilitate coping and extend hope to the patient. The health care team should invest time with the patient at the first office visit, explore therapeutic expectations and explain disease management. A trained nurse can handle 90% of the telephone calls and perform routine procedures, including PST testing. With input and support from the health care team and frequent follow-up throughout the long healing process, most patients can make the transition from a situation of pain, frustration and despair to one of self-help, optimism and improved quality of life (Figure 7).

Summary

Most patients who suffer from PBS/IC can now be simply and effectively treated. The first step to successful management is accurate and timely diagnosis, which has become easier with available and validated screening and diagnostic tools such as PUF

and PST. Once PBS/IC is correctly diagnosed, prompt treatment should address the main components of the disease, a dysfunctional urothelium, mast cell activation and neural upregulation. Multimodal treatment that has shown benefit includes oral PPS plus an antihistamine, such as hydroxyzine, and a TCA, such as amitriptyline. Behavioral interventions and intravesical instillation therapy are adjunctive measures that will promote symptom relief. Intravesical "rescue" solutions using lidocaine and heparin or PPS (dissolved in water or in the instillation solution [off-label use of PPS]) can provide immediate relief while patients develop a response to oral PPS. Patient education and support are critical in managing this complex but treatable disorder.

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