

## SECOND OF 2 PARTS

# When treating interstitial cystitis, address all sources of pain

↘ Dietary modification, oral and intravesical agents, and even physical therapy may be necessary to render the pain of interstitial cystitis and painful bladder syndrome manageable

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In Part 1 of this article (page 32), I discussed an actual case of interstitial cystitis and painful bladder syndrome (IC/PBS) that was diagnosed in our clinic. That diagnosis was challenging, made over a period longer than 1 year. Regrettably, such a delay is not unusual—especially in patients who already have another diagnosis, such as endometriosis, as was true in that case.

Once a diagnosis of IC/PBS has been made, the first, crucial step is educating and involving the patient in her diagnosis and treatment, as she is more likely to accept the need for chronic, multimodal therapy. As I mentioned in Part 1, early diagnosis may be especially important. Response to treatment in patients who have a short duration of symptoms (less than 2.5 years) is 75% to 80%, and treatment often leads to clinical remission.

Here, I lay out the numerous treatment modalities the clinician can draw from to manage this complex disease. Therapy generally involves dietary manipulation, urothelial therapy such as intravesical heparin or

oral pentosan polysulfate sodium (PPS), and a tricyclic antidepressant for its neurolytic properties. Second-line therapies include mast-cell stabilization with antihistamines and other neurolytic agents.

The only FDA-approved treatments, however, are intravesical dimethylsulfoxide (DMSO) and oral PPS.

## Eliminate as many sources of pain as possible

IC/PBS is a complex chronic pain syndrome, so it is critical to identify all potential sources of pain, or pain generators, and to eliminate or treat as many of them as possible. The goal of this approach is to decrease the volume of nociceptive input to the dorsal horn. Although we lack substantial supporting evidence, the hope is that this approach may allow the dorsal horn and central nervous system to “down-regulate” and potentially normalize, or at least allow pain-modulating mechanisms to “gate” the noxious stimuli arriving at the dorsal horn and decrease the intensity of pain. This approach leads to a need for multimodal therapy in most patients.

## Dietary changes may help

Patients who have IC often report exacerbation of symptoms with the intake of certain foods or fluids, suggesting that dietary mod-

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ification or restriction may be therapeutic (TABLE). More than 50% of patients report exacerbation of symptoms with acidic foods, carbonated drinks, alcoholic beverages, and caffeine. The elimination of these foods and beverages often results in significant improvement of symptoms. Calcium glycerophosphate (Prelief) prevents food-related exacerbation in about 70% of patients.

### DMSO may ease symptoms, but treatment can be painful

DMSO (RIMSO-50) was the first drug approved by the FDA for treatment of IC. It is approved for intravesical instillation, which can be performed in the office. A small urethral catheter (8–12 French) is inserted, and the bladder is emptied. A 50-mL volume of 50% DMSO is instilled, and the catheter is removed. After waiting 15 to 30 minutes, the patient voids. Treatments are usually repeated at 1- to 2-week intervals.

Some patients find DMSO treatment painful. In that case, a pretreatment dose of ibuprofen (800 mg orally), naproxen sodium (550 mg orally), or ketorolac tromethamine (10 mg orally) may be considered.

Some patients complain of significant irritation and burning of the urethra with DMSO. For them, the urethra may be anesthetized with 2% topical lidocaine. In addition, the catheter may be left inside the urethra and clamped during the 15 to 30 minutes of treatment, allowing emptying of the DMSO via the catheter before removal. In the 10% of patients who experience painful bladder spasms, anticholinergic medications or belladonna and opium suppositories may provide relief.

All patients note a garlic-like odor of breath and taste in the mouth for 24 to 48 hours after DMSO therapy, due to excretion via the respiratory system as dimethylsulfide. This can be personally and socially unpleasant for the patient, so it is critical that she be counseled about this side effect beforehand.

DMSO has very low systemic toxicity. However, it has been reported to be teratogenic in animal studies, so its use in pregnancy is contraindicated.

**TABLE** Foods that may irritate the urinary tract

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Alcoholic beverages
Apple and apple juice
Cantaloupe
Carbonated drinks
Chili and similar spicy foods
Chocolate
Citrus fruit
Coffee
Cranberry and cranberry juice
Grape
Guava
Peach
Pineapple
Plum
Strawberry
Sugar
Tea
Tomato and tomato juice
Vinegar
Vitamin B complex

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The one published randomized, clinical trial of DMSO showed marked improvement in symptoms in 53% of patients treated every 2 weeks for a total of eight treatments, compared with 18% of patients treated with placebo (number needed to treat [NNT], 2.8).<sup>1</sup>

### Oral PPS may ease symptoms—after several months of use

Pentosan polysulfate sodium (PPS) is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans. In 1996, PPS became the first oral drug approved for the treatment of IC. It is sold under the brand name Elmiron. Its efficacy is thought to derive from its glycosaminoglycan-like characteristics, which act to restore integrity of the urothelial barrier. The recommended dosage is 100 mg three times daily. PPS is cleared in the urine.

Randomized, controlled trials of the efficacy of PPS have produced mixed results; at 3 months, however, it appears to produce a 25% to 50% response rate, compared with a placebo response rate of 13% to 23%, yielding



**Although dimethylsulfoxide has very low systemic toxicity, it has proved to be teratogenic in animal studies**

a NNT of about 4.<sup>2,3</sup> Pelvic pain diminished in as many as 45% of patients, compared with about 18% in the placebo group.

Because of its mode of action, therapeutic response is delayed. The patient generally does not respond before about 3 months of treatment, but it can be as long as 12 months.<sup>4</sup> In general, a 6-month trial should be completed before concluding that the patient is unresponsive to PPS. A positive PST may be predictive of response to PPS.<sup>5</sup>

PPS has low toxicity and few side effects. In rare cases, the transaminase level may rise. Headache, nausea, diarrhea, dizziness, skin rash, peripheral edema, and hair loss are the most common side effects, but they occur in fewer than 10% of patients.<sup>6</sup> In randomized trials of PPS, in fact, adverse effects often occurred at a higher rate in the placebo group.<sup>3</sup> No serious interactions between oral PPS and other medications have been reported.

Some data suggest that PPS may be effective when it is administered intravesically.<sup>7</sup> This may be an option for patients who experience side effects after oral administration.

### Among tricyclics, amitriptyline is most effective

Tricyclic antidepressants have proved to be effective in the treatment of IC, particularly amitriptyline, the most commonly prescribed tricyclic for the disease. Amitriptyline has multiple modes of action. Its anticholinergic effects reduce urinary frequency, and its sedating effects improve sleep and help decrease nocturia. Tricyclics effectively treat neuropathic pain—a mode of action that is probably important in IC.

The efficacy of amitriptyline has been confirmed in at least one randomized, double-blinded, placebo-controlled trial of 50 patients with IC.<sup>8</sup> Mean symptom scores decreased by 31% among patients treated with amitriptyline, compared with 13% in the placebo-treated group. Pain scores diminished by 43% in the amitriptyline group, compared with a 2% increase in the placebo group. Among patients treated with amitriptyline, 53% rated their satisfaction “good” or

“excellent,” compared with 4% in the placebo group, yielding a NNT of 2. Anticholinergic side effects, especially dry mouth, were reported by 92% of patients treated with amitriptyline, compared with 21% of those treated with placebo. Final dosages of amitriptyline in this study were:

- 25 mg in 29% of patients
- 50 mg in 37.5%
- 75 mg in 21%
- 100 mg in 12.5%.

Patients self-titrated, based on efficacy and side effects.

This clinical trial confirms the clinical impression that amitriptyline is effective and relatively well tolerated, and that dosages lower than those used for the treatment of depression are adequate for treatment of IC.

### Physical therapy may be effective in intractable cases

The pelvic floor muscles can become a source of persistent pain even if bladder inflammation and up-regulation are aggressively treated. Treatment of any pelvic floor muscle dysfunction and hypertonus is an important component of management in patients who have IC. Physical therapy techniques that involve manual or soft-tissue manipulation can be used to improve symptoms moderately or markedly in as many as 83% of patients who have failed a more traditional approach to IC.<sup>9</sup> A published clinical trial suggests that physical therapy is effective in the treatment of IC/PBS.<sup>10</sup>

### Intravesical heparin has no effect on coagulation

Heparin is thought to repair the glycosaminoglycan layer of the bladder, or at least to coat and protect bladder epithelium. It can be used intravesically with minimal concern for anticoagulation. Because heparin is insignificantly absorbed into the circulation from the bladder, a partial thromboplastin time assay is not needed.

Heparin is usually instilled in combination with other medications—either



**Amitriptyline is the tricyclic antidepressant most commonly prescribed for interstitial cystitis and painful bladder syndrome**

dimethylsulfoxide or local anesthetic agents.

No randomized trials of intravesical heparin treatment have been performed.

### Local anesthetics are effective, observational data indicate

Intravesical administration of local anesthetic agents—usually lidocaine—appears to provide significant relief from pelvic pain arising from IC. Only observational data on their use are available, however.

Treatment with these agents reflects the newer concept that IC-related pain may be neuropathic and that local anesthetics may down-regulate the bladder afferent nerves.<sup>11</sup> Parsons noted that 80% of patients experienced pain relief after intravesical treatment with a therapeutic solution of 40,000 U of heparin, 8 mL of 2% lidocaine, and 3 mL of 8.4% sodium bicarbonate, given three times weekly for 2 weeks. Pain relief was sustained for at least 48 hours after the last instillation.

Lidocaine has also been used intravesically at a dosage of 20 mL of 1% solution. Most reports of local anesthetic usage have included heparin at dosages of 10,000 to 40,000 U, but not all have included the addition of sodium bicarbonate, which may increase absorption of local anesthetic agents into the bladder epithelium and improve efficacy.<sup>12</sup> The instillation of local anesthetics is common in practice, but clinical trials are needed to confirm its safety and efficacy.

### Consider an antihistamine if there is a history of allergy

Activated mast cells play a role in the inflammatory response of the bladder in many patients who have IC. Medications that stabilize and reduce mast cell activation may be effective, especially in patients who have a history of significant allergy. For example, in an open-label study, hydroxyzine reduced symptoms by 40% overall, but it reduced them by 55% in patients who had a history of significant allergy.<sup>13</sup> PPS is a potent antihistamine, as well as an effective glycosaminoglycan in the bladder micellar

formation. Hydroxyzine, like PPS, may have to be administered for several months before symptoms improve significantly, so patients should continue treatment for 3 to 6 months before making a decision about efficacy.

The one published randomized, clinical trial of hydroxyzine yielded a response rate of 31%, compared with 20% among patients who did not receive the drug, but this difference failed to reach statistical significance.<sup>14</sup>

### Anticonvulsants are largely untested in treatment of IC

Several anticonvulsants have proved to be effective in the treatment of neuropathic pain. Although they have been suggested as a possible treatment for IC, their efficacy in this regard has not been well established.

Gabapentin is an anticonvulsant commonly used to treat pain. In an uncontrolled, open-label trial, the drug reduced pain in 10 (48%) of 21 patients who had IC, but four patients (20%) dropped out due to side effects.<sup>15</sup>

### Is hormonal manipulation useful?

One observational study suggests that hormonal manipulation may improve bladder symptoms of IC.<sup>16</sup> Twenty-three of 46 women in this series experienced a notable perimenstrual increase in IC-related pain. Fifteen of the 23 were treated with leuprolide acetate, a combined oral contraceptive, or hysterectomy with bilateral salpingo-oophorectomy. All but one also had a gynecologic diagnosis of endometriosis, pelvic congestion syndrome, or chronic pelvic inflammatory disease. Thirteen of the 15 experienced sustained improvement of symptoms attributed to IC. The bottom line: Consider cyclic suppression in patients who have a history of perimenstrual flare.

### Three initial modalities yield good results

In our clinic, we tend to start patients on both PPS and amitriptyline. If the patient has



**Intravesical administration of local anesthetic agents such as lidocaine appears to provide significant relief from pelvic pain arising from interstitial cystitis and painful bladder syndrome**

a high level of pain, we include bladder instillation with lidocaine and heparin to see whether they provide immediate pain relief. More than 50% of our patients are adequately treated with these three modalities. The addition of other treatments depends on the patient's response to and tolerance of these initial treatments.

Other nonbladder sources of pain should also be identified and treated, such as irritable bowel syndrome, endometriosis, vulvodynia, and pelvic floor tension myalgia.

The effectiveness of multimodality therapy has not been well studied. A great deal more research is needed, particularly randomized, placebo-controlled studies.

**CASE RESOLVED** A multimodal approach alleviates severe pain

Twenty-five-year-old J. M. has just been given a diagnosis of IC/PBS. We advise her to avoid caffeine, carbonated drinks, alcoholic beverages, and acidic foods. We also prescribe oral PPS and teach her how to instill heparin and lidocaine into her bladder.

Because J. M. was given an earlier diagnosis of endometriosis, we also continue hormonal suppression with norethindrone acetate.

When her pain remains bothersome after 6 months, we add 600 mg of gabapentin each night.

Four years after her first visit to our office, J. M. reports pain levels that range from 0 to 4, with occasional flares to 4 with breakthrough bleeding. She now voids at intervals of 4 to 6 hours and reports no nocturia. ☺

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