Managing interstitial cystitis/bladder pain syndrome in female patients: Clinical recipes for success

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As one enters the twilight of their career, it is imperative to pass the wisdom of countless patient encounters to those who follow in their footsteps. I have been asked by urologists many times over the decades how to treat a specific patient with interstitial cystitis/bladder pain syndrome (IC/BPS) and found that I gave a different answer to each query based on the individual patient's clinical characteristics or what some might call each patient's "clinical picture." This is also how I have managed my patients in the IC/BPS clinic at Queen's University in Kingston.

I have learned, through over 800 unique patient interactions, 24 clinical trials, 200+ clinical studies, and countless hours researching the literature, that a stepwise, graded, monotherapy approach (as advocated in initial American Urological Association guidelines) is doomed for failure in the majority of patients suffering from IC/BPS. This compendium of treatment options and suggestions is not a guideline, not a formal recommendation, but rather a list of recipes of potentially effective therapies for individual patients. The recipes are based on what the older masters of urology have passed on, what my patients have taught me, what I learned from my clinical research studies, and my interpretation of the evidence in the literature.

I will concentrate on patient phenotypes that I most often see in my practice and, therefore, will miss some rare patient profiles, but this is the best one can do in such an enigmatic syndrome based on perceived bladder pain and variable urinary storage symptoms. For those readers who want a more traditional treatise on IC/BPS, I would refer them to our recent comprehensive chapter (including background supportive references) in Harrison's Textbook of Medicine.[1]

Recipes are based on preparation

The clinical recipes are based on phenotypes that are diagnosed with standard clinical assessment, which includes:

1. Screening

A screening assessment to determine whether the patient has the clinical criteria for the diagnosis of IC/BPS (perceived bladder pain, urinary storage symptoms, no active urinary tract infection [UTI] or other confusable diseases).

2. Questionnaire

A questionnaire should be completed by the patient prior to full history, physical examination, or decision of ancillary testing. I have used many in my career, including Interstitial Cystitis Symptom Index (ICSI), Pain Urgency Frequency (PUF), Bladder Pain Interstitial Cystitis Symptom Score (BPICSS), RAND Interstitial Cystitis Epidemiology (RICE), and the National Institutes of Health (NIH) Female Genitourinary Pain Index (F-GUPI) questionnaires, and my opinion is the that the F-GUPI provides the most comprehensive assessment for phenotyping IC/BPS patients. In nine questions it assesses location and/or association, frequency, and severity of pain, storage, and voiding symptoms, as well as impact/quality of life (Figure 1). These questionnaires are not diagnostic tools, but rather an excellent way to understand severity and track changes in symptoms over time.

Name: _____

Female Genitourinary Pain Index

Date: _____

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

a. Entrance to vagina	☐1 Yes	☐2 No
b. Vagina	☐1 Yes	☐2 No
c. Urethra	☐1 Yes	☐2 No
d. Below your waist, in your pubic or bladder area	☐1 Yes	☐2 No

2. In the last week, have you experienced:

a. Pain or burning during urination?	☐1 Yes	☐2 No
b. Pain or discomfort during or after sexual intercourse?	☐1 Yes	☐2 No
c. Pain or discomfort as your bladder fills?	☐1 Yes	☐2 No
d. Pain or discomfort relieved by voiding?	☐1 Yes	☐2 No

3. How often have you had pain or discomfort in any of these areas over the last week?

☐0 Never ☐1 Rarely ☐2 Sometimes ☐3 Often ☐4 Usually ☐5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days you had it, over the last week?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating over the last week?

☐0 Not at all ☐1 Less than 1 time in 5 ☐2 Less than half the time ☐3 About half the time ☐4 More than half the time ☐5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

☐0 Not at all ☐1 Less than 1 time in 5 ☐2 Less than half the time ☐3 About half the time ☐4 More than half the time ☐5 Almost always

Quality of Life

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

☐0 None ☐1 Only a little ☐2 Some ☐3 A lot

8. How much did you think about your symptoms, over the last week?

☐0 None ☐1 Only a little ☐2 Some ☐3 A lot

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

☐0 Delighted
☐1 Pleased
☐2 Mostly satisfied
☐3 Mixed (about equally satisfied and dissatisfied)
☐4 Mostly dissatisfied
☐5 Unhappy
☐6 Terrible

Scoring

Pain subscale: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 2c, 2d, 3, and 4 = _____

Urinary subscale: Total of items 5 and 6 = _____

QOL Impact: Total of items 7, 8, and 9 = _____

Total score: Sum of subscale scores = _____

Figure 1. The Female Genitourinary Pain Index (F-GUPI) was developed and validated by the National Institute of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) and is a public domain questionnaire for the evaluation of female patients with interstitial cystitis/bladder pain syndrome.

MEDICAL SYMPTOMS INVENTORY

Instructions: Please read the following list of symptoms. If you have had any of these symptoms for at least three (3) months in the past year, please mark the appropriate box. If you had a symptom for three (3) months at any other time in your life, then mark the appropriate box.

	Symptom	3 months during the last year	3 months during your lifetime
1	Muscle or joint pain		
2	Persistent fatigue not relieved with rest		
3	Impaired memory, concentration or attention		
4	Abdominal pain relieved with bowel movement		
5	Onset of abdominal pain with a change in frequency of bowel movements		
6	Onset of abdominal pain associated with a change in form or appearance of stool		
7	Constant burning or raw feeling at the opening of vagina		
8	Pelvic/bladder discomfort (pain or pressure)		
9	Urinary urgency (difficult to postpone urination)		
10	Urinary frequency, >8/day during waking hours		
11	Frequent nocturia (nighttime urination), at least 3/night		
12	Jaw and/or face pain		
13	Temple pain		
14	Pulsating and/or one-sided headache pain		
15	Pressing/tightening headache pain		
16	Pain, muscle tension, or stiffness in the low back region with or without leg pain		

Figure 2. This medical symptoms inventory is a non-validated, but very useful and quite comprehensive questionnaire that has allowed us to quickly accomplish an initial screening for interstitial cystitis/bladder pain syndrome (#8,9,10,11), irritable bowel syndrome (#4, 5,6), fibromyalgia (#1), chronic fatigue syndrome (#2), vulvodynia (#8), and other associated pain syndromes.

3. Full history

Full history, focusing on other potentially associated pain syndromes (i.e., irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, back pain, endometriosis, vulvodynia, osteitis pubis, etc.), is important. A useful screening medical inventory that can be used is shown in Figure 2. The history should also try and determine if the patient is suffering from depression, anxiety, stress, and catastrophizing (rumination, magnification, and/or helplessness). Once rapport has been established with the patient, I have found it very useful to gently and respectfully inquire about past or concurrent physical or sexual trauma.

4. Physical examination

Physical examination should be completed, focusing on the abdomen, perineum, and pelvis. The pelvic examination — performed after visually examining the vulva — includes first an assessment of vulvar/vaginal mucosal hypersensitivity/signs of genitourinary syndrome of menopause (can be done with a cue tip or even the end of a rolled tissue) and assessment of pelvic floor muscle tone, as well as myofascial and trigger point pain (unilateral vs. bilateral). While it is good practice to identify the actual muscle group associated with fascial or myofascial pain/trigger points, it is most important that it is at least recognized so that appropriate diagnosis and eventually treatment is realized. Only after examination of the pelvic floor is the bladder palpated, first via anterior vaginal wall and then bimanual with one hand on the abdomen. I generally find it best to examine the bladder empty.

5. Urine studies

Urine studies, such a urinalysis and urine culture, must be performed.

6. Cystoscopy

Cystoscopy is mandatory, and all the relevant clinical information can be obtained under local anaesthesia (Hunner's lesion, bladder wall inflammation, functional bladder cap-

acity). A modified hydrostatic bladder dilation (typically two minutes or so) without a general anesthetic can be performed by anesthetising only the bladder with 10 cc of 2% lidocaine followed by 10 cc of 3.8% sodium bicarbonate, held for 10 minutes. This also allows comparison to the functional bladder capacity (determined by pain threshold) and better pelvic floor assessment with the bladder pain resolved.

7. Other tests

Other tests, including frequency volume charts, can be extremely helpful in assessing and then monitoring a patient's urinary frequency and functional bladder capacity. Urodynamics (standard or video) and abdominopelvic imaging (ultrasound or computed tomography) can be employed as indicated.

Every recipe starts with the same ingredients

Before deciding on a specific treatment recipe, all patients should undergo the same management principles. For some, this is all that is necessary.

1. Education

Patients should be reassured that they have a very specific diagnosis despite negative findings, and that the symptoms of IC/BPS are significantly impacting their quality of life. They must understand that physicians do not have all the answers; an achievable goal is to improve their medical condition, but they need to be part of the solution. They must start with the mindset that the glass is half full.

2. Diet

Diet manipulation using a recognized elimination diet can be attempted. The idea is to eliminate all combustibles, such as coffee, tea, cola, fruit juice, chocolate, alcohol, nuts, spices, acidic foods, citrus, etc., until they are doing better and then add them back one by one to figure out what their individual diet plan should be going forward.

3. Exercise

Exercise regimens will focus on low-impact movements (walking, swimming, elliptical, etc.) and exercises that include stretching (e.g., yoga), as well as positive mind exercises (e.g., mindfulness).

4. Pain medications

Standard pharmacological pain medications, such as non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, and urinary analgesics should be considered early in all patients.

5. Opioids

As a general rule, chronic opioids should be avoided, as they not only denigrate the patient's own endogenous opioid system but also fail to provide pain benefit over time (at least compared to placebo). In our experience, an opioid cessation program has included strategic use of cannabis (marijuana) therapy, which may not actually reduce the chronic pain of IC/BPS, but seems to allow the patient to cope better.

6. Psychology

For patients with psychosocial associations (described above), recognition followed by psychological support from you, your staff, or a psychologist will be helpful. For most patients a psychology assessment is better than a psychiatric evaluation.

7. Dimethylsulfoxide and pentosanpolysulfate

In our clinic, I have been using the two Health Canada and U.S. Food and Drug Administration-approved medical therapies: dimethylsulfoxide (DMSO) and pentosanpolysulfate (PPS) sodium less frequently than in the past. This is due to the many perceived short-term side effects with DMSO and potential of long-term consequences (specifically maculopathy) possibly associated with PPS.

8. Avoid a stepwise approach

Experience has taught me that for most patients, a stepwise monotherapy strategy is not effective. For most IC/BPS patients, a phenotype-based, multimodal therapy strategy offers the best pathway to improvement.

9. Major surgery considerations

Urinary diversion ± bladder removal is a very last resort, limited to patients with end-stage bladders for whom all available therapies have failed and the quality of life may be better living with the consequences of such major surgery.

10. Manage associated pain conditions

It is imperative that pain outside the pelvis (widespread pain) associated with irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, back pain, etc. (identified in the screening form described in Figure 2) be managed. This may require the assistance of a multidisciplinary team that may include yourself, a gastroenterologist, gynecologist, rheumatologist, physiotherapist, or pain specialist.

Table 1. Most common clinical phenotypes identified in IC/BPS

IC/BPS phenotype	Description
Inflammatory IC/BPS	Bladder wall inflammation and/or Hunner's lesion confirmed on cystoscopy
Infection-mediated IC/BPS	Past history or currently experiencing recurrent urinary tract infections
Hypersensitivity-type	Mucosal neuropathic upregulation typically associated with a central sensitization causing pain outside the pelvis (widespread pain). No specific clinical findings
Allergy-type	Multiple allergies, including respiratory, environmental, and dietary allergic history. Mucosal "wheal and flare" with provocative cystoscopic testing
Associated pelvic floor pain	Pelvic floor trigger point, muscle or myofascial pain usually associated with increased pelvic floor tone or spasm
Primary storage symptoms	Dominant symptom is urinary urgency and frequency associated with bladder pain
Urethral syndrome	Localized urethral pain can be the only symptom, but is usually associated with other BPS symptoms, voiding, or coitus
Associated sexual pain	Vaginal, vulvar, bladder, and/or pelvic floor pain associated with sexual activity
Flares	A sudden worsening of bladder urination and pain symptoms

It is imperative that the preparation work be completed (as described in text) before the specific recipes described in the text for each individual phenotype are initiated. To make things more complicated, many, if not most, patients with IC/BPS present with multiple phenotypes and that must be taken into consideration when planning individual patient-directed management recipes. IC/BPS: interstitial cystitis/bladder pain syndrome.

Specific recipes

The clinical assessment above allows an almost infinite number of phenotype combinations, but once again, experience has taught that some phenotypes are more common than others (Table 1). We need to choose the correct ingredients for a personalized management recipe. Below, my recipes are described for the most common clinical phenotypes encountered in my, and likely most, urology practices. The recipes include medical, intravesical, surgical, and non-medical approaches. It is important to remember that many, if not most patients, can be categorized with multiple phenotypes. These are suggestions only and can be adapted for individual patient situations.

1. Inflammatory IC/BPS (bladder wall inflammation and/or Hunner's lesion)

If present, distinct Hunner's lesions should be cauterized. If this helps, it can be done several times, but after one or two successful treatments, we switch to injection of the lesion with triamcinolone (total dose not to exceed 80 mg). Intravesical treatment for early, mild recurrences can be managed with a combination of intravesical lidocaine (200 mg) and triamcinolone (80 mg) ± a glycosaminoglycan (e.g., hyaluronic acid, heparin sulfate, chondroitin sulfate) — the addition of triamcinolone being the key ingredient here. See Table 2 for details of intravesical administration of medications. For refractory cases, we have recently initiated an oral cyclosporin program (with collaborative advice from our nephrology transplant colleagues) with some success.

Table 2. Intravesical recipes

Intillation ingredient	Recipe
Glycosaminoglycan (GAG) - heparin - hyaluronic acid - chrondroitin sulfate	Heparin (10–20 000 units in 20 ml of 0.9% sodium chloride), hyaluronic acid (80 mg–50 ml of 0.16%), chrondroitin sulfate (20 ml of 2%) Remove catheter immediately. Patient retains solution as long as posible Induction: Weekly for 6 weeks Maintenance: Monthly as necessary
Triamcionolone	40–80 mg in 20 ml of 0.9% sodium chloride Remove catheter immediately. Patient retains solution as long as posible
Lidocaine	10 ml of 2% lidocaine with 5 ml of 8.4% sodium bicarbonate Catheter clamped for 10–20 minutes and then solution drained before catheter is removed Induction: Weekly (or biweekly if possible) until desensitization occurs (bladder pain improves)
Lidocaine + GAG	10 ml of 2% lidocaine with 5 ml of 8.4% sodium bicarbonate Catheter clamped for 10–20 minutes, solution is drained and GAG (see above) instilled and catheter removed. Patient retains solution as long as possible Induction: Weekly for 6 weeks Maintenance: Monthly as necessary
Lidocaine + Triamcinolone + GAG	10 ml of 2% lidocaine with 5 ml of 8.4% sodium bicarbonate Catheter clamped for 10–20 minutes, solution is drained and GAG plus triamcinolone (see above) instilled and catheter removed. Patient retains solution as long as possible Induction: Weekly for 6 weeks Maintenance: Monthly as necessary

Intravesical recipes, for the most part, have not undergone rigorous peer-reviewed evualation. These are suggestions based on our clinical experience in our interstitial cystitis/bladder pain syndrome clinic in Kingston. Before each treatment, point of care urinalysis is performed and if symptoms and this test suggest urinary tract infection, the treatment is postponed until a negative urine culture is achieved. A uroject type syringe is used to inject 10 cc of 2% lidocaine gel into urethra prior to urinary catheterization with a small calibre straight catheter.

2. Infection-mediated IC/BPS

These patients either have had a history of recurrent UTI (rUTI) or continue with flares secondary to current UTI. Episodic antibiotic treatment for UTI flares and low-dose, long-term antibiotic prophylaxis will help many. We do not have extensive experience with glycosaminoglycan (GAG) bladder instillation (hyaluronic acid instillations have recently been recommended as an option in the updated European Association of Urology rUTI guideline), but do use intravesical antibiotic instillation for culture-proven, refractory, chronic UTI. During our Health Canada-approved early clinical experience trial with a new submucosal vaccine, MV140, subjects with IC/BPS and rUTI not only had a significant reduction in subsequent UTIs, but also had an improvement in the pain and storage symptoms. We believe the symptoms in this subset of patients may develop from a bladder hypersensitivity syndrome secondary to the rUTI. I think that, in the future, non-culture molecular technology (e.g., next-generation sequencing) will be more helpful than standard cultures to help define this population; however, at this time, we must wait for the research needed to substantiate changes in clinical practice before we wholeheartedly adopt this technology to manage patients with IC/BPS.

3. Neurogenic hypersensitivity-type IC/BPS

These patients have no significant findings on investigation and likely have a mucosal neuropathic upregulation, with most eventually developing a central sensitization causing pain outside the pelvis (widespread pain). There is a high association with fibromyalgia and irritable bowel syndrome. It is important to diagnose and target other pelvic and widespread pain generators (see phenotype #5: pelvic floor dysfunction), but for the most part, these patients are managed systemically with medical neuromodulation (e.g., amitriptyline: titrating from 10 mg to 20 mg to 25 mg, and finally, 50 mg taken at night) with intravesical treatment employing GAGs. We have used gabapentin/pregabalin for this phenotype, with variable success, as the benefits are only appreciable when reaching doses that may not be tolerable. If the perceived bladder pain is dominant, we add intravesical alkalinized lidocaine. See Table 2 for details of intravesical administration of medications.

4. IC/BPS associated with multiple allergies

These patients have multiple allergies, including respiratory, environmental, and dietary allergic history. On cystoscopy, we identify these patients with a provocative test during which we gently "poke" the posterior bladder wall with the tip of the flexible cystoscope and wait to see if there is a typical mucosal wheal-flare reaction. Biopsy of areas showing mild inflammation will typically show high prevalence of mast cells and in some, eosinophils. Along with strict diet manipulation, we use an antihistamine (hydroxyzine 50 mg at night) while others believe in cimetidine (we did one small study that showed effectiveness but tend to go the antihistamine route). The use of intravesical triamcinolone ± lidocaine ± GAG has benefited some of these patients.

5. Associated pelvic floor pain

Over 50% of patients diagnosed with IC/BPS (fewer who are diagnosed with Hunner's lesion phenotype) will have pelvic floor trigger point — muscle or myofascial pain usually associated with increased pelvic floor tone or spasm. Along with the treatments directed against other pain or bladder pain, the pelvic floor must be addressed. This can be accomplished with local heat treatment, stretching and relaxation exercises, pelvic floor physiotherapy ± the use of skeletal muscle relaxants (such as diazepam via vaginal suppository [10 mg], cyclobenzaprine, or baclofen). It is imperative that pelvic floor physiotherapy be undertaken by specialists trained in pelvic floor pain manipulation. For cases with unilateral pain, pain that follows the distribution of one of the pudendal or other pelvic/perineal nerve branches, or localized pelvic floor pain (e.g., trigger point) that has not responded to other therapies, we use a digitally directed repetitive transperineal nerve block strategy. While we have included injectable corticosteroids in addition to local anesthetics (lidocaine, marcaine), we are unsure of the effectiveness unless there is a perception of underlying local inflammation. Others have recommended pelvic floor onabotulinum toxin A injections; we have no clinical experience to recommend it. If the urologist is uncomfortable with pelvic floor injections, I would suggest collaboration with urogynecologists who may be more familiar with the technique or pain/radiology specialists who use imaging to target specific nerve injections.

6. Primary storage symptom syndrome

It is important to differentiate patients with primary storage symptoms without pain (overactive bladder [OAB]) from the type of patient we are dealing with here (storage symptoms with bladder pain). In the latter group, the urgency and frequency are a learned attempt to avoid pain with bladder filling, as opposed to the OAB patient, whose storage symptoms are based on avoiding incontinence. We have found that antimuscarinic agents (e.g., solifenacin) are only beneficial once pain is controlled. The beta-3 agonist, mirabegron, on the other hand, seems to help some patients with both urinary urgency/frequency and bladder pain, but the optimal benefit is achieved once pain is under some control. The use of bladder retraining is essential to help these patients

increase functional bladder capacity and reduce bothersome storage symptoms. As a last resort, careful injection of low-dose onabotulinum toxin A, similar to its use in OAB, can provide short-term symptom amelioration, but perhaps at a potentially higher risk of urinary retention. This risk may be mitigated with doses as low as 50 units or trigonal injections only. We have seen a number of patients who responded to sacral neuromodulation (done elsewhere), but it is my somewhat biased opinion that it did not significantly impact bladder pain and seemed to be most effective in reducing urinary urgency and frequency when the pain was at least partially controlled.

7. Urethral pain syndrome

One of the most difficult phenotypes to help clinically are those with urethral pain. The localized urethral pain, usually described as burning, can be the only symptom, but is usually associated with other BPS, voiding, or coitus symptoms. It can be constant, episodic, or associated (or exacerbated) with voiding (dysuria). Management strategies include topical lidocaine (small amount of 2–5% gel), vaginal estrogen, local or oral amitriptyline, phenazopyridine, and/or diazepam ± periurethral block.

8. Associated sexual pain

If the patient has a desire to be sexually active, this can be a devastating situation and must be addressed. The pain from either the vagina or vulva (vulvodynia), the pelvic floor (pain and spasm), or the bladder (tender or painful bladder) is determined first and then addressed. Treatments include pelvic floor dysfunction management, as described above; the bladder with bladder-specific therapy, including lidocaine desensitization, as described above; and local treatment of hypersensitized vaginal mucosa. For the latter, urogynecology assistance may suggest antimicrobials (for yeast infection), vaginal estrogen for post-menopausal status, local application of lidocaine or amitriptyline, or sexual position education. Some of these women may report a flare of symptoms following intercourse, and a trial of post-coital antibiotic prophylaxis may be helpful in preventing those flares.

9. IC/BPS flares

IC/BPS flares — a sudden worsening of bladder urination and pain symptoms — can be triggered by diet, menstrual cycle, stress, other acute illnesses (particularly other infectious, inflammatory, and pain conditions), and sexual intercourse, and typically last for a few hours to several days (or even longer). Management of flares include patient-controlled therapies, such as diet modification (cutting out foods and drinks that trigger or aggravate flares), increasing water intake, stopping any supplements or vitamins, stress reduction (mind exercises), reducing high-impact exercise (or exercise causing perineal pressure, such as a bicycle seat), starting low-impact exercises (yoga, stretching), use of a heating pad (some find cold compresses better for acute flares), and modification of sexual intimacy practices. Medications for flares include pain medications (avoiding opioids is still a valid goal but occasionally I have prescribed opioids for acute, incapacitating flares), short-term antihistamines, phenazopyridine hydrochloride, and in the case of cyclic flares corresponding to menstrual periods, hormone therapy (I would request that be ordered by family physician or gynecologist). We have an established nurse-based intravesical treatment clinic on Friday afternoons (flares seem to occur more frequently just before the weekends) and as a last resort, we bring patients into clinic for a lidocaine, bicarbonate, and GAG intravesical cocktail (Table 2).

Conclusions

These are the most important recipes I have learned over the past three decades of taking care of IC/BPS patients. My hope is that this simple approach, based on developing individualized treatment recipes for each patient centered on their specific "clinical picture" or phenotype, will bring success to the management of your patients.

Competing interests: Dr. Nickel has been an advisory board member for Inmunotek, MicroGenDx, OM Pharma, Redleaf Medical, and UTIVA (all in UTI); and has participated in clinical trials supported by Inmunotek, MicroGenDx, and Red Leaf Medical.

This paper has been peer-reviewed.

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