2025 Canadian Urological Association Guideline: Selected treatment recommendations for interstitial cystitis/bladder pain syndrome

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Cite as: Doiron RC, Tadayon B, Violette PD, et al. 2025 Canadian Urological Association Guideline: Selected treatment recommendations for interstitial cystitis/bladder pain syndrome. *Can Urol Assoc J* 2025;19(4):90-103. http://dx.doi.org/10.5489/cuaj.9182

Appendix available at *cuaj.ca*

SUMMARY OF RECOMMENDATIONS

Recommendation 1: Among patients with interstitial cystitis/bladder pain syndrome (IC/BPS), the panel conditionally recommends against the use of oral pentosan polysulfate (PPS) as compared to standard of care (low certainty in evidence of effects).

Recommendation 2: Based on the available literature, it is not possible to recommend one intravesical agent, or combination of agents, over another for the treatment of IC/BPS.

Recommendation 3: Intradetrusor onabotulinumtoxin-A (BTX-A), with or without hydrodistension, is conditionally recommended as an option for the treatment of IC/BPS patients refractory to other treatments (very low certainty in evidence of effects).

Recommendation 4: Among patients with Hunner lesions (HLs), fulguration of the lesion, intralesional injection of triamcinolone, or intradetrusor BTX-A ± hydrodistension are conditionally recommended as treatment options (very low certainty in evidence of effects).

Recommendation 5: The panel did not make a recommendation for or against the use of cyclosporin-A (Cy-A) for the treatment of IC/BPS. Furthermore, the panel concluded there was insufficient evidence to determine if a Cy-A has different efficacy or harms among patients with or without HLs.

INTRODUCTION

In 2009, the Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) defined interstitial cystitis/bladder pain syndrome (IC/BPS) as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than six weeks duration, in the absence of infection or other identifiable causes."[1] The current American Urological Association (AUA) guideline[2] on IC/BPS adopted the 2009 SUFU definition, and this guideline will do the same.

Prevalence estimates of IC/BPS vary widely based on the lack of definitive diagnostic tests available and significant overlap with other conditions. Prevalence estimates fluctuate based on study methodology and diagnostic criteria used were estimated to be 1.08%

in women and 0.66% in men in a recent review that combined individual chart abstraction with a national population-based data set review.[3] To date, there appears to be a lack of data regarding the epidemiology of IC/BPS in gender-diverse populations.

Diagnosis & evaluation

A comprehensive history and physical exam are crucial to distinguish typical diagnostic symptoms of IC/BPS from other diseases with overlapping symptoms. Patients often suffer with IC/BPS symptoms for 4–7 years before the diagnosis is made.[4,5] The typical presentation of IC/BPS among adult patients consists of pain perceived to be related to the bladder or urethra, associated with urinary frequency, nocturia, and urgency. The primary symptom of IC/BPS is pain or discomfort, though symptoms may appear gradually or with only one voiding symptom.[6] A discussion of IC/BPS among pediatric patients would be considered beyond the scope of this guideline.

Patients may report feelings of "pressure," "burning," "sharp," or "uncomfortable sensation of having to urinate" instead of overt pain. Although it can be referred to any part of the pelvis, lower abdomen, or back, pain is usually felt in the suprapubic area. It can be helpful to describe the sort of pain, its location, and how long it takes to fill or empty the bladder. Pain may worsen with bladder filling. Individuals may talk about "flares," or times when their symptoms get worse. These can be brought on by certain factors, including stress, sexual activity, menstruation, or dietary factors. Caffeine, alcohol, citrus fruits, tomatoes, carbonated beverages, and spicy foods are common triggers of flare episodes.[7,8]

Frequency is the most prevalent presenting lower urinary tract symptom, accounting for >90% of cases. While also common, the presence of urgency is unable to differentiate between overactive bladder (OAB) and IC/BPS. The main distinction is that OAB patients void out of fear of incontinence, while IC/BPS patients void to reduce pain. OAB is suggested by a positive reaction to antimuscarinics; nevertheless, be aware that the illnesses may coexist and this could complicate the diagnosis.[8-10]

Up to 50% of patients will have had a urinary tract infection (UTI) in the past. A thorough medical history includes information about previous pelvic surgeries or radiation treatments, drugs that can cause cystitis (such as cyclophosphamide, ketamine, and nonsteroidal anti-inflammatory drugs), sexual dysfunction, autoimmune diseases, allergies, and other gynecologic diseases or symptoms (vulvodynia, endometriosis, dyspareunia). Gastrointestinal symptoms (e.g., constipation, diarrhea, pain) are common and should be explored. There is a strong relationship between past traumatic experiences and post-traumatic stress disorder (PTSD) with IC/BPS. Therefore, screening for a history of abuse, in a trauma-informed manner, is essential.[11]

Abdominal and pelvic exam must be part of the physical examination, with special attention paid to searching for masses, bladder distension, hernias, and areas of tenderness. Contributory testing may also include a focused neurologic exam and musculoskeletal exam. Although suprapubic and bladder neck point tenderness are not specific physical findings for patients with IC/BPS, they are frequently observed in both men and women. Palpating the perineal area between the scrotum and the anus in men may identify tenderness; in women, palpating the anterior vaginal wall along the urethra's path up to the bladder neck may elicit pain.

It is crucial to palpate the pelvic floor muscles in both sexes, feeling for trigger points, tight bands, and pain. Prostate characteristics should be recorded. In a study involving 70 women, Peters et al showed a correlation between IC/BPS and pelvic floor dysfunction, with 87% of them reporting pelvic floor muscle pain during pelvic examination.[12] Pudendal nerve entrapment may be suggested by hypo- or hypersensitivity of the perineum combined with a weak or nonexistent anal reflex. A screening exam for vulvodynia, vaginitis, periurethral masses/diverticulum, atrophic changes, and prolapse should be part of the female pelvic exam.

Frequency volume charts help distinguish polyuria from the traditional small voided volumes associated with IC/BPS. The average volume of voiding in a study of 47 adult women with IC/BPS was <100 ml.[13] IC/BPS patients typically void 86–174 ml of urine, as opposed to an asymptomatic woman's average of 289 ml. The average number of daytime voids for IC/BPS patients is 17–25 compared to six for non-IC/BPS patients.[14,15] A frequency volume chart can be used for positive reinforcement associated with behavioral and pharmaceutical interventions, as well as for assessing the severity of the storage symptoms.[16] The measurement of a postvoid residual is advised when there is a history of insufficient emptying and/or the bladder is palpable during the examination.

A urinalysis is the minimum laboratory testing needed. Leukocytes do not necessarily rule in or out IC/BPS. If a UTI is suspected, a culture and sensitivity test are necessary. If sterile pyuria continues, tests may also be considered for mycoplasma, ureaplasma, Corynebacterium species, Candida species, and

Mycobacterium tuberculosis. Gomes et al noted in a cohort of IC/BPS patients that up to 40% of patients with IC/BPS had microscopic hematuria (only 2/60 gross hematuria). In their study, None of the cases were reported to be linked to a potentially lethal urologic condition;[17] however, bladder cancer must be ruled out if hematuria (microscopic or gross) is found, and patients should be appropriately investigated with cystoscopy and upper tract imaging.

The Interstitial Cystitis Symptom Index (ICSI), the Interstitial Cystitis Problem Index (ICPI), and the Genitourinary Pain Index (GUPI) are self-administered symptom questionnaires for IC/BPS that have been evaluated to varying degrees.[18-21] Clinicians should be aware that while the surveys can be useful as diagnostic aids, none have enough specificity to be used as a stand-alone diagnostic instrument. The questionnaires may be used to establish a baseline in terms of symptom severity and monitor response to therapeutic intervention.

The role of a cystoscopy includes ruling out bladder malignancy (or other pathology) in patients with risk factors (e.g., hematuria), identifying Hunner lesions (HLs), assessing the impact of bladder filling on symptoms of pain, objectively evaluating the "functional" bladder capacity, facilitating a suitable pelvic examination, and providing reassurance to the patient. Taking into account all these factors, particularly the fact that HL diagnosis requires direct visualization, the authors recommend routine flexible cystoscopic evaluation in all patients suspected of IC/BPS. Treatment should not be delayed while awaiting cystoscopy in patients with symptoms of IC/BPS.[22]

Older individuals are more likely to have HLs; they may be found in 4% of patients <50 years old, in 20% of patients 50–70 years old, and as high as 55% for those over the age of 70.[23] Reduced urodynamic and anesthetic capacity, as well as more severe symptoms, are linked to HLs.[23-27] It is only after a formal hydrodistension performed under anesthesia that the classic findings of glomerulations can be accurately identified. Evidence, however, indicates that glomerulations are neither specific nor sensitive to IC/BPS.[28]

It is uncommon for bladder cancer to manifest with symptoms that are consistent with IC/BPS. According to Tissot et al, 1% of 600 patients who were referred with an IC/BPS diagnosis also had bladder cancer. All but two of the six cancer patients had microscopic hematuria or positive cytology. The majority were over 60 years of age.[29] Bladder biopsy should be carried out in settings where malignancy is suspected.

Urodynamic studies may be used in certain patients with IC/BPS when the diagnosis is unclear or to guide more invasive treatment options, but are not required for the diagnosis. There are no standard urodynamic criteria for the diagnosis of IC/BPS.

Clinical phenotyping

The concept of clinical phenotyping in urologic chronic pelvic pain was first popularized by Nickel et al among IC/BPS patients when they introduced their UPOINT phenotyping tool in 2009.[30] The NIH-funded Multidisciplinary Approach to Pelvic Pain (MAPP) Network then further explored clinical phenotyping through a comprehensive and thorough characterization of IC/BPS phenotypes[31] further highlighting the importance of this approach.

IC/BPS patients represent such a heterogenous patient population that identifying the clinical phenotype of the patient in front of you is vital. HL patients, for example, will require their own treatment algorithm. Patients with tenderness on pelvic floor examination — the pelvic floor phenotype — will benefit most from pelvic floor physiotherapy. The widespread pain phenotype will often exhibit one or multiple chronic overlapping pain conditions (COPCs), such as fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome, in addition to their bladder pain, and can be challenging to manage.

The best diagnostic tool at our disposal is still the history and physical exam. Recognizing the importance of clinical phenotyping may represent one of the more impactful advancements in terms of treatment of IC/BPS patients to date and should be sought at every encounter. Practitioners should strive for a phenotype-directed approach to treatment; incorporating phenotypes into clinical trial design is regarded as the key to identifying improved treatment options.

METHODOLOGY

The goal of this guideline was to address high-priority questions in the realm of IC/BPS and to aid practitioners in developing an up-to-date clinical approach to the management of IC/BPS. The panel compiled a list of priority questions to be addressed in a systematic manner using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology[32] and evidence-to-decision (EtD) framework.[33] Each question was developed using a PICO (population, intervention, comparison, outcome) format. The detailed PICO format questions are listed in Supplementary Table 1 (available at *cuaj.ca*). The

guideline panel was comprised of six urologists from across Canada who subspecialize in IC/BPS, and two methodologists. Two members of the panel were community urologists.

The GRADE methodology provides a systematic and rigorous approach to gathering, compiling, and interpreting evidence for a given clinical question, resulting in the determination of the level of certainty in the evidence (also known as the quality of the evidence). The certainty in the evidence can be rated as high, moderate, low, or very low. For a question regarding the treatment of diseases, this approach considers evidence arising from a body of randomized trials to represent high certainty and evidence from a body of observational studies to represent low certainty. These levels can be further rated down for methodologic limitations (risk of bias, inconsistency, imprecision, indirectness, and publication bias) or rated up in select circumstances (for high magnitude of effect and direction of plausible confounders).[34-39]

Following determination of the certainty in the effect of any given treatment, EtD framework puts forth clear areas of consideration for the panels to deliberate when formulating a recommendation. These areas include desirable effects, undesirable effects, certainty of evidence, values, balance of effects, resources required, cost-effectiveness, equity, acceptability, and feasibility. Recommendations are then framed as either for or against an intervention compared with a standard in a specific population. Recommendations can either be strong or conditional, largely depending on the quality of evidence and the balance between desired and undesired effects.

Interpreting recommendations

A strong recommendation implies that the guideline panel believes the vast majority of the patients would opt for the recommended treatment (or the comparator) when sufficiently informed about the benefits and risks of the treatment. More commonly, a conditional recommendation is made when the panel believes most of the patients would opt for the recommended course of action; however, a substantial minority of patients would choose the alternative. Therefore, it is crucial for the practitioner to focus on shared decision-making and informing the patient of the available evidence prior to making a decision.[40]

The panel identified five main areas of interest to the guideline. Corresponding clinical questions were formulated within those areas and were updated through the process by iterative panel discussions to arrive at the final questions. In addition, the panel identified the outcomes that were critical to decision-making for the areas of interest.[41] Notably, the area of intravesical cocktail could not be addressed systematically, given the variability of interventions and lack of evidence. In turn, the evidence was summarized narratively, and the recommendations were made having the EtD framework in mind. The clinical questions of interest are listed in Table 1.

It is important to recognize that the panel did not set out a priori to create a treatment-based guideline. Without guidance or instruction, the panel reached consensus and the questions rated highest in importance all happened to be treatment-related.

To synthesize the evidence, the panel identified the most comprehensive and most recent systematic reviews addressing the questions of interest and additional studies not included in the reviews. The original studies included from the reviews were assessed for eligibility and risk of bias. The data was then pooled de novo using direct comparison meta-analysis and certainty in the evidence was determined. The forest plots and summary of findings tables were created using STATA software and GRADEPro online software.[40-42] The panel then reviewed the evidence during online meetings and voted on each domain of the EtD framework and achieved final recommendation through consensus.

For the narrative section of the guideline, the panel members, who are experts with extensive experience on the subject and familiarity with the evidence, narratively reviewed the literature and summarized the accepted approach to this disease. Systematic evaluation of the evidence, as described above, was not conducted for this section of the guideline.

Table 1. Clinical questions of interest

1. Is oral pentosan polysulfate (Elmiron) indicated for the treatment of IC/BPS?
2. What is the optimal intravesical cocktail for treatment of IC/BPS?
3. Is intradetrusor onabotulinumtoxin-A indicated for the treatment of IC/BPS?
4. What is the optimal treatment modality for treating Hunner lesion-IC/BPS?
5. Is oral cyclosporin A indicated for the treatment of IC/BPS?

IC/BPS: interstitial cystitis/bladder pain syndrome.

GUIDELINE RECOMMENDATIONS

Is oral pentosan polysulfate (Elmiron) indicated for the treatment of IC/BPS?

■ RECOMMENDATION 1

Among patients with IC/BPS the panel conditionally recommends against the use of oral pentosan polysulfate (PPS) as compared to standard of care *(low certainty in evidence of effects).*

Note: The panel judged that the magnitude of benefit of PPS was trivial, and harms were infrequent but serious. The panel placed a higher importance on avoiding vision-threatening pigmentary maculopathy and high cost, and a lower importance on the modest benefit of PPS.

Oral PPS is the only oral medication approved by both the FDA and Health Canada for the management of IC/BPS. This synthetic polysaccharide compound has a molecular structure similar to glycosaminoglycans. Its mechanism of action in IC/BPS is through adherence to bladder mucosal cells, where it buffers cellular permeability and protects the bladder urothelium from irritants.

Several randomized controlled trials (RCTs)[43-47] and network meta-analyses[48,49] were identified comparing oral PPS to placebo or cyclosporin A or hydroxyzine, reporting contradictory results. As six RCTs provided a total of 1000 study participants from which to draw evidence, observational trials on PPS were not used. The majority of RCTs were small, with five reporting on less than 100 patients. Most studies were also limited due to the short duration of followup, with a mean of six months. The majority of pairwise comparisons in the network had considerable heterogeneity, but the results of closed-loop direct and indirect comparisons were mostly consistent. The definition of symptom improvement varied among the included trials. Summary of findings tables are presented in the Appendix (available at *cuaj.ca*).

Based on an analysis of three RCTs comparing oral PPS to placebo, the results suggest only 65 more (95% confidence interval [CI] 39 fewer–181 more) patients would experience symptom improvement out of every 1000 IC/BPS patients treated, with an odds ratio (OR) of 1.34 (95% CI 0.83–2.15). Importantly, the definitions of symptom improvement varied among these three studies. A single RCT reported on the outcome of ICSI and ICPI scores and found a mean difference from baseline of only 0.6 points and 0.4 points, respectively. Given the total ICSI score ranges from 0–20, and the ICPI score from 0–16, the panel considered a mean difference change of 0.6 and 0.4, respectively, to be clinically insignificant (Supplementary Table 2A; available at *cuaj.ca*).

A 2020 Cochrane systematic review and network meta-analysis also found that oral PPS, when compared to placebo, did not result in significant symptomatic improvement (OR 1.14, 95% CI 0.40–3.35) or reduction of pain (mean difference [MD] 0.42, 95% CI -1.04–1.91)[48] (Supplementary Table 2B; available at *cuaj.ca*).

The side effects of oral PPS include diarrhea, headache, nausea, pelvic pain, abdominal pain, nasopharyngitis, sinusitis, UTI, dizziness, and alopecia. Health Canada has recently issued a safety alert advising the risk of pigmentary maculopathy with prolonged PPS therapy.

PPS EXPOSURE AND VISION-THREATENING PIGMENTARY MACULOPATHY

Recent studies have linked prolonged PPS therapy with a vision-threatening maculopathy. This was first reported in 2018[50] and now corroborated in larger studies, suggesting a strong drug-disease association.[51-53]

The chronicity of PPS exposure seems to play a role, as affected patients report average cumulative dosages of 1000–2000 g over 10–15 years of exposure. Cross-sectional studies demonstrate evidence correlating cumulative dosing and the likelihood/severity of toxic retinopathy.[54] One study demonstrated that those with >1500 g of exposure were nearly five times as likely to have PPS maculopathy (OR 4.91, 95% CI 1.6–14.7) compared to those with 500–999 g cumulative exposure.[55]

It remains unclear if there is a minimum cumulative exposure required to develop PPS maculopathy; in one case, characteristic symptoms and diagnostic features developed with a cumulative dose of 435g.[56] There is also evidence to suggest that the daily dose of PPS may influence the risk of developing macular changes; a low daily dose may be tolerated in long-term PPS users.[55,57] The estimated prevalence rate is 20–23% among patients with >3–5 years exposure with standard daily doses of approximately 300 mg daily[53, 54] or 13% in those with 500–999 g cumulative exposure.[55]

Affected patients with PPS maculopathy typically report difficulty with reading, slow adjustment to low or reduced light environments, and blurred or wavy vision.[50,55] Most reported cases are predominately women, with variable age range of 30–70 years.

Multimodal retinal imaging (involving fundus photography, fundus autofluorescence, optical coherence tomography, and near-infrared reflectance) demon-

strates a distinctive clinical phenotype with the retinal pigment epithelium (RPE) and RPE-photoreceptor interface. In some cases, progressive RPE atrophy encroaches on the foveal center and may pose a long-term threat to central vision.[55] Visual acuity is not a sensitive measure of visual dysfunction, as it remained relatively preserved even in patients with signs of toxicity, except in advanced cases with center-involved atrophy, macular edema, or choroidal neovascularization.[51,58]

The mainstay of management is advising drug cessation. Importantly, patients should be warned that PPS-induced maculopathy can continue to progress despite PPS cessation. In a retrospective case series involving 11 patients with PPS-associated maculopathy and median cumulative PPS exposure of 1970 g, there was no evidence of disease regression in any eye following drug cessation. Rather, prospective retinal imaging demonstrated expansion of the area of involvement, suggesting PPS-associated maculopathy continues to evolve after drug cessation for at least 10 years.[55]

Caution is advised, as the true prevalence of PPS-associated maculopathy in the generalized population taking PPS is difficult to ascertain. PPS was widely prescribed as a mainstay of IC/BPS therapy for many years, and pre-symptomatic disease may not be easily detectable without implementation of formal retinal screening protocols. On the other hand, the current literature base may be subject to selection and screening biases, potentially overestimating reported prevalence rates. All studies to date have been retrospective, and a causative relationship has not been established. Further research is required to refine ideal screening protocols.

On December 15, 2020, Health Canada issued a safety alert warning to healthcare professionals regarding long-term use of PPS and risk of pigmentary maculopathy. (https://recalls-rappels.canada.ca/en/alert-recall/elmiron-pentosan-polysulfate-sodium-and-risk-pigmentary-maculopathy). PPS is now contraindicated in patients with a personal history of any macular pathology. Prescribers are advised to assess the risk and benefits before initiating PPS and to obtain baseline ophthalmologic history and retinal exams before starting treatment. Regular retinal exams are advised thereafter for early detection of macular pathology. Patients should be counseled to report changes in vision, such as difficulty reading, slow adjustment to low or reduced light, and blurred vision, including blurry or wavy vision near or in the centre of the field of vision.

Many practitioners have already been approached by legacy PPS patients seeking advice and many more are likely to come forward as concerns regarding PPS use continue to disseminate. There is no evidence to support a weaning protocol for legacy patients; however, the guideline panel suggests the following steps **for weaning legacy patients off oral PPS:**

1. Inform the patient of the perceived risk based on observational data (Table 2).
2. Engage in shared decision-making regarding the choice to continue therapy or not. Patients opting to remain on oral PPS should seek referral for consideration of baseline ophthalmologic assessment.
3. If a patient opts to discontinue the medication, use a weaning schedule that would be considered reasonable (e.g., a patient on 100 mg orally three times daily might follow twice daily x four weeks, then daily x four weeks, then discontinuing altogether).
4. Follow the patient closely for worsening of symptoms or symptom flares during wean and be prepared to offer alternative treatment options using a symptom phenotype-directed approach.

Table 2. Suggestions for informed consent regarding use of oral PPS

Patients counseled on the risks and benefits of PPS, and informed that PPS therapy involves a potential risk of permanent vision loss. A causative link has not been established, but the observational data highlighting an association is concerning.
PPS is contraindicated in patients with a history of any macular pathology.
The safe dosage, duration of therapy, and cumulative dosage limits remain unknown with respect to risk of maculopathy.
Presymptomatic disease may not be detectable in the absence of formal retinal screening procedures.
Vision-threatening maculopathy is likely to progress even after the drug is stopped.
PPS prescribing physicians should be aware of the high risk of retinal toxicity and maculopathy as cumulative dosages approach ≥ 1000 g.[59]
Patients opting for oral PPS should seek a referral for consideration of baseline ophthalmological assessment.
Any patient with vision changes and any degree of exposure to PPS should be evaluated by an ophthalmologist promptly.[60]

PPS: pentosan polysulfate.

What is the optimal intravesical cocktail for the treatment of IC/BPS?

■ RECOMMENDATION 2

Based on the available literature, it is not possible to recommend one intravesical agent, or combination of agents, over another for the treatment of IC/BPS. *Note: This highlights an important limitation in treating patients with IC/BPS using intravesical cocktails. While commonly done in practice, the evidence to support a specific intervention over another is poor.*

Multiple agents have been studied as intravesical treatment options for IC/BPS. Often these agents are combined into cocktails to achieve maximum symptomatic relief. Previous Canadian Urological Association (CUA)[61] and AUA guidelines[2] have recommended intravesical therapy as an option for the treatment of IC/BPS. Historically, heparin, dimethyl sulfoxide (DMSO), and lidocaine have commonly been used for intravesical therapy alone or in combination. Resiniferatoxin and bacillus Calmette-Guérin have been found to be ineffective and are no longer recommended. Several other agents have been studied, including hyaluronic acid (HA), chondroitin sulfate (CS), oxybutynin, PPS, triamcinolone, and bupivacaine. We sought to review RCTs evaluating the role of intravesical therapy for IC/BPS and to apply the GRADE framework for this guideline. The primary goal was to determine the optimal intravesical therapy for IC/BPS patients.

Initially, we attempted a comparison between RCTs looking at HA and CS.[62-66] Unfortunately, it was determined that due to the variability in study design, intravesical cocktails used, small numbers of participants, and inconsistent outcomes measured in each trial, it was impossible to make meaningful statements or ranking of preference for these interventions. The committee elected to provide background by completing a narrative review of commonly used intravesical cocktails.

Heparin

Heparin is thought to function as a glycosaminoglycan (GAG) analogue to help restore the lining of the urothelium. Previous non-randomized studies exist showing a symptomatic improvement in 56–73% of patients at three months with minimal side effects.[67,68] Parsons et al completed a placebo-controlled crossover trial comparing a cocktail consisting of 50 000 units of heparin, 200 mg of lidocaine hydrochloride, and 420 mg of sodium bicarbonate to a control of 420 mg of sodium bicarbonate in 18 patients. The mean reduction in pain 12 hours after instillation was 42% compared to 21% in favor of treatment (p=0.04). Urinary urgency was also reduced, 35% compared to 13% for the control group (p=0.33).[69]

In 2015, a pilot crossover study in 14 patients compared 50 000 units of heparin with 200 mg of lidocaine to 200 mg of lidocaine alone and found a significant reduction in bladder pain (38% vs. 13%, p=0.03) and urgency (42% vs. 8%, p<0.01).[70]

More recently, Moss et al completed a prospective RCT comparing 50 cc of DMSO and 10 mg of triamcinolone to a cocktail of 30 cc of 0.5% bupivacaine, 20 mg of triamcinolone, and 20 000 units of heparin (BTH group) over six weekly sessions. Data on 70 patients revealed that 63% of the DMSO group compared to 43% of the BTH group had a >30% reduction in ICSI score, which was statistically insignificant (p=0.15). Nocturia and pain were improved in the DMSO group, and both groups had an increase in bladder capacity. Three patients withdrew due to discomfort from instillations and one developed UTIs.[71]

DMSO

DMSO is an organic solvent with anti-inflammatory and analgesic properties. It is an FDA-approved intravesical treatment for IC/BPS that has been used for over 40 years. Several small RCTs have demonstrated improvement in IC symptoms with DMSO. Perez-Marrero reported a 93% objective improvement and 53% subjective improvement compared to 35% and 18%, respectively, in controls.[72] Gallego-Vilar randomized patients to DMSO cocktail (DMSO, heparin, hydrocortisone, sodium bicarbonate) vs. DMSO cocktail plus hyperbaric oxygen (HBO). Fourteen of the 20 patients who received DMSO experienced an improvement in pain, frequency, nocturia, and urgency. Those who received HBO in addition to DMSO (10/20) had a more substantive and prolonged effect of DMSO.[73]

A recent, multicenterr, placebo-controlled RCT compared 50% DMSO (n=49) to placebo (n=47). DMSO resulted in a statistically significant difference in change in ICSI score from baseline to week 12 compared to placebo (difference between groups -1.5 (95% CI -3.3 to -0.3, p=0.02). DMSO also improved ICPI score, frequency, volume voided, pain, and global assessment score, compared to placebo.[74] See section above entitled "Heparin" for details regarding the Moss et al study that showed DMSO as more effective than the compared cocktail.[71]

Lidocaine

Several studies have included lidocaine as part of an intravesical cocktail for the treatment of IC/BPS, as described in both sections above. Intravesical lidocaine may be of therapeutic benefit for symptomatic flares of IC/BPS,[67,75] and also when confirming that a patient's pelvic pain is indeed bladder centric. In a phase 2, multicenter RCT of 102 patients, Nickel et al reported a significant improvement in symptoms compared to placebo after a five-day course of buffered lidocaine (PSD597) (30% vs. 10%, p=0.01). This improvement was not sustained on evaluation at 10 days of followup (24% vs. 12%, p=0.10).[76]

Hyaluronic acid and chondroitin sulfate

Observational studies have suggested the benefit of both intravesical CS and HA.[77,78] Two small RCTs compared intravesical 2% CS to placebo.[62] The early study of 65 patients found a non-statistically significant difference between treatment and control arms (39% vs. 23%, p=0.15). A second, well-designed study of 95 patients also failed to identify a statistically significant difference in Global Response Assessment (GRA) or ICSI scores at 11 weeks (38% vs. 31%, p=0.48).[63]

Chondroitin sulfate 2% was compared to DMSO 50% in 36 patients. More patients in the CS group reported a moderate or marked improvement in symptoms (73% vs. 14%, p<0.01); however, in this small study, 57% withdrew consent in the DMSO group and 27% withdrew consent in the CS arm. The trial was stopped due to the high number of DMSO dropouts.[79]

Gulpinar et al randomized 42 patients to 120 mg/50 ml sterile sodium HA or 80 mg/40 ml sodium CS in a head-to-head comparison study. At six months, both groups had a statistically significant reduction in pain compared to baseline (p<0.05). There was no statistically significant difference between treatment arms for the primary outcome and there was no control group.[65]

Recently, Ozkidik et al randomized 72 patients to receive either HA 120 mg/50 ml, CS 80 mg/40 ml, or a combination of half a dose of each of HS and CS. All groups had a significant improvement in the primary outcome of health-related quality of life (HRQoL). Combination therapy was superior to both monotherapies for improving HRQoL (p=0.02).[64] This was also not a placebo-controlled study.

Cervigni et al studied a combination of HA (1.6%)/CS (2.0%) compared to DMSO 50% in a randomized, open-label, multicenter study of 110 women. A significant reduction in pain was found at six months in both treatment arms compared to baseline (p<0.001). HA/CS resulted in a non-statistically significant greater mean pain reduction compared to DMSO (-8.03, 95% CI -17.95–1.88, p=0.11) There was no significant difference in adverse events between treatment arms. DMSO was also found to be slightly more costly.[66]

Triamcinolone

Triamcinolone is a corticosteroid used for a variety of medical indications. It has been studied as an intravesical instillation for IC/BPS. In addition to the study by Moss et al mentioned above, Cardenes-Trowers randomized 90 women with IC/BPS to receive a cocktail instillation (10 000 units of heparin, 2% lidocaine, 8.4% sodium bicarbonate) plus 40 mg of triamcinolone vs. cocktail instillation alone for six treatments. Both groups had symptom improvement from baseline based on the change in O'Leary-Sant Questionnaire (triamcinolone -6.7 pts vs. control -5.8 pts); however, there was no significant difference between groups, indicating no additional benefit of triamcinolone (p=0.31).[80] Although unlikely to be harmful, to date, there is not enough evidence to support the routine use of triamcinolone as an intravesical therapy for IC/BPS.

Pentosan polysulfate

Three small RCTs have evaluated the role of intravesical PPS. Bade et al compared 300 mg of PPS in 50 cc of 0.9% sodium chloride (n=10) to placebo (n=10) twice a week for three months. Forty percent in the treatment group compared to 20% in the placebo group reported symptomatic improvement, which was not statistically significant.[81] Davis et al randomized 40 patients to intravesical PPS (200 mg in 30 cc saline) + oral PPS (200 mg twice daily) compared to intravesical saline + oral PPS (control). Intravesical PPS resulted in a significantly greater decrease in ICSI and ICPI scores (approximately 46% vs. 24% reduction, p=0.04).[82]

To date, there are no reports of pigmentary maculopathy resulting from the intravesical use of PPS.

Oxybutynin

Over 20 years ago, one small RCT compared bladder retraining with intravesical oxybutynin to intravesical saline via an indwelling catheter over a six-month period. Patients who underwent oxybutynin instillations had an improvement in bladder capacity, frequency, and quality of life scores compared to those treated with saline instillations.[83]

Summary
A variety of agents, at variable dosages and combinations, have been studied for the treatment of IC/BPS. Based on small, heterogeneous studies, it appears that intravesical therapy provides a marginal benefit in some patients with IC/BPS. Patients with a bladder-centric phenotype or whose bladder pain is particularly bothersome may benefit the most from this treatment approach. Intravesical therapy appears safe with minimal risk. Access to intravesical therapy may be limited in some centers due to hospital pharmacy restrictions and nursing resources.

Is intradetrusor onabotulinumtoxin-A (BTX-A) indicated for the treatment of IC/BPS?

■ RECOMMENDATION 3

Intradetrusor BTX-A, with or without hydrodistension, is conditionally recommended as an option for the treatment of IC/BPS patients refractory to other treatments *(very low certainty in evidence of effects).*

Note: The panel judged BTX-A to have a small magnitude of benefit and a small magnitude of harm, the balance of which probably favors the intervention in the context of important uncertainty in patient values and preferences. This underscores that the decision to proceed with BTX-A should be sensitive to patient values and preferences. The panel's opinion is that this approach may be more effective in a patient population that has more bothersome urgency and frequency, but the ideal population remains suboptimally defined.

BTX-A is a bacterial neurotoxin acting as a neuromuscular blocking agent and inhibiting the release of acetylcholine from presynaptic nerve fiber endings. It is currently indicated for the treatment of various disorders, including OAB, but remains off-label for the IC/BPS indication.

The panel reviewed seven small RCTs providing a total of 291 participants from which to draw evidence.[84-89] Observational studies were not included. Most studies were limited due to short duration of followup, with a mean of 4.7 months. It is difficult to comment on the effect of BTX-A alone, as all studies, except one, combined BTX-A with hydrodistension (HD). All treatment regimens were with 100 units except a subgroup from Kuo et al (15 patients treated with 200 units)[84] and Manning et al, who used 500 units of abobotulinumtoxin-A.[85] Additionally, there was variation in the technique of BTX-A injection across studies.

Small improvements in pain (assessed via visual analogue scale, [VAS]) (MD 0.6, 95% CI 1.3 lower to 0.2 higher), ICSI (MD 1.6, 95% CI 3.0 lower to 0.3 lower), and ICPI (MD 1.7, 95% CI 3.0 lower to 0.4 lower) symptom scores were observed for patients treated with BTX-A compared to control (HD or placebo) based on the panel's pooled analysis; however, uncertainty remains whether BTX-A results in little vs. no difference in pain in this patient population. It is worth mentioning that a potential increase in bladder capacity with BTX-A was not well-captured across studies and could potentially contribute to the overall clinical improvement IC/BPS patients may experience. Therefore, no absolute indication in favor of its efficacy can be assumed considering the paucity of data, risk of bias, and heterogeneity of study designs.

In terms of adverse events (AEs), the pooled results of three RCTs found that 39 more patients receiving BTX-A, compared to control, would experience acute urinary retention out of every 1000 IC/BPS patients (relative risk [RR] 1.56, 95% CI 0.44–5.53). Based on four RCTs, UTI would occur in 42 more patients receiving BTX-A, compared to control, out of every 1000 IC/BPS patients (RR 1.34, 95% CI 0.60, 3.02). Other known potential AEs include transient, mild gross hematuria, injection site pain, and flu-like symptoms (Supplementary Table 3; available at *cuaj.ca*). It should be highlighted that acute urinary retention requiring clean intermittent catheterization (CIC), although rare, may be quite troublesome in patients with IC/BPS due to their underlying pain. A thorough conversation about the possibility of needing to CIC should be undertaken. In some situations, it may be appropriate to teach patients how to do CIC in case it is needed post-injection of BTX-A.

Despite moderate resource requirements, short-term durability, and the need to appropriately counsel patients with regard to the possibility of self-catheterization, the panel deemed that it is acceptable and feasible to offer this as a treatment option, while emphasizing the need for further multicentric RCTs with prospective comparison and longer followup. In addition, studies should focus on eliciting the most effective technique for the administration of BTX-A injections. A multicenter, placebo-controlled RCT had completed accrual, with data collection ongoing at the time of publication (NCT05141006) and should provide important insight into this question.

What is the optimal treatment modality for treating Hunner lesion-IC/BPS?

■ RECOMMENDATION 4

Among patients with HLs, fulguration, intralesional injection of triamcinolone, or intradetrusor BTX-A ± HD are conditionally recommended as treatment options *(very low certainty in evidence of effects).*

Note: Due to the paucity of direct comparisons, the panel could not rank these interventions by preference. The panel's judgment of benefits and harms suggests that fulguration, intralesional injection of triamcinolone, and intradetrusor onabotulinumtoxin-A ± HD results in a similar improvement in pain and symptom scores with lower morbidity than transurethral resection (TUR). TUR may be preferred for cases where the diagnosis is unclear and malignancy is suspected.

Hunner lesions, described as a rare type of bladder lesion with an appearance of patches of red mucosa with small vessels radiating to a central pale scar, are more common in older patients. Deep phenotyping studies performed by MAPP noted a prevalence of 4% in IC/BPS in those <50 years old, and up to 55% in those >70 years old.[23] To date, the pathophysiology of HLs is unclear. IC/BPS patients with HLs typically present with more frequency, nocturia, higher ICSI scores, and are older when compared to patients without HLs.[91] The presence of HLs has been recognized as its own distinct phenotype[92] with a specific set of treatment recommendations.[2]

Patients with HLs may endure more favorable treatment responses than those without.[27] Therefore, **it is imperative to identify the presence of HLs via cystoscopy**. Treatment options for the HL phenotype may include lesion fulguration, triamcinolone injection into lesion, intradetrusor BTX-A injection, and oral cyclosporin-A. In some refractory cases, reconstructive surgery is indicated.

In this guideline, we sought to identify the optimal treatment modalities for the HL-IC/BPS phenotype. We found that the data available compared these treatments to no treatment in only uncontrolled, observational studies. One RCT compared TUR of HLs to fulguration. We summarize our findings on the pain and ICPI/ICSI outcomes in Supplementary Table 4 (available at *cuaj.ca*) and attempt a comparison of the available treatment modalities.

Fulguration

Analysis of observational studies found that pain (VAS) was significantly improved with fulguration compared to no treatment (MD -5.7, 95% CI -6.8 to -4.6). ICPI and ICSI scores were also improved with fulguration compared to no treatment (ICPI MD -9.6, 95% CI -12.2 to 7.0; ICSI MD -7.9, 95% CI -10.7 to -5.1).

Transurethral resection

Hunner lesions should undergo biopsy to rule out ominous pathology such as malignancy. Transurethral resection of the entire lesion has been studied as a therapeutic approach. In observational studies, pain was significantly improved with TUR alone (MD -7.8, 95% CI -7.9 to -7.7, n=218) and TUR with HD, as compared to no treatment (MD -8.4, -8.52 to 8.28, n=44). There was insufficient data to determine the effect on ICPI/ICSI scores TUR ± HD.

In one RCT, the efficacy and safety of TUR and fulguration were compared in 126 patients.[93] There were no differences in the recurrence-free time between treatment groups. Recurrence-free time was 12.2 months (95% CI 11.1–17.6) in those undergoing TUR compared to 11.5 months (95% CI 9.0–16.1) in the fulguration group (p=0.7). There were no significant differences in overall improvement in pain, ICSI, or ICPI at 12 months of followup. Both groups demonstrated significant improvement in all outcomes compared to prior treatment (all p<0.05); however, those undergoing TUR experienced a greater than two-fold higher rate of complication, with bladder injury occurring in 7.9% of the TUR group compared to 3.4% of the fulguration group.

Triamcinolone injection

Pain was significantly improved with triamcinolone injections as compared to no treatment in two observational studies (n=372, MD -2.8, 95% CI -6.13 to 0.53).[94,95] There was insufficient data to determine the effect on ICPI/ICSI scores for triamcinolone.

Intradetrusor onabotulinumtoxin-A

In one small, observational study, pain was significantly improved with intradetrusor BTX-A compared to no treatment (n=20, MD -3.4, 95% CI -4.4 to -2.4).[96] ICPI and ICSI scores following BTX-A treatment were both improved compared to no treatment (n=20; MD -5.9, 95% CI -6.9 to -4.9 for ICPI; MD -6.6, 95% CI -8.2 to -5.0 for ICSI).

Cyclosporin-A

See section below, "Is oral cyclosporin-A indicated for the treatment of IC/BPS?" for a discussion on the evidence for oral cyclosporin-A in both HL and non-HL-IC/BPS patients.

Is oral cyclosporin-A indicated for the treatment of IC/BPS?

■ RECOMMENDATION 5

The panel did not make a recommendation for or against the use of cyclosporin-A (Cy-A) for the treatment of HL-IC/BPS. The panel concluded that there was insufficient evidence to determine if Cy-A has different efficacy or harms among patients with HL or without HL.

Note: The panel considered the observed treatment effect moderate in both phenotypes, which was balanced with a moderate risk of undesirable effects. The AEs, particularly hypertension and renal dysfunction, were judged by the panel to be clinically important AEs, despite low observed rates. The panel recognizes that some practicing urologists in Canada use oral Cy-A as part of their treatment options for refractory IC/BPS patients. In general, the panel believes this therapy can be offered in settings with an adequate infrastructure for close monitoring of medication levels and side effects. A clinician's decision to use Cy-A must be made through shared decision-making with the patient, balancing the potential for modest benefit with risk of harm.

Cyclosporin-A is a calcineurin inhibitor used primarily in the transplant population and in a collection of autoimmune, inflammatory conditions, that primarily exerts immunosuppression via T-cell pathways.[97] Although it has been used in the IC/BPS population with some benefit for several years, as with most treatments for the disease, its evidence base in the IC/BPS space is poor. A single 2005 RCT has evaluated oral Cy-A vs. oral PPS among 64 participants,[98] while retrospective, uncontrolled observations make up most of the remaining evidence base.

The 2022 AUA guideline offers oral Cy-A treatments as an "option," supported with evidence strength "Grade C," "particularly" among patients with HLs.[2] The focus on HL patients is reasonable, given its mechanism of action and presumption that HL-IC/BPS may represent a particularly inflammatory phenotype of the disease.

In 2012, Forrest et al reported their retrospective series of 44 IC/BPS patients followed at three separate centers — overall, 34 with HLs and 10 without — treated with oral Cy-A with a mean followup ranging from 15 months up to 30 months.[99] Patients were considered responders if they experienced a 50% GRA improvement or at least a 50% improvement in total ICSI score. A higher response rate was noted among HL participants, with 23 of 34 responders, while only three of 10 non-HL-IC/BPS participants met the criteria for response. Observed AEs included cutaneous lymphoma, renal dysfunction, hypertension, alopecia, ulcers in the mouth, and gout; up to half of participants reported an AE. The study was not powered to show a difference in effect among IC/BPS phenotypes. In fact, this comparison of Cy-A efficacy among IC/BPS phenotypes has never been evaluated a priori.

Our panel attempted to evaluate the evidence base for oral Cy-A among IC/BPS phenotypes — those with HLs and those without — separately. In addition to the RCT[98] (included both HL-IC/BPS and IC/BPS patients without HLs) and observational study[99] (included both HL-IC/BPS and non-HL-IC/BPS patients but also included detailed data on the HL patients) previously discussed, an additional observational study was identified that evaluated Cy-A among 51 patients with HL-IC/BPS.[100] Among those 37 patients who completed the study, there was a mean followup of three years. Thirty-one of 37 (84%) participants were either moderately or markedly improved, with a decreased ICSI (8.9±5.7) compared to non-responders (21.3±7.0, p=0.001). Adverse event data was limited; however nine patients reported new or worsening hypertension after starting Cy-A treatment. The panel concluded there was insufficient evidence to make a Cy-A recommendation stratified on IC/BPS phenotype.

CONCLUSIONS

IC/BPS remains a challenging condition to treat, with a poor evidence base upon which to make our clinical decisions. For the purpose of this guideline, we selected five clinically relevant questions to evaluate using GRADE methodology. For the benefit of our readership, we also endeavored to provide more general background information to illustrate the usual care of patients with IC/BPS.

Overall, high-quality data to support many of the therapeutic options for IC/BPS is still lacking. This posed challenges when trying to make guideline recommendations. Notably, all recommendations made are conditional, which implies that the emphasis of clinical care should be on shared decisions with our patients and that the "best treatment" will primarily reflect our patients' values and preferences about the benefits and harms of a given therapy.

Conditional recommendations also imply that new, high-quality evidence is more likely to change the balance of desirable and undesirable effects and future guideline recommendations. In this way, the limitations

identified through the systematic process of producing this guideline can help direct future research efforts to provide better support for the treatments we offer our patients with IC/BPS.

COMPETING INTERESTS: Dr. Doiron has received research grants from Immunotek and Redleaf Medical. Dr. Andrews has been an advisory board member for Abbvie. Dr. Nadeau has been an advisory board member for Allergan/Abbvie, Astellas, and Hollister; has given talks supported by Allergan/Abbvie, Astellas, Laborie Pfizer, and Searchlight Pharma; and has received research grants from Searchlight Pharma/Boston Scientific. Dr. Cox has been an advisory board member and speaker for Abbvie. Dr. Nguyen has been an advisory board member for Allergan and Astellas; a speaker for Astellas; and has received grants and/or honoraria from Allergan, Astellas, and Pfizer. Dr. Nickel has been a consultant for Inmunotek, OM Pharma, and Redleaf Medical; has received honoraria from Immunotek (received vaccine Uromune "in kind" from Inmunotek for clinical trial); and has participated in clinical trials supported by Inmunotek (MV140 First in North America Study with "in kind' support from Inmunotek) and MIcroGenDx (urinary microbiome study); all support "in kind" (Dr. Nickel or his institution did not receive direct financial support). The remaining authors and reviewers do not report any competing personal or financial interests related to this work.

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