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### Guidelines

# Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome (2022)

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The purpose of this clinical guideline is to provide a clinical framework for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome (IC/BPS), including discussion of treatments that should and should not be offered.

[Unabridged version of this Guideline \[pdf\]](#)

[Interstitial Cystitis JU Summary Algorithm](#)

## Panel Members

Philip M. Hanno, David Allen Burks, J. Quentin Clemens, Roger R. Dmochowski, Deborah Erickson, Mary Pat FitzGerald, John B. Forrest, Barbara Gordon, Mikel Gray, Robert Dale Mayer, Robert Moldwin, Diane K. Newman, Leroy Nyberg Jr., Christopher K. Payne, Ursula Wesselmann, Martha M. Faraday; H. Henry Lai, Norma Varela, PhD.

## Executive Summary

Amended 2014; Amended 2022

# Purpose

The purpose of this Guideline is to provide a clinical framework for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome.

## Methods

A systematic review of the literature using the MEDLINE® database (search dates 1/1/83-7/22/09) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of IC/BPS. The review yielded an evidence base of 86 treatment articles after application of inclusion/exclusion criteria. The AUA update literature review process, in which an additional systematic review is conducted periodically to maintain guideline currency with newly-published relevant literature, was conducted in July 2013. The 2013 review identified an additional 31 articles relevant to treatment. An update literature review in 2022 (search dates: 06/2013 – 01/2021) identified 63 studies, 53 of which were added to the evidence base. These publications were used to create the majority of the treatment portion of the guideline. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate), or C (low). Additional treatment information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed. See text and algorithm for definitions and detailed diagnostic, management, and treatment frameworks.

## Guideline Statements

### Diagnosis

1. The basic assessment should include a careful history, physical examination, and laboratory examination to document symptoms and signs that characterize IC/BPS and exclude other disorders that could be the cause of the patient's symptoms. . *Clinical Principle*
2. Baseline voiding symptoms and pain levels should be obtained in order to measure subsequent treatment effects. *Clinical Principle*
3. Cystoscopy and/or urodynamics should be considered when the diagnosis is in doubt; these tests are not necessary for making the diagnosis in uncomplicated presentations. *Expert Opinion*
4. Cystoscopy should be performed in patients in whom Hunner lesions are suspected. *Expert Opinion*

### Management Approach

5. Treatment decisions should typically be made after shared decision-making, with the patient informed of the risks, potential benefits, and alternatives. Except for patients with Hunner lesions (Statement 19), initial treatment should be nonsurgical. *Expert Opinion*
6. Efficacy of treatment should be periodically reassessed and ineffective treatments should be stopped. *Clinical Principle*
7. Multimodal pain management approaches (e.g., pharmacological, stress management, manual physical therapy if available) should be initiated. Pain management should be continually assessed for effectiveness because of its importance to quality of life. If pain management is inadequate, then consideration should be given to a multidisciplinary approach and the patient referred appropriately. *Clinical Principle*
8. The IC/BPS diagnosis should be reconsidered if no improvement occurs after multiple treatment approaches. *Clinical Principle*

### Treatment Categories for IC/BPS

#### Behavioral/Non-pharmacologic Treatments

9. Patients should be educated about normal bladder function, what is known and not known about IC/ BPS, the benefits versus risks/burdens of the available treatment alternatives, the fact that no single treatment has been found effective for the majority of patients, and the fact that acceptable symptom control may require trials of multiple therapeutic options (including combination therapy) before it is achieved. *Clinical Principle*
10. Self-care practices and behavioral modifications that can improve symptoms should be discussed and implemented as feasible. *Clinical Principle*

11. Patients should be encouraged to implement stress management practices to improve coping techniques and manage stress-induced symptom exacerbations. *Clinical Principle*
12. Appropriate manual physical therapy techniques (e.g., maneuvers that resolve pelvic, abdominal and/or hip muscular trigger points, lengthen muscle contractures, and release painful scars and other connective tissue restrictions), if appropriately trained clinicians are available, should be offered to patients who present with pelvic floor tenderness. Pelvic floor strengthening exercises (e.g., Kegel exercises) should be avoided. *Standard (Evidence Strength: Grade A)*

## Oral Medications

13. Clinicians may prescribe pharmacologic pain management agents (e.g., urinary analgesics, acetaminophen, NSAIDs, opioid/non-opioid medications) after counseling patients on the risks and benefits. Pharmacological pain management principles for IC/BPS should be similar to those for management of other chronic pain conditions. *Clinical Principle*
14. Amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate may be administered as oral medications (listed in alphabetical order; no hierarchy is implied) *Option (Evidence Strength: Grades B, B, C, and B)*
15. Clinicians should counsel patients who are considering pentosan polysulfate about the potential risk for macular damage and vision-related injuries. *Clinical Principle*
16. Oral cyclosporine A may be offered—particularly for patients with Hunner lesions refractory to fulguration and/or triamcinolone. *Option (Evidence Strength: Grade C)*

## Intravesical Instillations

17. DMSO, heparin, and/or lidocaine may be administered as intravesical treatments (listed in alphabetical order; no hierarchy is implied). *Option (Evidence Strength: Grades C, C, and B)*

## Procedures

18. Cystoscopy under anesthesia with short-duration, low-pressure hydrodistension may be undertaken as a treatment option. *Option (Evidence Strength: Grade C)*
19. If Hunner lesions are present, then fulguration (with laser or electrocautery) and/or injection of triamcinolone should be performed. *Recommendation (Evidence Strength: Grade C)*
20. Intradetrusor onabotulinumtoxin A may be administered if other treatments have not provided adequate improvement in symptoms and quality of life. Patients must be willing to accept the possibility that post-treatment intermittent self-catheterization may be necessary. *Option (Evidence Strength: Grade C)*
21. A trial of neuromodulation may be performed if other treatments have not provided adequate symptom control and quality of life improvement. If a trial of nerve stimulation is successful, then a permanent neurostimulation device may be implanted. *Option (Evidence Strength: Grade C)*

## Major Surgery

22. Major surgery (e.g., substitution cystoplasty, urinary diversion with or without cystectomy) may be undertaken in carefully selected patients with bladder-centric symptoms, or in the rare instance when there is an end-stage small fibrotic bladder, for whom all other therapies have failed to provide adequate symptom control and quality of life improvement. *Option (Evidence Strength: Grade C)*

## Treatments that Should Not be Offered

The treatments below appear to lack efficacy and/or appear to be accompanied by unacceptable adverse event profiles. See body of guideline for study details and rationales.

23. Long-term oral antibiotic administration should not be offered. *Standard (Evidence Strength: Grade B)*

24. Intravesical instillation of bacillus Calmette-Guerin should not be offered outside of investigational study settings. *Standard (Evidence Strength: Grade B)*

25. High-pressure, long-duration hydrodistension should not be offered. *Recommendation (Evidence Strength: Grade C)*

26. Systemic (oral) long-term glucocorticoid administration should not be offered. *Recommendation (Evidence Strength: Grade C)*

# Purpose

This guideline's purpose is to provide direction to clinicians and patients regarding how to recognize interstitial cystitis /bladder pain syndrome (IC/BPS); conduct a valid diagnostic process; and approach treatment with the goals of maximizing symptom control and patient quality of life (QoL) while minimizing adverse events (AEs) and patient burden. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. IC/BPS nomenclature is a controversial issue; for the purpose of clarity the Panel decided to refer to the syndrome as IC/BPS and to consider these terms synonymous. There is a continually expanding literature on IC/BPS; the Panel notes that this document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician and patient. As the science relevant to IC/BPS evolves and improves, the strategies presented here will require amendment to remain consistent with the highest standards of clinical care.

# Methodology

A systematic review was conducted to identify published articles relevant to the diagnosis and treatment of IC/BPS. Literature searches were performed on English-language publications using the MEDLINE database from January 1, 1983 to July 22, 2009 using the terms "interstitial cystitis," "painful bladder syndrome," "bladder pain syndrome," and "pelvic pain" as well as key words capturing the various diagnostic procedures and treatments known to be used for these syndromes. The American Urological Association (AUA) update literature review process, in which an additional systematic review is conducted periodically to maintain guideline currency with newly published relevant literature, was conducted in July 2013, which identified an additional 31 articles relevant to treatment. An update literature review in 2022 (search dates: 06/2013 – 01/2021) identified 63 studies, 53 of which were added to the evidence base. These publications were used to create the majority of the treatment portion of the guideline. Preclinical studies (e.g., animal models), pediatric studies, commentary, and editorials were eliminated. Review article references were checked to ensure inclusion of all possibly relevant studies. Studies using treatments not available in the US, herbal or supplement treatments, or studies that reported outcomes information collapsed across multiple interventions also were excluded. Studies on mixed patient groups (i.e., some patients did not have IC/BPS) were retained as long as more than 50% of patients were IC/BPS patients. Multiple reports on the same patient group were carefully examined to ensure inclusion of only nonredundant information. In a few cases, individual studies constituted the only report on a particular treatment. Because sample sizes in individual studies were small, single studies were not considered a sufficient and reliable evidence base from which to construct an evidence-based statement (i.e., a Standard, Recommendation, or Option). These studies were used to support Clinical Principles as appropriate.

## IC/BPS Diagnosis and Overall Management

The review revealed insufficient publications to address IC/BPS diagnosis and overall management from an evidence basis; the diagnosis and management portions of the algorithm (see Figure 1), therefore, are provided as Clinical Principles or as Expert Opinion with consensus achieved using a modified Delphi technique if differences of opinion emerged.<sup>1</sup> A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on Panel members clinical training, experience, knowledge, and judgment for which there is no evidence.

## IC/BPS Treatment

With regard to treatment, a total of 86 articles from the original literature searches met the inclusion criteria; an additional 31 relevant studies were retrieved as part of the update literature review process in 2014. An update literature review in 2022 (search dates: 06/2013 – 01/2021) identified 63 studies, 53 of which were added to the evidence base. The Panel judged that these were a sufficient evidence base from which to construct the majority of the treatment portion of the guideline and algorithm. Data on study type (e.g., randomized controlled trial (RCT), randomized crossover trial, observational study), treatment parameters (e.g., dose, administration protocols, follow-up durations), patient characteristics (i.e., age, gender, symptom duration), AEs, and primary outcomes (as defined by study authors) were extracted. The primary outcome measure for most studies was some form of patient-rated symptom scales, including the Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), and a Visual Analog Scale (VAS) as available. In short supply are objective parameters and placebo-controlled trials.

# Quality of Individual Studies and Determination of Evidence Strength

Quality of individual studies that were RCTs or crossover trials was assessed using the Cochrane Risk of Bias tool.<sup>2</sup> Because placebo effects are common in controlled trials conducted with IC/BPS patients, any apparent procedural deviations that could compromise the integrity of randomization or blinding resulted in a rating of increased risk of bias for that particular trial. Because there is no widely agreed upon quality assessment tool for observational studies, the quality of individual observational studies was not assessed.

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, the consistency of findings across studies, the adequacy of sample sizes, and the generalizability of samples, settings, and treatments for the purposes of the guideline. AUA categorizes body of evidence strength as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies), or Grade C (observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). Because treatment data for this condition are difficult to interpret in the absence of a placebo control, bodies of evidence comprised entirely of studies that lacked placebo control groups (i.e., observational studies) were assigned a strength rating of Grade C.

**Table 1: AUA Nomenclature**

<b>Table 1: AUA Nomenclature Linking Statement Type to Level of Certainty and Evidence Strength [Updated Version]</b>
Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A (high quality; high certainty) or B (moderate quality; moderate certainty) evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C (low quality; low certainty) evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A (high quality; high certainty), B (moderate quality; moderate certainty), or C (low quality; low certainty) evidence
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

## AUA Nomenclature

**Linking Statement Type to Evidence Strength.** The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, and the Panel's judgment regarding the balance between benefits and risks/burdens.<sup>1</sup> Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A (high level of certainty) or Grade B (moderate level of certainty) evidence. Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C (low level of certainty) evidence. Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; Options may be supported by Grade A (high certainty), B (moderate certainty), or C (low certainty) evidence. In the treatment portion of this guideline, most statements are Options because most treatments demonstrate limited efficacy in a subset of patients that is not readily identifiable a priori. The Panel interpreted these data to indicate that for a particular patient, the balance between benefits and risks/burdens is uncertain or relatively equal and whether to use a particular treatment is a decision best made by the clinician who knows the patient with full consideration of the patient's prior treatment history, current quality of life, preferences and values.

# Limitations of the Literature

The Panel proceeded with full awareness of the limitations of the IC/BPS literature, which include: poorly-defined patient groups or heterogeneous groups; small sample sizes; lack of placebo controls for many studies, resulting in a likely over-estimation of efficacy; short follow-up durations; and, use of a variety of outcome measures.

## Background

### Definition

The bladder disease complex includes a large group of patients with bladder and/or urethral and/or pelvic pain, lower urinary tract symptoms, and sterile urine cultures. IC/BPS comprises a part of this complex. The Panel used the IC/BPS definition agreed upon by the Society for Urodynamics and Female Urology (SUFU): "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes."<sup>2</sup> This definition was selected because it allows treatment to begin after a relatively short symptomatic period, preventing treatment withholding that could occur with definitions that require longer symptom durations (i.e., six months). Definitions used in research or clinical trials should be avoided in clinical practice; many patients may be misdiagnosed or have delays in diagnosis and treatment if these criteria are employed.<sup>3</sup>

## Epidemiology

Since there is no objective marker to establish the presence of IC/BPS, studies to define its prevalence are difficult to conduct. Population-based prevalence studies of IC/BPS have used three methods: surveys that ask participants if they have ever been diagnosed with the condition (self-report studies); questionnaires administered to identify the presence of symptoms that are suggestive of IC/BPS (symptom assessments); and, administrative billing data used to identify the number of individuals in a population who have been diagnosed with IC/BPS (clinician diagnosis). Not surprisingly, the use of different methods yields widely disparate prevalence estimates.

## Self-Report Studies

Two large-scale studies in the United States have utilized self-report to estimate the prevalence of IC/BPS. The first was conducted as part of the 1989 National Health Interview Survey (NHIS), and the second was part of the third National Health and Nutrition Examination Surveys (NHANES III), which was conducted between 1988 and 1994. The same definition of IC/BPS was used in both studies. Participants were asked, "Have you ever had symptoms of a bladder infection (such as pain in your bladder and frequent urination) that lasted more than 3 months?" Those who gave a positive response were then asked, "When you had this condition, were you told that you had interstitial cystitis or painful bladder syndrome?" An affirmative answer to both questions was considered to define the presence of IC/BPS. The prevalence estimates obtained from these two studies were virtually identical. In the NHIS, the overall prevalence was 500 per 100,000 population, and the prevalence in women was 865 per 100,000.<sup>6</sup> In NHANES III, the prevalence was 470 per 100,000 population, including 60 per 100,000 men and 850 per 100,000 women.<sup>6</sup> This equals approximately 83,000 men and 1.2 million women across the US.

## IC/BPS Symptoms

Multiple studies have estimated the prevalence of IC/BPS symptoms, using a variety of different case definitions. A mailed questionnaire study to 1,331 Finnish women aged 17-71 identified probable IC/BPS symptoms in 0.45%.<sup>4</sup> Another questionnaire mailing study to enrollees aged 25-80 in a managed care population in the US Pacific Northwest identified IC/BPS symptoms in 6-11% of women and 2-5% of men, depending on the definition used.<sup>5</sup> Investigators in the Boston Area Community Health study conducted door-to-door interviews about urologic symptoms in a sample of Black, Hispanic and White individuals aged 30-79.<sup>6</sup> They identified IC/BPS symptoms using six different definitions, which yielded prevalence estimates ranging from 0.6% to 2.0%. Across these definitions, symptoms were typically two to three times as common in women as men, but no clear variations were observed by race/ ethnicity. Questions about IC/BPS symptoms were included in the 2004 version of the US Nurses Health Study (NHS), which was administered to women aged 58 to 83 years.<sup>7</sup> In this cohort of women, the prevalence of IC/BPS symptoms was 2.3%. The prevalence increased with age, from 1.7% of those younger than 65 years up to 4.0% in women aged 80 years or older. In a study of 981 Austrian women aged 19-89 at a voluntary health screening project in Vienna, the prevalence of IC/BPS symptoms was determined to be 0.3% (306 per 100,000).<sup>8</sup>

Further information is provided in three additional papers that reported data from the RAND Interstitial Cystitis Epidemiology (RICE) study.<sup>9-11</sup> One of the RICE study objectives was to develop an IC/BPS case definition for use in epidemiological studies that had known sensitivity and specificity for use in epidemiological studies. Berry et al. (2010) report findings from a literature

review, a structured expert panel process, and a telephone interview validation study to derive an IC/BPS definition.<sup>9</sup> The authors note that none of the existing epidemiological definitions had high sensitivity or high specificity. As a result of this process, two definitions emerged. One with high sensitivity that correctly identified IC/BPS cases 81% of the time (with 54% specificity) and one with high specificity that correctly excluded non-IC/BPS cases 83% of the time (with 48% sensitivity). The definitions are captured in an 11-item questionnaire. See Table 2 for definitions; the Panel notes that these are epidemiological case definitions and are not appropriate for use as diagnostic criteria.

## Table 2: RICE BPS/IC Case Definitions<sup>10</sup>

Table 2: RICE BPS/IC Case Definitions <sup>10</sup>	
High Sensitivity Definition (sensitivity 81%, specificity 54% for BPS/IC v. endometriosis, vulvodynia and overactive bladder)	High Specificity Definition (sensitivity 48%, specificity 83% for BPS/IC v. endometriosis, vulvodynia and overactive bladder)
Pain, pressure, or discomfort in the pelvic area	Pain, pressure, or discomfort in the pelvic area
AND	AND
Daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, not fear of wetting	Daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, not fear of wetting
	AND
	Symptoms did not resolve after treatment with antibiotics
	AND
	No treatment with hormone injection therapy for endometriosis
Exclusion criteria: bladder cancer, urethral diverticulum, spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, spina bifida, cyclophosphamide treatment, radiation treatment to pelvic area, tuberculosis affecting the bladder, uterine cancer, ovarian cancer, vaginal cancer, genital herpes, pregnancy	

Berry et al. (2011) used the questionnaire to determine prevalence of IC/BPS among adult females in the US.<sup>10</sup> This study yielded prevalence estimates of from 2.7% to 6.53% (approximately 3.3 to 7.9 million US women age 18 or older). Only 9.7% of women who met the definitions reported having been given an IC/BPS diagnosis. Suskind et al. (2013) modified the case definition for use in men and used an additional case definition derived from the NIH-Chronic Prostatitis Symptom Index to assess the prevalence and overlap between IC/BPS and chronic prostatitis/chronic pelvic pain syndrome in men (CP/CPPS).<sup>11</sup> This study yielded a prevalence estimate of from 2.9% to 4.2% for IC/BPS and a prevalence of 1.8% for CP/CPPS. The overlap between the two syndromes was approximately 17%. The authors note that these findings suggest that the prevalence of IC/BPS in men approaches its prevalence in women; therefore, it may be greatly under-diagnosed in the male population.

## Clinician Diagnosis

Female participants in the NHS were asked by mailed questionnaires in 1994 and 1995 whether they had ever been diagnosed with 'interstitial cystitis (not urinary tract infection)'. In participants with a positive response, medical record reviews were performed to confirm a physician diagnosis, including cystoscopy performed by a urologist. Using these methods, the prevalence of IC/BPS was found to be 52/100,000 in the NHS I cohort, and 67/100,000 in the NHS II cohort.<sup>12</sup> A subsequent study was performed using administrative billing data from the Kaiser Permanente Northwest managed care population in the Portland, Oregon metropolitan area.<sup>5</sup> Patients with IC/BPS were identified by the presence of ICD-9 code 595.1 ('interstitial cystitis') in the electronic medical record, and the prevalence of the diagnosis was found to be 197 per 100,000 women and 41 per 100,000 men.

## Typical Course and Comorbidities

IC/BPS is most commonly diagnosed in individuals over 40, although the diagnosis may be delayed depending upon the index of suspicion for the disease, and the criteria used to diagnose it.<sup>13</sup> For instance, in European studies, where more strict criteria are typically used to make the diagnosis, the mean age is older than is typical for the US. A history of a recent culture-proven urinary tract infection (UTI) can be identified on presentation in 18-36% of women, although subsequent cultures are negative.<sup>14, 15</sup> Initially it is not uncommon for patients to report a single symptom such as dysuria, frequency, or pain, with subsequent progression to multiple symptoms.<sup>16, 17</sup> Symptom flares, during which symptoms suddenly intensify for several hours, days, or weeks, are not uncommon.<sup>18</sup> There is a high rate of prior pelvic surgery (especially hysterectomy) and levator ani pain in women with IC/BPS, suggesting that trauma or other local factors may contribute to symptoms.<sup>19</sup> It is important to note, however, that the

high incidence of other procedures such as hysterectomy or laparoscopy may be the result of a missed diagnosis and does not necessarily indicate that the surgical procedure itself is a contributing factor to symptoms. It is also common for IC/BPS to coexist with other unexplained medical conditions such as fibromyalgia, (IBS), chronic fatigue syndrome, Sjogren's syndrome, chronic headaches, and vulvodynia.<sup>20, 21</sup> These associations suggest that there may be a systemic dysregulation in some patients. Finally, patients with IC/BPS frequently exhibit mental health disorders such as depression and anxiety. While these symptoms may be reactive in some IC/BPS patients, there is also some evidence that there may be a common biologic mechanism involved. For instance, a link between IC/BPS and panic disorder has been suggested from genetic linkage studies.<sup>22, 23</sup>

## Conceptualizing IC/BPS

It is not known whether IC/BPS is a primary bladder disorder or whether the bladder symptoms of IC/BPS are a secondary phenomena resulting from another cause. Converging data from several sources suggest, however, that IC/BPS can be conceptualized as a bladder pain disorder that is often associated with voiding symptomatology and other systemic chronic pain disorders. Specifically, IC/BPS may be a bladder disorder that is part of a more generalized systemic disorder, at least in a subset of patients.

Initial observations suggesting this conceptualization were made by Clauw and colleagues (1997). He noted among chronic pelvic pain patients that other chronic overlapping pain conditions (COPCs) such as IC, IBS, chronic fatigue syndrome, and fibromyalgia tended to co-occur.<sup>24</sup> More comprehensive studies conducted by the NIH-funded Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network found that 44% of IC/BPS patients had at least one additional COPC.<sup>25</sup> IC/BPS patients with widespread pain had more severe urologic symptoms, worse psychosocial symptoms and functioning, poorer QoL, and a worsening symptom trajectory over time.<sup>25-27</sup> Furthermore, IC/BPS patients displaying widespread pain showed multiple indications of central neurobiological pain sensitization, correlating with quantitative sensory testing, fMRI (functional magnetic resonance imaging), and inflammatory markers.<sup>28-31</sup> These findings imply that there might be a common central pathogenesis and pathophysiology for these disorders.

Considering these data, it has been suggested that IC/BPS is a member of a family of hypersensitivity disorders which affects the bladder and other somatic/visceral organs, and has many overlapping symptoms and pathophysiology.<sup>32, 33</sup> An additional hypothesis is that IC/BPS might be just a part of the continuum of painful versus non-painful overactive bladder syndrome (OAB).<sup>34, 35</sup>

IC/BPS is a heterogeneous clinical syndrome. Even though patients present with similar symptoms of bladder/pelvic pain and pressure/discomfort associated with urinary frequency and strong urge to urinate, there are subgroups or phenotypes within IC/BPS. Some IC/BPS patients have bladder-centric phenotypes (e.g., Hunner lesions, small bladder capacity, pain improved with intravesical local anesthetics). Patients with Hunner lesions should be treated differently from those without Hunner lesions (Statement 19 and Algorithm). Others have pelvic-floor phenotype (e.g., pelvic floor tenderness on exam). Women with this feature respond better to pelvic floor manual physical therapy (Statement 12). A third group have systematic or widespread symptoms characterized by the presence of "widespread pain"<sup>26</sup> (significant non-urologic pain outside the pelvis), COPC (e.g., fibromyalgia, IBS),<sup>25</sup> widespread psychosocial difficulties (e.g., anxiety, depression, higher levels of current and lifetime stress, early life and adult traumatic events, negative affect, poor illness coping),<sup>36</sup> or poly-symptomatic, poly-syndromic(PSPS) presentation with widespread somatic symptoms across multiple organ systems.<sup>37</sup>

## Impact on Psychosocial Functioning and Quality of Life

The effects of IC/BPS on psychosocial functioning and QoL are pervasive and insidious, damaging work life, psychological well-being, personal relationships and general health.<sup>6</sup> QoL is poorer in IC/BPS patients than in controls.<sup>6, 38, 39</sup> Rates of depression are also higher.<sup>38-40</sup> In addition, IC/BPS patients have significantly more pain, sleep dysfunction, catastrophizing, depression, anxiety, stress, social functioning difficulties and sexual dysfunction than do non-IC/BPS age-matched women.<sup>41, 42</sup> The impact of IC/BPS on QoL is as severe as that of rheumatoid arthritis and end-stage renal disease.<sup>6, 43</sup> Health-related QoL in women with IC/BPS is worse than that of women with endometriosis, vulvodynia or OAB.<sup>39</sup> Given that IC/BPS causes considerable morbidity over the course of a patient's life and loss of work during their most productive years, significant negative psychological and QoL impacts are not surprising.<sup>6</sup>

Sexual dysfunction has an especially important impact on the QoL of IC/BPS patients. In IC/BPS patients, sexual dysfunction is moderate to severe<sup>44</sup> and occurs at high rates compared with controls.<sup>45, 46</sup> In women with treatment-refractory IC/BPS, poor sexual function is a primary predictor of poor mental QoL.<sup>47</sup> Pain appears to mediate sexual dysfunction and its associated effects on QoL. Adult women with IC/BPS report rates of intercourse, desire, and orgasm frequency in their adolescence that are similar to those reported by controls, but rates diverge in adulthood, when IC/BPS patients report significantly more pain and fear of pain with intercourse and more sexual distress.<sup>45</sup>

The strong link between IC/BPS symptoms and psychosocial functioning and QoL make clear the critical importance of optimizing treatment of IC/BPS symptoms. Successful treatment of the medical condition clearly brings improvement in functioning and QoL. Response to therapy is associated with improved overall QoL.<sup>48</sup> In addition, response to therapy is associated with improved sexual function and sleep, with concomitant improvements in QoL.<sup>41, 44</sup>

**Cost.** Quantifying the economic burden of IC/BPS on the American health care system is difficult because of the lack of an objective marker for diagnosis, resulting in uncertainty regarding its true prevalence. Direct costs associated with IC/BPS are incurred through physician visits, prescription medications, outpatient procedures, and hospitalization. These costs are greater than the mean annual per-person direct costs of diabetes mellitus, depression, hypertension, and asthma.<sup>49</sup>

They are also more consistent across geographic regions of the United States than other urologic conditions.<sup>50</sup> Because of the chronicity of the condition, these costs typically persist over years. The indirect costs of IC/BPS, including time away from work and lost productivity while working, are particularly significant since the condition primarily affects working age adults, and especially women aged 25-50 years. The psychosocial costs such as social, educational and career related activities not pursued, as well as the emotional distress, depression, social isolation, and diminished QoL have not been measured, but are almost certainly substantial.

Analysis of data extracted from multiple databases, including the Centers for Medicare and Medicaid Services, National Center for Health Statistics, Medical Expenditure Panel Survey, NHANES, Department of Veterans Affairs, National Association of Children's Hospitals and Related Institutions, and various private data sets between 1994 and 2000 revealed an increase of 29% from \$37 to \$66 million among persons with a formal diagnosis of IC/BPS. Similarly, the direct annual costs associated with BPS rose from \$481 million to \$750 million (amounts standardized to 1996-1998 values).<sup>50</sup> Between 1992 and 2001 the rate of visits to physician's offices increased three-fold and the rate of visits to hospital outpatient visits increased two-fold.<sup>50</sup> Only the rate of ambulatory surgery visits declined during this period, which may be attributed to a shift to diagnosis based on a symptom-based approach rather than the more traditional procedure-based diagnostic evaluation.<sup>50</sup> While these findings are thought to reflect an increased awareness and diagnosis of IC/BPS, existing evidence reveals that more than 92% of office visits among patients with a diagnosis of IC/ BPS were to urologists.<sup>50</sup> In contrast, visits attributed to IC/BPS are found under a variety of less specific codes including urinary frequency, other specified symptoms associated with female genital organs, or other unspecified symptoms associated with the female genital organs.<sup>50</sup> These findings suggest that misdiagnosis and under-diagnosis remain common, especially in the primary care setting.

The economic burden of IC/BPS for the individual patient is even greater than the impact on the health care system at large. The mean annual health care costs following a diagnosis of IC/BPS are 2.0 to 2.4 times higher than age matched controls.<sup>49, 50</sup> A study of 239 women diagnosed with IC and cared for in a managed care setting found a mean cost of \$6,614, including \$1,572 for prescription medications, and \$3,463 for outpatient medical services.<sup>49, 51</sup> In addition, a woman who is diagnosed with IC/BPS will incur a higher mean cost than a male patient diagnosed with the same condition.<sup>50</sup> A cross-sectional study of 43 women cared for in an outpatient urology center found that the annual direct cost associated with a diagnosis of IC/BPS based on Medicare rates was \$3,631 per person, while the estimated costs based on non-Medicare rates was nearly twice that amount.<sup>51</sup> Indirect individual costs were estimated by querying lost wages due to symptoms within a three month period. Nineteen percent of patients with IC/BPS reported lost wages, resulting in a mean annual cost of \$4,216. The magnitude of these indirect costs was greatest among women with severe symptoms as compared to those with mild symptoms.<sup>51</sup> Although clearly substantial, these additional costs fail to reflect the economic burden associated with commonly occurring coexisting conditions.<sup>52</sup>

## Patient Presentation

### Symptoms

Pain (including sensations of pressure and discomfort) is the hallmark symptom of IC/BPS. Typical IC/BPS patients report not only suprapubic pain (or pressure, discomfort) related to bladder filling but pain throughout the pelvis, including the urethra, vulva, vagina, rectum, as well in extragenital locations such as the lower abdomen and back.<sup>15, 46, 53</sup> Warren and colleagues (2006) found that by using "pelvic pain" as the key descriptor that 100% of his population fit the case definition.<sup>54</sup> It is important that the term "pain" encompass a broad array of descriptors. Many patients use other words to describe symptoms, especially "pressure" and may actually deny pain.<sup>53, 55</sup> Finally, pain that worsened with specific foods or drinks, and/or worsened with bladder filling, and/or improved with urination contributed to a sensitive case definition of IC/BPS.<sup>15</sup>

The prototypical IC/BPS patient also may present with marked urinary urgency and frequency but because these symptoms may indicate other disorders, they do not exclusively indicate the presence of IC/BPS. Voiding frequency is almost universal (92% of one population),<sup>46</sup> but does not distinguish the IC/BPS patient from other lower urinary tract disorders. Change in urinary frequency is valuable to evaluate response to therapy but is of little help in diagnosis. Urinary urgency is also extremely common (84% of the same population),<sup>46</sup> but urgency is considered a characteristic symptom of OAB and can confound the diagnosis.

There maybe qualitative differences in the urgency experienced by IC/BPS patients compared to OAB patients; IC/BPS patients may experience a more constant urge to void as opposed to the classic International Continence Society definition of a "compelling need to urinate which is difficult to postpone."<sup>56, 57</sup> Typically IC/BPS patients void to avoid or to relieve pain; OAB patients, however, void to avoid incontinence. Symptoms of urinary urgency and frequency may precede symptoms of pain.<sup>17</sup> A

key characteristics of pain related to IC/BPS is that the pain is worsened with bladder filling ("painful bladder filling") and/or their strong urge to urinate was due to pain, pressure, or discomfort ("painful urgency").<sup>58</sup> Median time to the development of a full symptom complex of frequency, urgency, and pain was reported to be two years in one study.<sup>17</sup>

## Presentation of Male IC Patients

Historically, IC/BPS in men has been considered relatively unusual with a female to male ratio of 10:1.<sup>3, 59</sup> However, uncontrolled clinical series over the past two decades have suggested the incidence of male IC/BPS may be higher than previously observed.<sup>5, 60</sup> IC/BPS in men is diagnosed by identifying the same symptom complex that makes the diagnosis in women. That is, if the man fulfills the criteria established by the definition of IC/BPS (i.e., urinary frequency, "painful urgency" and/or "painful bladder filling"), he can be assumed to have the disorder. In the MAPP Study which enrolled men and women with IC/BPS and/or CP/CPPS, about 3 out of 4 men had symptoms of "painful bladder filling" and/or "painful urgency", consistent with IC/BPS. The data suggested that the overlap between IC/BPS and CP/CPPS in men is under-appreciated; and that many men with CP/CPPS-like symptoms may in fact have IC/BPS if the bladder pain/storage symptoms are inquired. Men with IC/BPS is less likely to report perineal pain as their most bothersome symptom. Instead, men with IC/BPS are more likely to have suprapubic tenderness.<sup>58</sup> Early clinical symptoms may begin with mild dysuria or urinary urgency. Mild symptoms may progress to severe voiding frequency, nocturia, and suprapubic pain.

Clinical findings mirror those of the female IC/BPS patient. On examination, suprapubic tenderness is common along with external (perineal) tenderness and internal (levator muscle) tenderness/spasticity. Cystoscopy with hydraulic distention of the bladder in men with IC/BPS commonly demonstrates diffuse glomerulations.<sup>56</sup> The presence of glomerulations on endoscopy is too non-specific to make the diagnosis of IC/BPS. Hunner lesions can be identified on cystoscopy in men with IC/BPS.<sup>61</sup> Some data suggest that Hunner ulcers are more common in male IC/BPS patients.<sup>62</sup>

## Male IC/BPS versus Chronic Prostatitis

CP/CPPS, or NIH Type III prostatitis,<sup>63</sup> is characterized by pain in the perineum, suprapubic region, testicles or tip of the penis.<sup>64</sup>

The pain is often exacerbated by urination or ejaculation. Voiding symptoms such as sense of incomplete bladder emptying and urinary frequency are also commonly reported, but pain is the primary defining characteristic of CP/CPPS. It is clear that the clinical characteristics which define CP/CPPS are very similar to those previously described for IC/BPS. In general, the Panel believes that the diagnosis of IC/BPS should be strongly considered in men whose pain is perceived to be related to the bladder, or they have symptoms of "painful bladder filling" and/or "painful urgency". However, it is also quite clear that certain men have symptoms which meet criteria for both conditions (IC/BPS and CP/CPPS).

In such cases, the treatment approach can include established IC/BPS therapies as well as other therapies that are more specific to CP/CPPS. It is interesting to note that some studies of patients with CP/CPPS have high rates of bladder glomerulation under anesthesia.<sup>65</sup> Additionally, empiric IC/BPS strategies in those CP/CPPS patients have demonstrated clinical symptomatic improvement.<sup>62, 65, 66</sup>

## Diagnosis

### The Diagnostic Approach

The diagnosis of IC/BPS can be challenging. Patients present with a wide spectrum of symptoms, physical exam findings, and clinical test responses. This complexity causes significant misdiagnosis, under-diagnosis, and delayed diagnosis.<sup>67</sup> Insufficient literature was identified to constitute an evidence base for diagnosis of IC/BPS in clinical practice. The lack of evidence is not surprising given the many definitions of the disorder employed and the focus of most trials on National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) diagnostic criteria (note that the NIDDK diagnostic criteria are not appropriate for use outside of clinical trials).<sup>64, 68</sup> For this reason, the section below titled Diagnosis is based on Clinical Principles or Expert Opinion with consensus achieved using a modified Delphi technique when differences of opinion emerged. This section is intended to provide clinicians and patients with a framework for determining whether a diagnosis of IC/BPS is appropriate; it is not intended to replace the judgment and experience of the individual clinician faced with a particular patient.

## Guideline Statements

### DIAGNOSIS

## Guideline Statement 1

The basic assessment should include a careful history, physical examination, and laboratory examination to document symptoms and signs that characterize IC/BPS and exclude other disorders that could be the cause of the patient's symptoms. *Clinical Principle*

The clinical diagnosis of IC/BPS requires a careful history, physical examination, and laboratory examination to document basic symptoms that characterize the disorder and exclude infections and other disorders (see Figure 1: IC/BPS Diagnostic and Treatment Algorithm).<sup>69-72</sup> The clinical history should include questions about symptom duration. IC is a chronic disorder and symptoms should be present for at least six weeks with documented negative urine cultures for infection. The number of voids per day, sensation of constant urge to void, and the location, character and severity of pain, pressure or discomfort should be documented. Dyspareunia, dysuria, ejaculatory pain in men, and the relationship of pain to menstruation in women should also be noted.

The physical examination should include an abdominal and pelvic examination noting masses, tenderness, and presence of hernias. The pelvic examination should include palpation of the external genitalia, bladder base in females, and urethra in both sexes. The pelvic floor muscles in both sexes should be palpated for locations of tenderness and trigger points. The pelvic support for the bladder, urethra, vagina, and rectum should be documented. A focused evaluation to rule out vaginitis, urethritis, tender prostate, urethral diverticulum, or other potential sources of pain or infection is important. For a more detailed discussion, please see Weiss 2001.<sup>73</sup> A trial of antibiotic therapy is appropriate when infection is suspected; if symptoms resolve a course of antibiotic suppression may be considered to allow for full recovery. A brief neurological exam to rule out an occult neurologic problem and an evaluation for incomplete bladder emptying to rule out occult retention should be done on all patients.

The basic laboratory examination includes a urinalysis and urine culture. A proper hematuria workup should be performed for patients with unevaluated hematuria, and considered for patients with tobacco exposure given the high risk of bladder cancer in smokers.<sup>74</sup> Urine culture may be indicated even in patients with a negative urinalysis in order to detect lower levels of bacteria that are clinically significant but not readily identifiable with a dipstick or on microscopic exam.

## Guideline Statement 2

**Baseline voiding symptoms and pain levels should be obtained in order to measure subsequent treatment effects.**  
*Clinical Principle*

It is important to establish baseline values in order to evaluate later treatment responses. Very low voiding frequencies or high voided volumes should prompt a diligent search for an alternate diagnosis. At least a one-day voiding log should be used to establish the presence of a low volume frequency voiding pattern that is characteristic of IC/BPS.<sup>75</sup> These values can then be used to determine if a clinically significant response to treatment has occurred. Similarly, self-report instruments such as the Genitourinary Pain Index (GUPI), ICSI, or ICFI<sup>76</sup> can be used to establish a standardized symptom profile baseline for later evaluation of treatment response.<sup>32 77, 78</sup> These self-report instruments, however, are only useful to establish baseline symptom values; they are not valid tools for establishing a diagnosis.

The isolated pain component also should be evaluated in patients who report pain or other descriptors of discomfort such as pressure. The goal of this evaluation is to gather information regarding pain/discomfort location(s), intensity, and characteristics, and to identify factors that exacerbate or alleviate pain or discomfort. There are several ways in which to assess pain and discomfort. Validated questionnaires such as the GUPI or the ICSI are useful to gather comprehensive symptom information, including symptoms in addition to those of pain or discomfort.<sup>78 76, 77</sup> A 1 to 10 Likert-style VAS is a simple, easily administered instrument that can capture pain intensity. Pain body maps can be used with patients whose presentation suggests a more global pain syndrome or "widespread pain."<sup>26</sup> Patients should be queried with regard to pain characteristics (e.g., burning, stabbing) or a pain adjective checklist can be offered (e.g., McGill Pain Questionnaire – Short Form).<sup>79</sup> Patients also should be queried regarding factors known to worsen or improve pain or discomfort. Patients should be asked if their pain is worsened with bladder filling ("painful bladder filling") and/or their strong urge to urinate was due to pain, pressure, or discomfort ("painful urgency"), since these are characteristic symptoms of IC/BPS.<sup>58</sup>

This information is an important component to establish a diagnosis of IC/BPS, provides a baseline against which treatments can be evaluated, and is used to determine the appropriate level of entry into the treatment algorithm. Many patients present with pain symptoms suggesting involvement of multiple organ systems. The PSPS questionnaire can be used to evaluate for PSPS presentation with widespread somatic symptoms across multiple organ systems.<sup>37</sup> In such cases a multidisciplinary team of gastroenterology, neurology, rheumatology, gynecology, pain clinic specialists, and other disciplines should be considered.

Disorders such as bacterial cystitis, urinary calculi, vaginitis, and less common problems like carcinoma in situ of the bladder and chronic bacterial prostatitis have significant symptom overlap and must be systematically excluded or identified and treated appropriately. The role of other tests can support the diagnosis but have poor specificity for IC/BPS.<sup>80</sup> Clinicians should carefully weigh the potential risks and burdens of particular tests against the potential benefit to patients. For example, urodynamic evaluation can identify bladder outlet obstruction or detrusor overactivity. The finding of sensory urgency at low bladder volumes with or without detrusor overactivity is not specific for IC/BPS.

In general, additional tests should be undertaken only if findings will alter the treatment approach. As described in Statement 1, a key goal of the evaluation is to identify and exclude other disorders that may be causing symptoms. In contrast to cystoscopy, urodynamics, and radiologic imaging, the potassium sensitivity test (PST) does not result in the identification of other disorders. In fact, it is consistently positive in some alternate disorders, including bacterial cystitis and radiation cystitis.<sup>81</sup> If a patient has typical symptoms of IC/BPS (e.g., frequent urination driven by pain that increases with bladder filling and improves after voiding), then the clinician will begin treatment after excluding alternate disorders. PST results do not change this decision. A positive test is consistent with the existing clinical plan. A negative test will not change the clinical plan, because 26% of patients who met the strict NIDDK criteria for IC/BPS had a negative test.<sup>81</sup> Another proposed role for the PST is to identify the subset of patients who have urothelial dysfunction.<sup>81</sup> Thus, in theory, PST might help to identify the patients who are most likely to respond to urothelium-restoring treatments. However, the evidence to date reveals minimal predictive value. PST findings did not predict at least 50% improvement with pentosan polysulfate (PPS)<sup>81</sup> or with combined heparinoid and tricyclic antidepressant treatment.<sup>82</sup> PST findings also did not predict success in a randomized trial of PPS versus cyclosporine A.<sup>83</sup>

Findings from a modified PST predicted response to intravesical hyaluronic acid in one study<sup>84</sup> but this treatment is not used in the US and unpublished data from two large multicenter RCTs failed to demonstrate efficacy. In addition, the PST is painful and risks triggering a severe symptom flare. In view of the paucity of benefits, the Panel concluded that the risk/benefit ratio was too high for routine clinical use.

## Guideline Statement 3

**Cystoscopy and/or urodynamics should be considered when the diagnosis is in doubt; these tests are not necessary for making the diagnosis in uncomplicated presentations. *Expert Opinion***

Cystoscopy and urodynamic testing are appropriate as part of the diagnostic approach when the IC/BPS diagnosis is in doubt or when information that can be gleaned from cystoscopy is needed to guide therapy. The value of cystoscopy is in excluding conditions that may mimic IC/BPS and in the identification of a Hunner lesions. Identification of entities such as bladder cancer, bladder stones, urethral diverticula, and intravesical foreign bodies is most consistently accomplished with cystoscopy. Therefore, suspicion for these entities is an indication for the diagnostic use of cystoscopy.

There are no agreed-upon cystoscopic findings diagnostic for IC/BPS, however. The only consistent cystoscopic finding that leads to a diagnosis of IC/BPS is that of one or several inflammatory appearing lesions or ulcerations as initially described by Hunner in 1918.<sup>85</sup> There is evidence that Hunner lesions are more common in IC/BPS patients of age over 50 years.<sup>86, 87</sup> In patients for whom Hunner lesions are suspected, it is appropriate to proceed to cystoscopy in order to assess for the presence of Hunner lesions (Statement 4).

These lesions may be identified in an acute phase (as an inflamed, friable, denuded area) or a more chronic phase (blanched, nonbleeding area).<sup>88</sup> An atlas is available to facilitate the visual diagnosis of Hunner lesions, since variations in cystoscopic appearance have been reported.<sup>89</sup> Glomerulations (pinpoint petechial hemorrhages) may be detected on cystoscopy but these lesions are non-diagnostic and non-specific for IC/BPS and are commonly seen in other conditions which may co-exist with or be misdiagnosed as IC/BPS such as chronic undifferentiated pelvic pain or endometriosis.<sup>61, 90, 91</sup>

Glomerulations may also be present in asymptomatic patients undergoing cystoscopy for other conditions.<sup>92</sup> Bladder biopsy may be indicated to exclude other pathologies if a lesion of uncertain nature is present but is not part of the routine diagnostic process and presents a risk of perforation.

When cystoscopy is performed with hydrodistension under anesthesia, interpreting findings relevant to an IC/BPS diagnosis becomes even more complicated. Hydrodistension methods vary widely. Duration, pressure, and number of hydrodistension episodes per session vary greatly in clinical practice or survey analysis.<sup>93</sup> Given the differing approaches, the finding of glomerulations on hydrodistention (less than 80 cm H<sub>2</sub>O, less than 5 minutes) is variable and not consistent with clinical presentation.<sup>94, 95</sup> For the same reasons, the absence of glomerulations can lead to false negative assessment of patients who present with clinical findings consistent with IC/BPS.<sup>96</sup> In addition, glomerulations may be seen in patients who have undergone radiation therapy, in the presence of active bladder carcinoma, associated with chemotherapeutic or toxic drug exposure, and in patients with defunctionalized bladders, and in patients without any urologic symptoms. Therefore, hydrodistension is not necessary for routine clinical use to establish a diagnosis of IC/BPS diagnosis.

Cystoscopic exam can be indicated if other sources of symptoms remain unclear. If hydrodistension is performed to determine whether Hunner lesions are present or as a treatment, then the technique should be specified and the bladder capacity determined. It is useful for the clinician and patient to understand when bladder capacity is severely reduced (a low capacity due to fibrosis).<sup>97</sup>

As with cystoscopy, there are no agreed-upon urodynamic criteria diagnostic for IC/BPS. There can be significant discomfort associated with the testing methodology and findings in IC/BPS patients are inconsistent. Bladder sensations reported during cystometric bladder filling may be normal or markedly abnormal, possibly due to the subjective nature of bladder sensory function.<sup>98</sup> Pain with filling (hypersensitivity) is consistent with IC/BPS. Most patients will have normal filling pressure and compliance. Detrusor overactivity (DO) is seen in approximately 12-20% of IC/BPS patients.<sup>98</sup> In these cases, it can be difficult to determine whether the diagnosis is DO alone or IC/BPS in combination with DO. Patients with DO alone may report discomfort during cystometric bladder filling and may be non-responsive to antimuscarinic drugs. However, if the patient also meets the clinical definition criteria for IC/BPS, then it is reasonable to diagnose both conditions. Pelvic floor muscle dysfunction may manifest as high resting urethral pressure, functional bladder outlet obstruction due to poor relaxation of the sphincter associated with pain-induced pelvic floor muscle dysfunction, and poor contractility due to bladder inhibition from non-relaxing pelvic floor muscles.<sup>99</sup> Therefore, urodynamic evaluation may provide information regarding concomitant voiding dysfunction. Specific indications that urodynamic evaluation may be useful include suspicion of outlet obstruction in either sex, possibility of poor detrusor contractility, or other conditions that could explain why patients are initially refractory to first-line therapy. In general, however, urodynamics are not recommended for routine clinical use to establish an IC/BPS diagnosis.

## Guideline Statement 4

**Cystoscopy should be performed in patients for whom Hunner lesions are suspected. *Expert Opinion***

Men or women over the age of 50 are more likely to have Hunner lesions on cystoscopy, thus it is reasonable to offer cystoscopy to IC/BPS patients over the age of 50. The higher odds of identifying Hunner lesions and directing Hunner patients to more effective therapies (e.g., triamcinolone and/or fulguration) are balanced against the mild discomfort associated with office cystoscopy. Cystoscopy should also be considered in those who fail conventional therapies but have never had a cystoscopy before in order to evaluate for the presence or absence of Hunner lesions. In patients who report abnormal findings in previous cystoscopy, if it is unclear to the clinician what the abnormal findings are, cystoscopy may be performed to visualize directly.

A recent systematic review and meta-analysis shows that IC/BPS with Hunner lesions represents a different phenotype than IC/BPS without Hunner lesions.<sup>100</sup> Most patients with Hunner lesions will respond to treatment directed at resolving these lesions (see Statement 19). Therefore, early diagnosis by cystoscopy is justified in patients suspected to have Hunner lesions, without requiring them to fail other behavioral or medical treatments before recommending cystoscopy. If Hunner lesions are found on cystoscopy, triamcinolone injection and/or fulguration can be performed; and for those who fail triamcinolone and/or fulguration, oral Cyclosporine A (CyA) and/or other multi-modal therapies may be offered (see Figure 1).

Although comparative studies have showed that Hunner lesions patients are older,<sup>86, 87, 101-103</sup> have greater urinary frequency and nocturia,<sup>86, 87, 102, 103</sup> higher ICSI scores,<sup>86, 87, 103</sup> and lower bladder capacity<sup>101, 103</sup> compared to those without Hunner lesion, cystoscopy remains the only reliable way to diagnose the presence or absence of Hunner lesions given the overlaps in clinical symptomatology.<sup>86, 102</sup> Most Hunner lesions can be diagnosed with office cystoscopy under local anesthesia without hydrodistention.<sup>86, 102, 104</sup> Although most IC/BPS patients may tolerate office flexible cystoscopy, some may prefer to have cystoscopy performed under anesthesia. Being able to gently distend the bladder under anesthesia may bring out additional Hunner lesions that may bleed with distention in some patients. An atlas is available to facilitate the visual diagnosis of Hunner lesions, since variations in cystoscopic appearance have been reported.<sup>104</sup> Classically, the lesions are inflamed and friable and have a stellate appearance with blood vessels radiating from the center with or without a coagulum. Alternatively, they may be blanched in appearance without inflammation or bleeding or may have a red waterfall bleeding appearance with bladder distention. The clinician should look for and map out the locations of Hunner lesions during the early phase of cystoscopy since the lesions may begin to bleed during bladder filling and may be obscured later.

Men or women over the age of 50 are more likely to have Hunner lesions on cystoscopy. Doiron et al. showed that the prevalence of Hunner lesion was significantly higher in patients over the age of 50 compared to those younger than 50 (14.9% vs. 7.8%, p=0.0095).<sup>86</sup> In the MAPP research study, Hunner lesions were found in 4.0% of cystoscopy in patients less than 50 years old, 19.7% between ages 50 to 70, and 54.5% over the age of 70.<sup>87</sup> In a different clinical study, Hunner lesions were found in 8.6%, 23.8%, and 55.6% of patients less than 30 years old, between 30 to 60 years old, and older than 60 years old, respectively.<sup>105</sup> Thus it is reasonable to offer cystoscopy to men and women over the age of 50, since the odds of identifying Hunner lesions are higher in this age group, and the potential benefits of identifying Hunner patients and directing them to more effective therapies (see Statement 19) outweigh the potential risks. In the Panel's opinion, performing cystoscopy to every IC/BPS patient is not advisable since the benefits/risks ratio is unfavorable for younger patients who have much lower prevalence of Hunner lesions. Hunner lesions may be present in both men and women. There are potential overlaps between CP/CPPS and IC/BPS in men. There should be high vigilance to look for Hunner lesions in men who present with chronic pelvic pain that is worse with bladder filling, associated with urinary frequency and strong urge to urinate, and in whom the diagnosis of CP/CPPS is in doubt, or do not respond to conventional treatments of CP/CPPS. In a case series that examined 32 men who were diagnosed with CP/CPPS according to the NIDDK classification and who were refractory to behavioral and pharmacological therapies, 41% (13 of 32) had Hunner lesion on cystoscopy. Men with voided volume less than 150 mL were more likely to have Hunner lesions than those with voided volume exceeding 150 mL.<sup>106</sup>

## Management Approach

The published literature regarding the typical course of IC/BPS is conflicting. Some studies suggest that IC/BPS is a chronic condition with a waxing and waning course with, on average, little improvement over time while other studies suggest that most patients seem to improve over time.<sup>107, 108</sup>

Conflicting information is not surprising given that studies have been conducted on different patient populations and have had different purposes (e.g., documenting disease course versus treating the disease in the context of a controlled trial). It is clear, however, that there is a limited understanding of IC/BPS pathophysiology and that most treatments are targeted at symptom control. In addition, treatment studies suggest that no single treatment works well over time for a majority of patients. Until more definitively effective therapies are identified, the treatment approach should be tailored to the specific symptoms of each patient in order to optimize QoL. To optimally treat patients with a more complex presentation and/or when standard treatment approaches are ineffective, urologists may need to partner with other clinicians such as primary care providers, nurse practitioners, registered dietitians, physical therapists, pain specialists, gastroenterologists, and/or gynecologists.

This section is offered to provide clinicians and patients with a framework and strategy for determining optimal treatment approaches (see Figure 1); it is not intended to replace the judgment and experience of the individual clinician faced with a particular patient.

## Guideline Statement 5

**Treatment decisions should typically be made after shared decision-making, with the patient informed of the risks, potential benefits, and alternatives. Except for patients with Hunner lesions, initial treatment should be nonsurgical. Expert Opinion**

In contrast to the prior versions of this guideline, this update no longer divides treatments into first-line through sixth-line tiers. Clinicians do not need to proceed in a linear algorithm or a hierarchy from first-line to sixth-line treatments described in the previous guideline. Instead, treatment is categorized into behavioral/non-pharmacologic, oral medicines, bladder instillations, procedures, and major surgery. Except for patients with Hunner lesions (see Statement 19), initial treatment should be nonsurgical. Concurrent, multi-modal therapies may be offered. The Panel made this change in order to emphasize that shared decision-making, individual patient factors and clinical judgment are the most important factors in treatment choice.

Education, self-care and behavioral modification are essential to any treatment plan (Statements 9-11). Also, for patients with pelvic floor tenderness, physical therapy should be offered if appropriately trained clinicians are available (Statement 12). While some patients may opt to start with education, behavior modification, or physical therapy alone, other patients will benefit from concomitant oral and/or intravesical treatments. As part of shared decision-making, clinicians should counsel patients on all applicable options, with their risks and benefits. Please see the Treatment section for details on individual treatments.

It is essential to set reasonable expectations. While most patients are able to achieve an acceptable QoL, very few go into complete remission. Most patients have persistent baseline symptoms and intermittent symptom flares. Patients must strike a balance between tolerating residual symptoms versus pursuing higher-risk treatments that are unlikely to provide additional relief. A reliable plan for dealing with flares (e.g., prompt bladder instillations with local anesthetic) may be formulated in advance to decrease stress and improve QoL.

It is critical to document symptoms at appropriate intervals. Treatments that are effective (singly or in combination) should be continued. Ineffective treatments should be stopped (Statement 6).

## Guideline Statement 6

**Efficacy of treatment should be periodically reassessed, and ineffective treatments should be stopped. *Clinical Principle***

IC/BPS treatment alternatives are characterized by the fact that most treatments may benefit a subset of patients but that no treatment reliably benefits most or all patients. It is not uncommon, therefore, for a particular patient to experience lack of benefit from a particular treatment. For this reason, if a clinically meaningful trial of a therapy has been conducted without efficacy, then the therapy should be discontinued and other therapeutic alternatives considered and other therapeutic alternatives should then be considered. This practice reduces expense, burden, side effects, and risk to the patient.

## Guideline Statement 7

**Multimodal pain management approaches (e.g., pharmacological, stress management, manual therapy if available) should be initiated. Pain management should be continually assessed for effectiveness because of its importance to quality of life. If pain management is inadequate, then consideration should be given to a multidisciplinary approach and the patient referred appropriately. *Clinical Principle***

Because the underlying pathophysiology of IC/BPS is unknown, treatment goals are to manage symptoms and optimize QoL. Effective pain management is an important component of QoL and, particularly for complex patient presentations, may require a multidisciplinary, multimodal approach. Please see Statement 13 on pain management for a thorough discussion of pain management.

## Guideline Statement 8

**The IC/BPS diagnosis should be reconsidered if no improvement occurs after multiple treatment approaches. *Clinical Principle***

If the usual IC/BPS therapies provide no improvement in symptoms, then the clinician should revisit the diagnosis of IC/BPS and consider whether an unidentified disorder may be present that is producing symptoms. This consideration may require additional diagnostic workup and/or referral to appropriate specialists.

# Treatment Categories for IC/BPS

The Panel assessed the available data for each treatment to determine whether a specific intervention demonstrated sufficient efficacy to be included as a treatment alternative. The types of studies available (RCTs, observational studies), quality of individual studies, consistency of outcome across studies, and generalizability of samples, settings, and interventions were examined, and overall evidence strength determined. The quality of individual studies is conceptually distinct from the categorization of overall evidence strength. For example, individual studies may be of high quality but if findings are contradictory or samples do not generalize well to the patient population addressed by the guideline, then evidence strength may be downgraded.

The balance between benefits and risks/burdens (i.e., AEs) was considered. The Panel conceptualized potential AEs in terms of severity, duration and reversibility. With regard to severity, potential AEs vary in the extent to which they can compromise QoL. Medication side effects vary from mild to intolerable. Some procedures and substances have the potential for rare but life-threatening AEs (e.g., sepsis with intravesical bacille Calmette-Guerin (BCG) administration, or risks associated with major surgery). With regard to duration of AEs, some AEs either diminish over time and/or readily cease upon cessation of the

treatment. Some AEs, however, can persist for long periods after the treatment has been discontinued (e.g., the need for intermittent self-catheterization in some patients several months after intradetrusor onabotulinumtoxin A [BTX-A] treatment. AEs also vary in their reversibility. Some medication side effects (e.g., macular damage from PPS) are irreversible. Major surgery is also irreversible.

Each set of treatments is presented below. Most treatments are designated as Options, except for physical therapy in the setting of pelvic floor tenderness (Standard) and triamcinolone injection and/or fulguration of Hunner lesions (Recommendation). In most cases, the designation of Option reflects the Panel's judgment that uncertainty existed for the balance between benefits and risks/burdens for a particular treatment. One source of uncertainty was the Panel's observation that most treatments may benefit a subset of patients that is not readily identifiable pre-treatment and but that no treatment reliably benefits most or all patients. Therefore, on average and for a particular patient, uncertainty exists for most treatments regarding the balance between benefits and risks/burdens. Uncertainty also is present when the available studies appear to demonstrate efficacy, but the total number of patients exposed to a particular treatment is small (e.g., cimetidine studies). In this circumstance the Panel judged that the small sample size constituted an additional source of uncertainty. For one treatment designated an Option (oral PPS), several randomized trials were available. In this case, the available evidence resulted in the judgment of relative certainty that the balance between benefits and risks/burdens was approximately equal because the trials were contradictory and that treatment is most appropriately designated as an Option.

Given the lack of understanding regarding pathophysiological causal factors in IC/BPS and the consequence that treatment goals are to control symptoms to optimize QoL, the Panel judged that the most appropriate course was to preserve treatments as clinical choices as long as some efficacy for some patients was demonstrated and the risk of serious harms was low. In contrast, fulguration of Hunner lesions was designated a Recommendation (based Grade C evidence) because little to no uncertainty existed regarding the fact that benefits (large and sustained treatment effects) clearly outweighed risks/burdens. The same rationale led to the designation of manual physical therapy as a Standard if appropriately trained clinicians are available.

## Behavioral/Non-pharmacologic Treatments

### Guideline Statement 9

**Patients should be educated about normal bladder function, what is known and not known about IC/BPS, the benefits versus risks/burdens of the available treatment alternatives, the fact that no single treatment has been found effective for the majority of patients, and the fact that acceptable symptom control may require trials of multiple therapeutic options (including combination therapy) before it is achieved. *Clinical Principle***

Patients should be educated on normal bladder function and what is known and not known about IC/BPS. Patients should be made aware that it is typically a chronic disorder requiring continual and dynamic management and. of that no single treatment has been found to be effective for a majority of patients. Adequate symptom control is achievable but may require trials of multiple therapeutic options to identify the regimen that is effective for that patient. Patients should be counseled that identifying an effective pain relief regimen may require multiple trials of different medications in order to identify the medication(s) that produce optimal effects for that particular patient. Further, patients should be informed that, given the chronic nature of IC/BPS, the typical course involves symptom exacerbations and remissions.

### Guideline Statement 10

**Self-care practices and behavioral modifications that can improve symptoms should be discussed and implemented as feasible. *Clinical Principle***

Clinical experience and a limited literature suggest that modifying certain behaviors can improve symptoms in some IC/ BPS patients.<sup>109</sup> Suggesting that patients become aware of and avoid specific behaviors which, reproducibly for a particular patient, worsen symptoms, is appropriate and can provide some sense of control in a disease process which can be a devastating ordeal. Behavioral modification strategies may include: altering the concentration and/or volume of urine, either by fluid restriction or additional hydration; application of local heat or cold over the bladder or perineum; avoidance of certain foods known to be common bladder irritants for IC/BPS patients such as coffee or citrus products; use of an elimination diet to determine which foods or fluids may contribute to symptoms; over-the-counter products (e.g., nutraceuticals, calcium glycerophosphates, phenazopyridine); techniques applied to trigger points and areas of hypersensitivity (e.g., application of heat or cold); strategies to manage IC/BPS flare-ups (e.g. meditation, imagery); pelvic floor muscle relaxation; and bladder training with urge suppression.<sup>110-114</sup> Other controllable behaviors or conditions that in some patients may worsen symptoms include certain types of exercise (e.g., pelvic floor muscle exercises – see below under Physical Therapy), sexual intercourse, wearing of tight-fitting clothing, and the presence of constipation. Triggers of flares and self-management strategies of flares have been described.<sup>114</sup>

NIDDK sponsored a multicenter trial that focused on treatment naïve IC/BPS patients. All patients underwent a standardized education and behavioral modification program (EBMP), including increased understanding of the bladder and voiding, techniques to manage stress and pain symptoms, management of fluid intake, bladder training and urge suppression, as well as avoidance of food and beverage "symptom triggers." Forty-five per cent of patients (n=136) assigned to the EBMP with placebo group were markedly or moderately improved on the Global Response Assessment, suggesting the significant benefits of self-care practices and behavioral modification even without the active drug.<sup>111</sup>

## Guideline Statement 11

**Patients should be encouraged to implement stress management practices to improve coping techniques and manage stress-induced symptom exacerbations. *Clinical Principle***

Psychological stress is associated with heightened pain sensitivity in general.<sup>115, 116</sup> In laboratory studies, stress increases IC/BPS symptoms.<sup>117</sup> Effective coping with family, work, and/or past traumatic experiences is an important component of symptom management. Recommendations for specific coping strategies are beyond the scope of this guideline. However, clinicians and patients should be cognizant of stressors as triggers for symptom exacerbation and patients should be encouraged and assisted to seek appropriate support for these issues from stress management or psychological counselors.

Clinicians also may want to include multi-disciplinary assistance as appropriate, to manage as many factors as possible that appear to precipitate or exacerbate symptoms for each individual patient. These factors may include IBS, endometriosis, recurrent vaginitis/vestibulitis, severe predictable flares occurring with phase of menstrual cycle, panic attacks, depression, etc.

## Guideline Statement 12

**Appropriate manual physical therapy techniques (e.g., maneuvers that resolve pelvic, abdominal and/or hip muscular trigger points, lengthen muscle contractures, and release painful scars and other connective tissue restrictions), if appropriately trained clinicians are available, should be offered to patients who present with pelvic floor tenderness. Pelvic floor strengthening exercises (e.g., Kegel exercises) should be avoided. Standard (Evidence Strength: Grade A)**

Many patients with IC/BPS exhibit tenderness and/or banding of the pelvic floor musculature, along with other soft tissue abnormalities.<sup>19, 73</sup> It is not known whether those muscular abnormalities are usually primary pain generators (giving rise to associated secondary bladder pain) or are themselves secondary phenomena elicited by the primary bladder pain of IC/BPS. Whatever their etiology, when such soft tissue abnormalities are present, clinical experience and a limited but high-quality literature suggest that manual physical therapy can provide symptom relief.<sup>118-123</sup> Specifically, Fitzgerald et al. (2012) reported findings from an RCT that tested ten 60 minute sessions over 12 weeks of myofascial physical therapy (MPT) compared to global therapeutic massage (GTM) in female IC/BPS patients. At 3 months, 59% of the MPT group reported moderate or marked improvement compared to 26% in the GTM group – a statistically significant difference. Improvements in pain, urgency, frequency, and scores on the ICSI, ICPI, and FSFI also were greater in the MPT group than in the GTM group, although the differences were not statistically significant. Very importantly, there is no evidence that physical therapy aimed at pelvic floor strengthening (such as Kegel exercises) can improve symptoms, and in fact this type of pelvic floor therapy may worsen the condition.

Appropriate manual physical therapy techniques include maneuvers that resolve pelvic, abdominal and/or hip muscular trigger points, lengthen muscle contractures, and release painful scars and other connective tissue restrictions.<sup>124</sup> Unfortunately, appropriate physical therapy expertise and experience is not available in all communities. In the absence of appropriate expertise, routine forms of pelvic physical therapy that are primarily aimed at strengthening of the pelvic floor are not recommended.

No well-designed studies have evaluated the possible therapeutic role for other forms of massage or other forms of bodywork, though interventions aimed at general relaxation have proven helpful in most other forms of chronic pain and can be recommended to IC/BPS patients.

## Guideline Statement 13

**Clinicians may prescribe pharmacologic pain management agents (e.g., urinary analgesics, acetaminophen, NSAIDs, opioid/non-opioid medications) after counseling patients on the risks and benefits. Pharmacological pain management principles for IC/BPS should be similar to those for management of other chronic pain conditions. *Clinical Principle***

Pain is a potent disrupter of QoL; pain management should be an integral part of the treatment approach and should be assessed at each clinical encounter for effectiveness. Despite the fact that IC/BPS is a chronic pain syndrome, little is known about effective pharmacological treatment for chronic pain in these patients.<sup>109, 21, 125</sup> The Panel's clinical experience reflected diverse approaches to effective pain management, ranging from primary management by the practicing urologist to use of a multidisciplinary team incorporating an anesthesia/pain specialist. The decision regarding how to approach this issue depends on the judgment and experience of the involved clinician(s), the severity of the patient's symptoms, and the availability of expertise and resources.

The goal of pharmacotherapy is to find medication/medications that provide significant pain relief with minimal side effects. Pain management tools include urinary analgesics, NSAIDs, narcotics, and a wide variety of nonnarcotic medications used for chronic pain which have been "borrowed" from the treatment of depression, epilepsy, arrhythmias, etc.

Given the current state of knowledge, pharmacological pain management principles for IC/BPS should be similar to those for management of other chronic pain states. Currently, there is no method to predict which drug is most likely to alleviate pain in a given IC/BPS patient. Clinicians and patients should be aware that a multimodal approach in which pharmacologic agents are combined with other therapies is likely to be the most effective. In addition, effective treatment of symptom flares may require a pain treatment protocol with some flexibility to manage flare-related breakthrough pain. Due to the global opioid crisis, the judicious use of chronic opioids is advised and only after informed decision-making with the patients and with periodic follow-ups to assess efficacy, adverse side effects, compliance, and potential of abuse or misuse. Non-opioids alternatives to manage pain should be used preferentially. The CDC has published guideline on prescribing opioids to manage chronic pain<sup>126</sup> and the AUA published a position statement on opioid use in 2016.

Some of the essential principles of pain management include:

1. The rights and responsibilities of the patient and clinician should be clearly stated at the outset; this may take the form of a pain management "contract."
2. All narcotic prescriptions must come from a single source.
3. Increasing doses of medication should be tied to improving function in activities of daily living (e.g., work, parenting, sexual intimacy, ability to exercise) rather than to just relief of pain. The patient and clinician should set mutual goals in these areas.
4. Patients who require continuous narcotic therapy should be primarily managed with long-acting narcotics. Small doses of short acting narcotics can be used for "breakthrough" pain.
5. Multimodality therapy may help to minimize narcotic use and the risk of tolerance. Narcotic medications should be used in combination with one of the non-narcotic drugs.
6. Complementary therapy (e.g., physical therapy, counseling/pain psychology, stress management), should be considered as they may minimize the dependence on pain medications.

It is important that the patient understand that finding the medication or combination of medications that provide effective pain control requires a 'trial and error' method of prescribing. The efficacy of each analgesic administered should be determined and only one drug should be titrated at a time; otherwise it is not possible to assess the effects of a certain drug on pain scores. The starting dose should always be the smallest available and titration should occur at frequent intervals, guided by pain scores and side effects. This requires frequent contact between the patient and the clinician. It is important for the patient and the prescribing clinician to understand that some side effects actually improve as the patient continues to take the drug for several weeks. If these side effects are not intolerable, then the patient should be guided through this period. Using these general guidelines of pain management, a pain medication or combination of pain medications can often be identified that significantly relieve pain in IC/BPS patients. Patients and clinicians should be aware that 100% pain relief is often not achievable; the focus of pain management is to minimize discomfort and maximize the patient's ability to function in daily life.

Whether pain management is best accomplished by the primary treating clinician and/or by a multidisciplinary team or other pain specialists should be determined by the individual clinician in consultation with the patient. Patients with intractable pain and/or complex presentations may require referral to other specialists to achieve satisfactory pain control. It is important to note that pain management alone does not constitute sufficient treatment for IC/BPS; pain management is one component of treatment. To the extent possible, it is essential that patients also are treated for the underlying bladder related symptoms.

## Oral Medications

### Guideline Statement 14

Amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate may be administered as **second-line** oral medications (listed in alphabetical order; no hierarchy is implied). **Option (Evidence Strength: Grades B, B, C, and B)**

**Amitriptyline (Evidence Strength: Grade B)** One randomized controlled trial reported efficacy of oral amitriptyline (25 mg daily titrated over several weeks to 100 mg daily if tolerated) to be superior to placebo (63% of treatment group clinically significantly improved compared to 4% of placebo group) at four months.<sup>127</sup> Two observational studies reported similar findings of 50% to 64% of patients experiencing clinically significant improvement using a similar dosing regimen at up to 19 months of follow-up.<sup>128, 129</sup> AEs were extremely common (up to 79% of patients) and, although not life-threatening, had substantial potential to compromise QoL (e.g., sedation, drowsiness, nausea). Medication side effects were the major reason for withdrawal from the studies. The

available data suggest that beginning at low doses (e.g., 10 mg) and titrating gradually to 75-100 mg if tolerated is an acceptable dosing regimen. Given that amitriptyline appears to benefit a subset of patients in the setting of a high likelihood for AEs that compromise QoL, it was designated as an Option. The 2013 update literature review retrieved an additional RCT. Foster and colleagues (2010) reported randomizing patients to 75 mg amitriptyline or placebo with all participants receiving a standardized education and behavioral modification program. The intention to treat analysis indicated that at three months the proportion of successes in each group defined by the Global Response Assessment (GRA) as moderate or marked improvement were statistically similar (drug – 55%; placebo – 45%). Patients that were able to titrate up to at least 50 mg in the drug group, however, had higher improvement rates – 66% (significantly greater than the placebo group). Of note is that the standardized education and behavioral modification program alone produced substantial improvement rates.<sup>111</sup>

**Cimetidine (Evidence Strength: Grade B)** One RCT reported efficacy of oral cimetidine (400 mg twice daily) to be statistically significantly superior to placebo in terms of total symptoms, pain, and nocturia after three months of treatment.<sup>130</sup> Two observational studies reported that oral cimetidine (300 mg twice daily or 200 mg three times daily) resulted in 44% to 57% of patients reporting clinically significant improvement at follow-up intervals of one and more than two years.<sup>131, 132</sup> No AEs were reported. Given the possibility that cimetidine may benefit a subset of patients without significant AEs in the context of a small total sample exposed to the drug (n=40, including the RCT), the lack of long-term follow-up data on sufficient numbers of patients, and its potential to interact with other drugs, oral cimetidine was designated as an Option.

**Hydroxyzine (Evidence Strength: Grade C)** One randomized controlled trial reported that more patients in the treatment group (23%) experienced clinically significant improvement compared to patients in the placebo group (13%) in response to oral hydroxyzine for six months (10 mg daily titrated to 50 mg daily over several weeks if tolerated); this difference was not statistically significant in this pilot study (study was a full factorial design that included a PPS arm which is discussed below).<sup>133</sup> One observational study reported that 92% of patients experienced clinically significant improvement (25 mg daily titrated up to 75 mg daily over several weeks); the patients in this study all had systemic allergies and may represent a patient subset that is more likely to respond to hydroxyzine.<sup>134</sup>

AEs were common (up to 82% of patients but with a similar proportion of placebo and treatment group patients reporting AEs in the RCT) and generally not serious (e.g., short-term sedation, weakness). The Panel interpreted the disparate findings between the RCT and the observational study to indicate uncertainty regarding the balance between benefits and risks/ burdens. Given the lack of serious AEs and the possibility that the medication may benefit a subset of patients, the administration of oral hydroxyzine was designated as an Option.

**Pentosanpolysulfate (Evidence Strength: Grade B).** PPS is the only FDA-approved oral agent for the treatment of IC/BPS and is by far the most-studied oral medication in use for IC/BPS. Because there were seven randomized trials reporting on more than 500 patients from which to draw evidence (including five trials that compared PPS to placebo, one trial that examined PPS dose-response effects, and one that compared PPS to CyA), the numerous observational studies on PPS were not used. The body of evidence strength was categorized as Grade B because although the individual trials were of high quality, the findings from the trials were contradictory.

Of the five trials that included PPS and placebo arms, four were RCTs. One multicenter RCT reported no differences at four months of follow-up in total symptom scores between PPS (200 mg twice daily) and placebo patients with statistically similar rates of clinically significant improvement in both groups (56% versus 49%, respectively).<sup>97</sup> One underpowered trial that included hydroxyzine and PPS-hydroxyzine arms also reported no statistically significant differences on any measured parameter at six months between PPS (100 mg three times daily) and placebo patients with statistically similar proportions reporting improvement (PPS 28% versus placebo 13%).<sup>133</sup> The other two trials by Mulholland and colleagues (1990) and Parsons and colleagues (1993) reported that at three months, a significantly greater proportion of the PPS patients (28% and 32%, respectively) reported improvement compared to placebo patients (13% and 16%, respectively).<sup>135, 136</sup> Both trials administered 100 mg PPS three times daily. The fifth trial was a randomized crossover design; data from Phase A (before the crossover) are most useful because they are free of any effects that may have persisted into Phase B.<sup>137</sup> This trial reported statistically significantly greater proportions of patients experiencing improvements in pain in the PPS group (44%) compared to the placebo group (15%) with trends in the same direction for urgency and frequency. One open-label randomized trial without a placebo control group compared PPS to CyA and reported that CyA patients experienced a statistically significantly higher rate (83%) of clinically significant improvement compared to PPS patients (21%).<sup>138</sup> The dose-response trial also lacked a placebo control group and reported at eight months no differences in proportions of patients experiencing clinically significant improvements (300 mg daily – 50%; 600 mg daily – 40%; 900 mg daily – 45%). A search on [clinicaltrials.gov](https://clinicaltrials.gov) for relevant unpublished trials revealed that NCT00086684, sponsored by Johnson & Johnson, was terminated early for lack of efficacy. This trial compared 100 mg PPS once daily, 100 mg PPS three times daily, and placebo for 24 weeks. The primary outcome was at least a 30% reduction in the ICSI. The proportion of responders was statistically indistinguishable: Placebo - 48/118 (40.7%); PPS 100 mg once daily – 51/128 (39.8%); PPS 100 mg three times daily – 52/122 (42.6%).

Overall, this relatively high-quality evidence demonstrates substantial overlap between proportions of patients expected to experience clinically significant improvement from PPS (21% to 56%) compared to from placebo treatment (13% to 49%). A meta-analysis of the five trials that included PPS and placebo arms revealed a statistically significant, but clinically somewhat weak, relative risk ratio of 1.69 (95% confidence interval = 1.16 to 2.46). AE rates were relatively low (10 to 20% of patients), generally not serious, and similar in treatment and placebo groups. Overall, the Panel judged that these findings provided some certainty

that the balance between benefits and risks/burdens on average is relatively equal and that, similar to other oral treatments, oral PPS may benefit only a subset of patients not readily identifiable a priori. Administration of oral PPS, therefore, is designated an Option. Note that there is some evidence that PPS has lower efficacy in patients with Hunner lesions.<sup>139</sup>

## Guideline Statement 15

Clinicians should counsel patients who are considering pentosan polysulfate sodium on the potential risk for macular damage and vision-related injuries. *Clinical Principle*

There have been recent reports of a unique retinal pigmentary maculopathy that is associated with PPS use. Symptoms have included difficulty reading, slow adjustment to low or reduced light environments, and blurred vision. The initial evidence consisted of case reports and small case series, but subsequent large retrospective cohort studies confirmed the association.<sup>140-142</sup> The prevalence of maculopathy varies widely in PPS users but appears to be related to the cumulative amount of PPS exposure. Given these concerns, the FDA approved a new warning label for PPS in June 2020<sup>143</sup> which states that:

- A detailed ophthalmologic history should be obtained in all patients prior to starting treatment with PPS.
- For patients with preexisting ophthalmologic conditions, a comprehensive baseline retinal examination is recommended prior to starting therapy.
- In addition, a retinal examination is suggested for all patients within six months of initiating treatment and periodically while continuing treatment. If pigmentary changes in the retina develop, then risks and benefits of continuing treatment should be reevaluated, since these changes may be irreversible.

## Guideline Statement 16

Oral cyclosporine A may be offered particularly for patients with Hunner lesions refractory to fulguration and/or triamcinolone. *Option (Evidence Strength: Grade C)*

One randomized trial with an oral PPS group for comparison reported that CyA (3 mg/ kg/day divided into two doses) resulted in 75% of patients experiencing clinically significant improvement compared to 19% of a PPS comparison group after six months of treatment.<sup>138</sup> In addition, 38% of the CyA group reported a 50% decrease in frequency compared with 0% of the PPS group. Two observational studies reported similar high rates of efficacy, including significant pain relief in 91% of patients after six weeks of treatment accompanied by decreases in frequency and increases in voided volumes<sup>144</sup> and after an average one year of treatment, 87% of patients reporting that they were pain-free with similar improvements in voiding parameters.<sup>182</sup> In the second study, some patients had been followed for more than five years, with continued reports of efficacy as long as the medication was maintained.<sup>145</sup> In the randomized trial, AE rates were higher in the CyA arm (94%) than in the PPS arm (56%), with three serious AEs in the CyA arm (increased blood pressure, increased serum creatinine) and one serious AE in the PPS arm (gross hematuria).<sup>138</sup> In the observational studies, AE rates ranged from 30% to 55% and included hypertension, gingival hyperplasia, and facial hair growth.<sup>144, 145</sup>

The update literature review in 2014 retrieved two new observational studies. One retrospective study<sup>146</sup> pooled findings from three centers (Urologic Specialists of Oklahoma – USO; Stanford University – SU; University of Kentucky – UK). This paper reports on a total of 44 patients followed for from mean 15 months (USO) to mean 30 months (SU and UK). Overall, 59% of patients reported a meaningful response measured as either a GRA-based improvement or 50% reduction in ICSI score. Improvements were generally maintained as long as the medication was maintained. Success rates, however, were much higher (29/34; 85%) among patients with Hunner lesions compared to those without lesions (3/10; 30%). In addition, the authors note that the patients without Hunner lesions who had improvement did not improve to the same degree as patients with Hunner lesions. AE rates were high with approximately half of patients reporting at least one AE. AEs included increased serum creatinine (some cases managed by adjusting dose downward), hypertension (managed with anti-hypertensive meds), alopecia, cutaneous lymphoma, mouth ulcers, and acute gout (managed with allopurinol). Of the 34 patients with Hunner lesions, although 29/34 (85%) had a successful response, six of these patients stopped the medication for AEs, leaving a final success rate of 68% (23/34).

Ehren and colleagues (2013) evaluated responses to CyA for 16 weeks (3 mg/kg/day for 12 weeks with reduced dosage for final four weeks) in 10 patients with Hunner ulcers.<sup>147</sup> These investigators also measured bladder nitric oxide as a putative marker for treatment effects. ICSI and ICPI scores decreased during treatment (baseline mean symptom score 16, dropping to 8 at 12 weeks of treatment, and rising to 12 after discontinuation of CyA for two weeks; baseline mean problem score 14, dropping to 6 at week 12, rising to 9 two weeks post CyA discontinuation). All patients exhibited elevated bladder nitric oxide formation at baseline that gradually decreased with treatment and began rising with treatment discontinuation. An additional six patients withdrew for side effects (diarrhea, abdominal pain, elevated bilirubin; n=5) or were excluded (UTI; n=1).

In a prospective study of 26 patients with refractory IC/BPS (including 7 with Hunner lesions), patients received CyA at 3 mg/Kg twice a day for 3 months.<sup>148</sup> Based on intention to treat analysis at 3 months, 31% of the patients reported improvement in the GRA scale, 15% in the ICSI, and 19% in the ICPI scores. On univariate analysis, the presence of Hunner lesions was associated

with >50% improvement in ICSI and ICPI scores, but the results are not precise (OR=15.4; 95% CI: 1.7 – 224.6; p=0.01, and OR=11.3; 95% CI: 1.11 – 114.4; p=0.04, respectively). A decline in renal function at three months of treatment, which then improved back to baseline levels at one to two months after drug discontinuation, was reported.

Taken together, these data suggest sustained efficacy, particularly in patients with Hunner lesions or with active bladder inflammation; however, because of the relatively small number of patients treated, the lack of long-term follow-up data on large numbers of patients, and the potential for serious AEs (e.g., immunosuppression, nephrotoxicity), the Panel judged some uncertainty remains in the balance between benefits and risks/burdens. The decision to use oral CyA, therefore, is an Option. Patients taking CyA should have close monitoring, especially for renal function and blood pressure. A monitoring protocol should also take into account the risks of hepatotoxicity, hyperuricemia, hypomagnesemia, hematologic abnormalities and malignancies, especially skin cancer and lymphomas.

## Intravesical Instillations

### Guideline Statement 17

**DMSO, heparin, and/or lidocaine may be administered as intravesical treatments (listed in alphabetical order; no hierarchy is implied). Option (Evidence Strength: Grades C, C, and B)**

**DMSO (Evidence Strength: Grade C)** Two randomized crossover trials reported on the efficacy of intravesical DMSO for IC/BPS patients. Given the potential for placebo effects to persist for long periods, only the data from the first phases were examined if reported (i.e., before the crossover). In the first study, blinded evaluators used urodynamic and voiding parameters to rate patient improvement ("objective criteria") and patients rated global improvement ("subjective criteria").<sup>149</sup> The protocol was four treatments of 50 cc 50% DMSO instilled at two-week intervals with 15-minute retention; patients were evaluated at one month post-treatment. At the end of Phase 1, evaluators indicated that 93% of DMSO patients and 35% of placebo patients were improved. Patient ratings of improvement were similar to evaluator ratings in the DMSO group (87%) and higher than evaluator ratings in the placebo group (59%). The second trial used six weekly instillations and reported that 47% of patients administered DMSO (retention interval not specified) reported improvement compared to 0% of a BCG (two hour retention) instillation group at three months.<sup>150</sup> There was no placebo group in this study and data were not broken out between phases. Several observational studies using similar formulations and instillation protocols ranging from weekly to monthly to PRN and follow-up intervals of a few months to several years reported efficacy rates of 25 to 90%.<sup>151-153</sup> AE rates varied widely across studies, likely reflecting different author thresholds for what constituted an AE, but did not appear serious. Given the available data, particularly the wide range of efficacy rates reported, intravesical DMSO instillation was designated as an Option. If DMSO is used, then the panel suggests limiting instillation dwell time to 15-20 minutes; DMSO is rapidly absorbed into the bladder wall and longer periods of holding are associated with significant pain. DMSO is often administered as a part of a "cocktail" that may include heparin, sodium bicarbonate, a local steroid, and/or a lidocaine preparation. New studies published since the publication of the original guideline report combining DMSO with heparin, hydrocortisone, sodium bicarbonate, bupivacaine, and/or triamcinolone.<sup>154-158</sup> At follow-up durations ranging from six weeks to 12 months, efficacy rates ranged from 61% to 70% with some studies also reporting significant improvements in voiding parameters and validated questionnaires. The Panel notes that if a clinician chooses to administer a "cocktail" preparation, then he or she should be aware that DMSO potentially enhances absorption of other substances, creating the possibility for toxicity from drugs such as lidocaine. No clinical studies have addressed the safety or increased efficacy of these preparations over DMSO alone or of various cocktails in comparison to one another.

**Heparin (Evidence Strength: Grade C)** Three observational studies reported findings from the use of intravesical heparin. Using 10,000 IU heparin in 10cm<sup>3</sup> sterile water three times a week for three months with retention of one hour, at three months 56% of patients reported clinically significant improvement.<sup>159</sup> A subset of responders continued the treatments for up to one year, resulting in 40% of patients overall reporting continued relief at the one year point. Using 25,000 IU in 5 ml distilled water twice a week for three months, at three months 72.5% of patients reported significant relief.<sup>160</sup> Efficacy also was reported when combining heparin with lidocaine (40,000 IU heparin, 3 ml 8.4% sodium bicarbonate with 8 ml 1% or 2% lidocaine; see Parsons [2005], under intravesical lidocaine) and when combined with lidocaine and triamcinolone (20,000 units heparin, 20 ml 2% lidocaine, 40 mg triamcinolone; see Butrick under intravesical lidocaine).<sup>161, 162</sup>

Two new studies retrieved as part of the update literature review in 2014 reported findings from instillation of heparin in combination with alkalinized lidocaine.<sup>163, 164</sup> One study was a randomized double-blind placebo-controlled crossover; the other was a prospective observational design. The crossover study (Parsons et al., 2012) reported that at 12 hours after a single instillation, 50% of patients reported a successful response to the active instillation with a 42% reduction in pain but only 13% reported a successful response to the placebo instillation accompanied by a 21% reduction in pain.<sup>163</sup> The observational study (Nomiya et al., 2013) administered instillations weekly for 12 weeks and followed patients for 6 months.<sup>164</sup> The proportion of responders rose from 33.3% at week 1 to 90% one month after completion of 12 instillations and then diminished to 16.7% by 6 months after the last instillation. Up to approximately 2 months after the last instillation, significant improvement in OSSI and OSPI scores, pain VAS, voided volumes, frequency, and nocturia also were reported.

AEs were infrequent and appear minor. In the absence of placebo-controlled trials, it is difficult know the balance between benefits and risks/burdens. It does appear that intravesical heparin on its own and in combination with other substances may benefit a subset of patients. For these reasons, it is designated an Option.

**Lidocaine (Evidence Strength: Grade B)** One multi-center RCT reported that 3 and 10 days after treatment (10 mL PSD597; patented combination of 200 mg lidocaine alkalinized with sequential instillation of 8.4% sodium bicarbonate instilled once daily for 5 consecutive days with one hour retention), more patients in the treatment group (30% and 24% respectively) experienced clinically significant improvement compared to patients in the placebo group (10% and 11.5%, respectively); these differences were statistically significant at day 3 but not at day 10.<sup>165</sup> An open-label phase followed the placebo control phase in this trial; in the open-label phase after five treatments 54% of patients at three days and 48% at ten days reported significant improvement. The available observational studies reported even higher short-term efficacy rates.<sup>161, 166, 167</sup> Alkalization increases urothelial penetration of lidocaine and therefore is expected to improve efficacy, but it also can increase systemic absorption and potential toxicity. No published studies have directly compared lidocaine with and without alkalinization. In one series from a large gynecology practice, a lidocaine cocktail without bicarbonate (20,000 units heparin, 20 ml 2% lidocaine, 40 mg triamcinolone) improved symptoms for 73% of BPS/IC patients.<sup>162</sup>

No studies have directly compared different lidocaine concentrations. In one open-label trial, patients originally received 40,000 units heparin, 8 mL 1% lidocaine and 3 mL 8.4% sodium bicarbonate, with a success rate of 75%. The success rate increased to 94% after increasing the lidocaine concentration to 2%.<sup>161</sup> AEs are typically not serious but include dysuria, urethral irritation, and bladder pain.

Given that intravesical lidocaine instillation appears to offer relief to a subset of patients but that the relief is short-term (i.e., less than two weeks) and the procedure can be associated with pain, this treatment alternative was designated an Option.

Heparin or PPS may be added to lidocaine alone. In one study comparing lidocaine plus PPS versus lidocaine alone, some outcome measures were better in the lidocaine plus PPS group.<sup>168</sup> An update to the literature in 2022 further showed the efficacy of heparin and lidocaine combined for relieving pain and urgency symptoms associated with IC/BPS in two studies (prospective and randomized cross-over). In the first study, 32 patients with refractory IC/BPS were given intravesical instillation of heparin-lidocaine (20,000 units heparin, 5 mL 4% alkalinized lidocaine, 25 mL 7% sodium bicarbonate) weekly for 12 weeks. Response rate during treatment was 33%, 60%, and 77% after the first, fourth, and 12<sup>th</sup> instillation, respectively. At one month after the last instillation, 90% of the patients reported relief of symptoms, but this rate declined to 46.7% and to 16.7% at 2 and 6-months, respectively.<sup>164</sup> In the second study, patients were randomly allocated to receive either 10 mL lidocaine solution (10 mL 2% lidocaine, 3 mL 8.4% sodium bicarbonate, 2 mL pH 7.2 sterile water) or 15 mL heparin-lidocaine combined (50,000 units heparin, 200 mg lidocaine hydrochloride) and followed for 24 hours.<sup>169</sup> Heparin-lidocaine combined significantly reduced the percentage of bladder pain (38% versus 13%; p=0.029) and urgency (42% versus 8%; p=0.003) compared to lidocaine alone. Similarly, the GAR of symptoms was significantly improved in the heparin-lidocaine group at 1 hour compared to lidocaine alone (77% versus 50%; p=0.04) and at 24 hours (57% versus 23%; p=0.002).

Another study administered 20 mL of either alkalinised lidocaine (n=16) or normal saline (n=8) for 20 minutes to patients with signs of suggestive BPS on urodynamics.<sup>170</sup> Eleven patients in the lidocaine group (68.7%) responded to treatment. Administration of lidocaine significantly improved the maximal cystometric capacity (MCC) among responders (192-261 mL, p=0.005) while no significant difference in the MCC was observed among patients treated with the normal saline (190-183 mL; p=0.879).

## Procedures

### Guideline Statement 18

**Cystoscopy under anesthesia with short-duration, low-pressure hydrodistension may be undertaken as a treatment option. Option (Evidence Strength: Grade C)**

Cystoscopy under anesthesia with low-pressure (60 to 80 cm H<sub>2</sub>O), short duration (less than 10 minutes) hydrodistension may be undertaken and serves three purposes. First, before distension, the bladder is inspected for other potential symptom causes (e.g., stones, tumors) and for Hunner lesions. If these are found, then they are treated appropriately. Second, if no bladder abnormalities or ulcers are found, then the distension may proceed and serve as a treatment. Hunner lesions can be easier to identify after distension when cracking and mucosal bleeding become evident. Third, distension allows for disease "staging" by determining anatomic as opposed to functional bladder capacity and identifying the subset of patients who suffer reduced capacity as a result of fibrosis.

Most Hunner lesions can be diagnosed with office cystoscopy without hydrodistention of the bladder under anesthesia.<sup>86, 102, 104</sup> Therefore, office cystoscopy should be performed in patients in whom Hunner lesions are suspected, unless patients prefer to have cystoscopy performed under anesthesia (Statement 4). If Hunner lesions are identified, patients can proceed to receive fulguration and/or injection of triamcinolone under anesthesia (Statement 19). If Hunner lesions are not identified, hydrodistention under anesthesia remains an option (see Figure 1).

Three observational studies reported that one or two exposures to low-pressure, short-duration hydrodistension resulted in clinically significant relief of symptoms for a subset of patients that declined over time: at one month efficacy ranged from 30% to 54%; at two to three months, from 18% to 56%; at five to six months, from 0% to 7%.<sup>171-173</sup> No AEs were reported. Two additional studies identified in the 2014 update literature review reported improvement rates for various symptoms that ranged from 65% to >90% at 6 to 9 months of follow-up.<sup>174, 175</sup> In the absence of placebo controls, it is difficult to know the size of the true treatment effect and the precise balance between benefits and risks/burdens. Given the procedure may benefit a subset of patients, low-pressure, short-duration hydrodistension is designated as an Option. However, the possible benefits must be balanced against the possibility of a (usually temporary) flare of symptoms after distention. If Hunner lesions are detected, then their treatment is recommended.

An update to the literature in 2022 found three retrospective studies that showed short-duration (<5 min) hydrodistension with either 80 cm (n=2) or 100 cm (n=1) H<sub>2</sub>O pressure provides significant symptom relief of bladder pain and does not decrease bladder capacity, even with multiple procedures.

In a chart review study comparing 48 patients treated with transvaginal trigonal block with hydrodistension versus 58 patients treated with hydrodistension alone, hydrodistension was associated with decreased pain regardless of trigonal block or time of distension.<sup>176</sup> A trigonal block consists of injecting 0.25% bupivacaine with 1.0% xylocaine into the anterior vagina under the trigone prior to hydrodistension; and hydrodistension was performed at low-pressure (80 cm H<sub>2</sub>O), short duration (2-5 min). At one month post-hydrodistension, both groups reported significant improvement in pain scores ( $p<0.0001$ ) with no significant differences observed between groups (-2.9 versus 2.6;  $p=0.694$ ). No significant difference in post-treatment pain score was observed between 2-min versus > 5 min hydrodistension (-3.0 versus -2.2;  $p=0.061$ ).

In a second study, multiple procedures (median 3, range 2-18) of hydrodistension (80 cm H<sub>2</sub>O for 2 min) did not decrease bladder capacity in patients with IC/BPS (initial and final bladder capacities: 730 cc versus 750 cc;  $p=0.40$ ), and significantly improved the AUA symptom and QoL scores, as well as GUPI urinary and QoL scores.<sup>177</sup> Similar results were reported for patients with and without Hunner lesions for whom multiple therapeutic hydrodistension with 100 cm H<sub>2</sub>O for 5 minutes, over several years, did not significantly change bladder capacity.<sup>178</sup>

## Guideline Statement 19

If Hunner lesions are present, then fulguration (with electrocautery) and/or injection of triamcinolone should be performed. **Recommendation (Evidence Strength: Grade C)**

If Hunner lesions are found, then the Panel recommends that fulguration (with laser, cautery) and/or injection of triamcinolone be undertaken. Patients should be counseled that periodic retreatment is likely to be necessary when symptoms recur. One observational study using diathermy reported at follow-up intervals ranging from two to 42 months that 100% of patients experienced complete pain relief and 70% experienced reduced or normalized frequency.<sup>179</sup>

Three additional observational studies were retrieved in the 2014 update literature review. Two studies used primarily fulguration; one used electrocautery.<sup>151, 180, 181</sup> All three studies reported that a large proportion of patients (range 75% to 86%) experienced marked or complete pain relief post-treatment. Treatment response durations varied, with Payne et al. (2009) reporting a treatment response duration of mean 22.3 months, Hillelsohn et al. (2012) reporting a duration of mean 20.3 months, and Jhang et al. (2013) reporting a duration of mean 2.4 months with longer durations obtained after re-treatment. AEs were not addressed (Hillelsohn 2012), reported as not occurring (Payne 2009), or reported as one case of minor bladder perforation treated with an indwelling catheter for one week (Jhang 2013).

Two observational studies using Nd:YAG lasers (delivering 15 to 30 watts, pulse duration of one to three seconds) reported at follow-up intervals of 10 to 23 months that from 80 to 100% of patients experienced sustained and clinically significant relief from pain, urgency, and nocturia.<sup>182, 183</sup> The laser studies suggest that at follow-up durations up to 23 months, a large proportion of patients (up to 46%) may require periodic re-treatment to maintain symptom control; clinical experience suggests that this proportion is probably much higher, particularly at longer follow-up durations.

Lesions also may be treated using submucosal injections of a corticosteroid (10 mL of triamcinolone acetonide, 40 mg/mL, injected in 0.5 mL aliquots into the submucosal space of the center and periphery of ulcers using an endoscopic needle); this procedure resulted in 70% of patients reporting improvement with an average improvement duration of seven to 12 months.<sup>184</sup>

Thirteen studies were found to support the statement in 2022. Seven studies used electrocautery, four used triamcinolone injection, one used electrocautery and triamcinolone injection in those with recurring symptoms after electrocautery, and two studies used transurethral resection. All the studies reported that clinical symptoms and QoL improved after treatment, but there was recurrence of symptoms. A recent systematic review summarized the results of Hunner lesions treatments and also supported this statement.<sup>100</sup>

**Electrocautery** Six retrospective and one prospective study reported on the efficacy of electrocauterization of Hunner lesions. In the first study, hydrodistension with electrical fulguration significantly decreased nocturia and improved mean voided volume at 1-month post-treatment in patients with and without nocturnal polyuria; the change in the number of nocturia episodes per 24 hours

was  $-2 \pm 1.7$  (p=0.001) and  $-1.5 \pm 1.8$  (p=0.003) and the mean voided volume improved from 95 to 176 mL, and from 99 to 174 mL in those with and without nocturnal polyuria, respectively.<sup>185</sup>

Another study reported symptom improvement in 89.6% of patients (56.3% reported marked improvement, 20.8% moderate, and 12.5% mild improvement). On a 0-10 scale (none to worst possible) before and after electrocautery, frequency improved from  $9.04 \pm 1.30$  to  $3.65 \pm 2.75$  (p<0.001), urgency from  $8.40 \pm 2.38$  to  $3.28 \pm 2.71$  (p<0.001), and pain from  $8.62 \pm 2.36$  to  $2.68 \pm 2.55$  (p<0.001).<sup>186</sup> The study further reported that multiple electrocauterizations of Hunner lesions did not diminish bladder capacity significantly (mean difference  $-16.22 \pm 20.72$  mL; p=0.437) but the number of electrotherapies was negatively correlated with the change in bladder capacity (r=-0.285; p=0.05).

Four more studies reported pain relief after treatment, but response decreased gradually over time. Jhang et al.<sup>187</sup> reported bladder pain relapse at 2-4 months in 66% (6/9) of the patients, Ryu et al.<sup>188</sup> reported a decrease in fulguration success rates from 94.1% to 70% to 33.3% at 2-, 5-, and 10 months, respectively. Kajiwara et al.<sup>189</sup> reported symptoms recurrence in 26% (6/23) of the patients after a mean response of 16.2 months. The fourth study was comprised of 126 patients with Hunner lesions and evaluated long-term outcomes of hydrodistension and outcome predictors.<sup>190</sup> The mean time to therapeutic failure defined as repeated hydrodistension, bladder instillation therapy, or narcotic use for pain control, was 28.5 months. A multivariable analysis identified lumbar spinal stenosis (LSS) as a predictor for failure (HR = 18.8; p=0.001); the mean time to therapeutic failure was shorter in patients with concomitant LSS than in those without LSS. According to a final retrospective study, repeated bladder hydrodistension and transurethral fulguration (TUF) with electrocautery of recurrent Hunner's lesions improved symptoms for 44 patients who had undergone 117 procedures. There was a tendency toward an increase in bladder capacity, and repeated hydrodistension with TUF did not reduce bladder capacity.<sup>191</sup>

**Triamcinolone Injection** Four retrospective studies reported significant improvement in clinical symptoms (urinary frequency, urgency, pain) and QoL of patients after treatment of Hunner lesions with triamcinolone injection. Two of the studies used 60 mg at the site of the lesion,<sup>192, 193</sup> and the other two studies used 40 mg.<sup>194, 195</sup> The study by Jiang et al.<sup>195</sup> (n=35; 22 type II, 13 type III) reported efficacy at 4-weeks of submucosal injection at the bladder hemorrhage site and/or into the center of Hunner lesions (0.5 mL, 40 mg/mL per point, up to 20 points). Patients with an advanced age (p=0.015), high pain scores (p=0.040), higher International Prostate Symptom Scores (p=0.037) and Pelvic Pain and Urgency/Frequency (PUF) symptom scale scores (p=0.020) were more likely to benefit from treatment. A study by Funaro et al.<sup>192</sup> comprising 36 patients refractory to conservative treatment reported that 26 (72.2%), 8 (22.2%), and 2 (5.6%) of the patients received 1, 2, or at least 3 sets of injections, respectively, with similar initial improvement observed in all patients, followed by deterioration over several months. Mateu et al.<sup>194</sup> reported that patients required retreatment due to either nonresponse (15%; 3/20) or pain recurrence after 4 months (25%; 5/20).<sup>194</sup>

**Electrocautery versus Triamcinolone Injection** One retrospective study reported subjective improvement in 81.8% of the patients after biopsy/fulguration at 3 years follow-up, and in 91.4% of the patients with recurrent lesions after fulguration underwent triamcinolone injection. Seventy-four percent of the patients (26/35) had repeat injections; the median number of injections was 1.5, median time between injections was 8 months.<sup>196</sup> Mean AUA symptom scores and QoL improved significantly with both biopsy/fulguration and triamcinolone injection. At the last follow-up, 34.3% (12/35) of the patients were planning for repeat injection for symptom recurrence. Concurrent CyA was used in patients with recurrent symptoms 47.2% (26/55), and 7.2% (4/55) went on to have a cystectomy.

Hunner lesion treatment appears to constitute one of the few IC/BPS therapies that results in improvement measured in months with only a single exposure to the procedure. AEs for laser and injection studies were minimal. For these reasons, the Panel judged that the benefits of Hunner lesion treatment outweigh risks/burdens and recommend that it be offered.

## Guideline Statement 20

**Intradetrusor onabotulinumtoxin A may be administered if other treatments have not provided adequate improvement in symptoms and quality of life. Patients must be willing to accept the possibility that intermittent self-catheterization may be necessary. Option (Evidence Strength: Grade C)**

**Intradetrusor onabotulinumtoxin A** Six observational studies reported on the use of BTX-A to treat IC/BPS symptoms. Two studies reported high initial efficacy rates of 74% and 86% at three months.<sup>197, 198</sup> One study reported that BFLUTS and KHQ scores and frequency improved significantly at 3.5 months.<sup>199</sup> Effectiveness diminished over time, however, and at one year symptoms were indistinguishable from baseline values.<sup>200</sup> One study reported a low efficacy rate at three months with only 20% of patients exhibiting improvement.<sup>201</sup>

The update literature review in 2014 retrieved ten new studies, including one RCT<sup>202</sup> and nine prospective observational studies reporting on a total of 378 patients. It should be noted that several studies appear to include overlapping patient groups.<sup>203-207</sup> As a group, these studies represent a major shift in how BTX-A is employed to treat IC/BPS in several ways, including the combination of BTX-A with hydrodistension, the use of primarily the 100 unit dose, the use of repeat treatments with symptom return, and following of patients for years rather than months. Some interpretive challenges remain given that injection sites vary across studies and that several studies appear to use overlapping patient groups and do not constitute independent replications.

**Combining BTX-A with hydrodistension** An RCT (Kuo & Chancellor 2009) compared three groups: BTX-A 200 units in the posterior and lateral bladder walls with hydrodistension two weeks later; BTX-A 100 units in the same sites with hydrodistension; and hydrodistension with a second hydrodistension two weeks later. Patients were followed for two years. Patients designated as successes based on a GRA were 80% at 3 months to 47% at 24 months in the BTX-A 200 + hydrodistension group, 72% at 3 months to 21% at 24 months in the BTX-A 100 + hydrodistension group, and 48% at 3 months to 17% at 24 months in the hydrodistension only group. Only the BTX-A groups demonstrated significant improvements in pain VAS scores and maximum bladder capacity; importantly the 200 unit dose did not exert a greater effect than the 100 unit dose. Rates of AEs were much higher and more serious in the 200 unit group with almost half of the group experiencing dysuria and a third of the group exhibiting a large post-void residual. These AEs were of sufficient concern such that the remaining patients that had been randomized to receive 200 units instead were treated with 100 units accounting for the imbalance in group size.

Chung (2012) also combined BTX-A (100 units in the posterior and lateral bladder walls) with hydrodistension and reported significant improvement in virtually all measured outcomes with a GRA-based success rate of 52.2% at 6 months of follow-up.<sup>208</sup> About one-third of patients had dysuria but there were no cases of urinary retention and no need for clean intermittent self-catheterization (CISC).

**Re-treatment with BTX-A** Giannantoni, Mearini (2010) treated patients with 200 units in the lateral bladder walls and trigone with re-treatment when benefits began to decline (mean re-treatment interval 5.25 months).<sup>209</sup> Patients were followed for two years. Most measured outcomes exhibited significant improvement that was maintained over time with repeat injections. More than half of patients experienced dysuria (200 unit dose); this AE was managed with alpha blocker medications and no CISC was required. Over the course of the study, there were two UTIs that responded to antibiotics.

Pinto (2010 and 2013) injected 100 units into the trigonal wall with retreatment upon symptom return and followed patients for up to three years.<sup>206, 207</sup> Duration of improvements in pain VAS, frequency, voided volume, and QoL were 9 to 10 months after each treatment. In Pinto (2010), nearly one-third of patients had UTIs after the second treatment (but not after the other treatments); there was no urinary retention or CISC required.<sup>206</sup> In Pinto (2013), a similar pattern of AEs was reported.<sup>207</sup>

Shie (2012) injected 100 units in the posterior and lateral bladder walls with re-treatment every six months regardless of symptom status for a total of four treatments.<sup>210</sup> After treatment one, but not treatments two through four, hydrodistension was performed. Patients were followed for two years with improvements in pain VAS, O'Leary-Sant scores, and frequency restored with each treatment. These authors did not address AEs.

**Re-treatment with BTX-A and hydrodistension** Kuo (2013a, 2013b) and Lee and Kuo (2013) injected 100 units into the posterior and lateral bladder walls followed by hydrodistension.<sup>203-205</sup> The BTX-A plus hydrodistension treatment was repeated every six months unless improvements were maintained. Patients were followed for two years. Generally, after each treatment improvements were noted in pain VAS scores, ICSI and ICPI scores, frequency, nocturia, and bladder capacity. GRA-based success rates were high, ranging from 50% to 77% at various time points. Importantly, two of the three papers note that patients with Hunner lesions did not improve with this regimen and were treated successfully with electrocautery (Kuo 2013) or electrofulguration (Lee & Kuo 2013). AEs consisted of approximately 10% of patients with UTIs (after one of up to four treatments), approximately 42% with dysuria with rates diminishing as number of treatments increased, one patient with acute urinary retention (after treatment 2), one patient with hematuria, and only one patient requiring CISC (after treatment 3).

In 2022, two new randomized controlled trials, one prospective, and one retrospective observational study were added to the evidence base.

In a Phase II trial, 10 trigonal injections of 1 mL BTX-A produced statistically significant improvement in bladder pain and QoL and was well tolerated when compared to sodium chloride (placebo).<sup>211</sup> In another trial, patients were randomly allocated into either immediate (group A) or 1-month delayed injection (group B) of BTX-A 100 units. After one-month delayed injection, participants from both groups were considered a single cohort and followed-up every month for one year.<sup>212</sup> As a comparative cohort in the first month, the response rate was significantly higher among those who received the intervention when compared to those who did not (72.2% and 25.0%, respectively; p=0.01). All the symptom scores and QoL index significantly improved, whereas none of the frequency volume chart variables showed significant changes. One month after allocation as a single cohort (one month after delayed injection), all the symptomatic parameters, except nocturia, significantly improved. No significant differences were observed when comparing patients with (n=24) and without (n=10) Hunner lesions.

A prospective study reported that intratrigonal BTX-A injection (100 units in 10 trigonal sites, each receiving 10 units in 1 mL of saline) in patients with (n=10) and without (n=14) refractory ulcerative IC/BPS significantly improved pain intensity, frequency, nocturia, OSS, QoL, and urinary levels of neurotrophines, with similar efficacy duration (9±2.8 and 10.5±2 months, respectively).<sup>213</sup> Similar results were reported in a retrospective study where BTX-A intravesical injection effectively improved symptoms with a remarkable reduction in bladder pain. Furthermore, a multivariable analysis identified maximum bladder capacity ≥760 as the only predictive factor for a satisfactory BTX-A, 100 U injection outcome.<sup>214</sup>

In the absence of placebo-controlled studies, the true effect of BTX-A is not possible to determine. However, overall, the BTX-A studies suggest that a subset of patients experiences symptom relief for several months after treatment with a return to baseline symptom levels over time. Common AEs included dysuria, the need for abdominal straining to void, large post-void residuals (greater than 100 mL), and the need for CISC that persisted for one to three months and in some cases longer.

The Panel notes that patients must be willing to accept the possibility that CISC may be necessary post-treatment. This option is not appropriate for patients who cannot tolerate catheterization and is relatively contraindicated for patients with any evidence of impaired bladder emptying. Given the potential short-term efficacy in the context of a possibly serious AE profile, the Panel judged that intradetrusor BTX-A administration is an Option with the decision best made by the individual clinician and patient.

## Guideline Statement 21

**A trial of neuromodulation may be performed if other treatments have not provided adequate symptom control and quality of life improvement. If a trial of nerve stimulation is successful, then the permanent neurostimulation device may be implanted. Option (Evidence Strength: Grade C)**

Three studies reported findings from permanent implant of sacral or pudendal neuromodulation devices. It is important to note that neuromodulation is not currently FDA-approved for IC/BPS treatment; however, many patients meet the frequency/urgency indication for which sacral neuromodulation is approved. One study used a randomized crossover design to test temporary sacral versus pudendal neuromodulation and allowed patients to select the preferred lead for permanent implantation.<sup>215</sup> At six months post-implant, 66% of patients reported clinically significant improvement with patients who had selected pudendal implants reporting greater symptom relief than those who selected sacral implants. Two additional observational studies reported on post-implant outcomes at 14 months.<sup>216</sup> In one study, 94% of patients reported improvements in bladder capacity, frequency, voided volume, nocturia, pain, and ICSI/ICPI scores; the remaining 6% reported improvement in all parameters except for ICSI/ICPI scores.<sup>216</sup> In the other study (a chart review), patients reported sustained improvements in frequency, nocturia, the UDI-6, and fecal incontinence. AEs appeared to be minor (i.e., need for reprogramming, sterile seroma around the electrode).<sup>217</sup>

New evidence retrieved in the update literature review in 2014 was comprised of four retrospective observational studies reporting on a total of 109 patients.<sup>218-221</sup> All four studies used sacral placement of neuromodulation. Of note is that Powell & Kreder (2010) report that patients are significantly less likely to experience success at the testing phase with use of percutaneous nerve evaluation compared to use of a permanent quadripolar lead in the testing phase.<sup>221</sup> Mean/median follow-up ranged from 60 to 86 months with some patients having been followed for much longer (e.g., up to 14 years). Success rates (variously measured) ranged from 72% to 80%. Significant improvements in urgency, frequency, nocturia, voided volumes, and pain scores as well as decreases in use of other medications also were reported. Device explant for lack of efficacy or for intractable AEs despite efficacy occurred in from 0% to 28% of patients. Revision procedures to replace batteries, to successfully restore efficacy if lost, or to eliminate AEs such as radiation of stimulation to leg or pain at implant or lead site ranged from 21% to 50%. Two studies reported that mean battery life was approximately 93 months. Only one case of infection (out of 109 patients) was reported.

In 2022, two retrospective studies on sacral neurostimulation (SNM) were found. The first reported on outcomes of SNM patients after a pulse generator was implanted.<sup>222</sup> Of the 247 patients included in the study, 59 (23.4%) were IC /BPS patients. In the IC/BPS group specifically, at a median follow-up of  $20.1 \pm 12.8$  months, > 65% of the patients reported improvement in urinary urgency, frequency, nocturia, and daily volume ( $p \leq 0.001$ ). The VAS, OSS, and PUF scores were significantly decreased in > 90% of the patients. Fourteen adverse events occurred including 8 patients experiencing symptom relapse.

A second study compared 105 women with a motor response of  $\leq 3$  V to 65 women with a motor response of  $\geq 4$  V for medically refractory IC/BPS.<sup>223</sup> Significant improvement was achieved with the  $\leq 3$  V motor response when compared to the traditional  $\geq 4$  V approach. Stage 1 to stage 2 conversion rates were 95.4% vs. 73.8% ( $p < 0.001$ ), and success rates were 87.6% versus 66.2% ( $p < 0.001$ ), respectively. Mean postoperative VAP and PUF scores were  $3.3 \pm 1.2$  with  $\leq 3$  V versus  $5.0 \pm 0.8$  with  $\geq 4$  V ( $p < 0.001$ ), and  $10.2 \pm 2.7$  with  $\leq 3$  V versus  $14.7 \pm 3.5$  with  $\geq 4$  V ( $p < 0.001$ ), respectively.

Given the small number of patients studied, the invasiveness of the procedure, and the lack of long-term follow-up data on a sufficient number of patients, the Panel judged that sacral/pudendal neurostimulation may be effective in carefully selected patients and this decision should be left to the individual clinician and patient. Clinicians and patients are cautioned that the procedure is indicated for frequency/urgency symptoms and is much less effective and potentially ineffective for pain.<sup>224, 225</sup>

Unlike SNM, the data supporting the use of transcutaneous electrical nerve stimulation (TENS) are sparse. One small prospective study reported on transcutaneous electrical nerve stimulation (TENS). The study ( $n=30$ ) compared equal number of patients treated with and without TENS therapy (four electrodes, two positioned suprapubically and two under the lower back - T10-L1).<sup>226</sup> Transcutaneous electrical nerve stimulation was found to be effective as manifested by the significant reduction in pain VAS and clomipramine intake among patients who received TENS. Non-significant reduction in pain VAS and clomipramine intake was observed among patients treated without TENS. An older study applied suprapubic TENS to 60 IC/BPS patients (33 with Hunner lesions, 27 without Hunner lesions). Improvement in pain was better in Hunner than non-Hunner patients. 54% of Hunner patients reported good results or remission of symptoms, compared to 26% in non-Hunner patients.<sup>227</sup>

One prospective study reported on percutaneous tibial nerve stimulation (PTNS)<sup>228</sup>. Twenty women with refractory IC/BPS symptoms were treated with 30-min session of PTNS weekly for 12 consecutive weeks. As compared to baseline, no significant changes in pain VAS, ICSI, ICPI, GRA, and voiding were observed over the 12 weeks. At 6-weeks, 15 patients (75%) reported no improvement in their symptoms and 3 patients (15%) reported worsening of symptoms. At 12-weeks, 17 patients (85%) reported having no effect whereas 1 patient (5%) reported more deterioration of symptoms.

# Major Surgery

## Guideline Statement 22

**Major surgery (substitution cystoplasty, urinary diversion with or without cystectomy) may be undertaken in carefully selected patients with bladder-centric symptoms, or in the rare instance when there is an end-stage small fibrotic bladder, for whom all other therapies have failed to provide adequate symptom control and quality of life improvement.**

**Option (Evidence Strength: Grade C)**

Major surgery is irreversible and life-altering. While some patients have complete or near-complete symptom resolution after surgery, others have poor outcomes including persistent pain (even if the bladder is removed), complications or new symptoms with lifelong significant bother. Published evidence is limited by small numbers of patients and variability in patient selection, surgical methods and outcome reporting. For these reasons, uncertainty exists in the overall balance between benefits and risks/burdens and surgical treatments are options.

The most common operations are supravesical urinary diversion +/- cystectomy, or suprarectal cystectomy + cystoplasty with ileum and/or cecum. While a few centers perform total cystectomy and orthotopic diversion, the updated literature review did not identify new publications for this procedure.

## Patient selection

Patient selection has by far the greatest influence on outcome. It is much more important to select the right patient than the type of operation (e.g., cystoplasty versus diversion; diversion with versus without cystectomy). Clinicians must be rigorous in patient selection. Persistent pain after irreversible surgery is a result that can lead to suicide.<sup>229</sup>

Major surgery should be reserved for patients who have exhausted all other feasible options and whose symptoms are caused by the bladder. Symptoms from other sources (e.g., neuropathic pain, pelvic muscle dysfunction) will not improve with lower urinary tract reconstruction. The best-known predictors of success are end-stage fibrotic bladder,<sup>230 231</sup> small bladder capacity under anesthesia<sup>230, 232-236 231</sup> and presence of Hunner lesions.<sup>233, 237-239</sup> These factors often coexist and point unequivocally to a bladder source of symptoms. Conversely, a large capacity under anesthesia suggests a functional or extravesical source of pain and is associated with treatment failure.

Patients considering major surgery need a diligent evaluation for pain sources outside the bladder. Pain location outside the pelvis can be evaluated by careful history and a body map with pain locations.<sup>26</sup> Clinicians must not overlook the PSPS presentation, for which “do no harm” is the most important consideration.<sup>37</sup> Pelvic exam is crucial, especially to evaluate for surface hyperesthesia or pelvic muscle tightness/tenderness. Patients who have reached the point of major surgery will have tried at least one local anesthetic bladder instillation. If pain does not change while the anesthetic is in the bladder, then an extravesical source is likely. Unless there is clear evidence of primary bladder pathology (e.g., small capacity under anesthesia, Hunner lesions), patients should have a multidisciplinary evaluation including assessment for neuropathic pain and psychological profile.<sup>236, 240</sup>

## Surgical method selection

Essentially all publications on major surgery are retrospective reviews in which choice of operation was based on surgeon and patient-specific factors. Each procedure has its own advantages and disadvantages.

*Suprarectal cystectomy and augmentation with ileum and/or cecum.*

This approach avoids the need for an external appliance, and many patients are able to void spontaneously. Another advantage is to preserve the ureteric orifices, avoiding the risk of anastomotic stricture. Disadvantages of augmentation in general include metabolic changes, the risk of rupture and the possible need for intermittent catheterization. Specific to IC/BPS, there is a risk of persistent pain or recurrent ulcers in the trigone.<sup>241-244</sup>

In the 2014 and 2022 literature reviews, 11 publications reported on cohorts who underwent suprarectal cystectomy and augmentation with ileum and/or cecum.<sup>192 128, 230, 232, 235, 237, 239, 241, 243-245</sup> Cohort sizes ranged from 4 to 40 patients (total 170). Success rates ranged from 100% (6 of 6)<sup>232</sup> to zero (4 of 4 failed).<sup>192</sup> Total combined failure rate was 23% (39 of 170). Of note, 27 patients underwent secondary cystectomy and diversion for persistent pain. Unfortunately, some of these patients continued to have pain even after diversion.

Combining eight studies that reported voiding ability after cystoplasty, 103 of 144 patients (72%) voided spontaneously without the need for intermittent catheterization.

Some of these articles analyzed predictors of success or failure. Combining five studies that reported outcomes specifically for patients with Hunner lesions, 59 of 69 (86%) had complete relief.<sup>232, 237, 239, 241, 244</sup> With regard to bladder capacity under anesthesia, Linn et al. noted complete pain relief in 6 of 6 patients with capacity < 200 mL.<sup>232</sup> Nielsen et al. described complete relief for 2 of 2 patients with small contracted bladders, but failure in 6 of 6 patients with large capacities under anesthesia.<sup>230</sup> Webster and Maggio also noted that patients with large capacities under anesthesia were more likely to fail.<sup>235</sup>

#### *Supravesical urinary diversion*

Urinary diversion resolves frequency and nocturia and eliminates contact of urine with the bladder and urethral mucosa. Diversion also avoids any need for intermittent catheterization per urethra. Comparing continent versus conduit diversion, the latter requires an appliance but has fewer metabolic alterations and lower risk of recurrence of pain in the bowel segment. Leaving the bladder *in situ* is a matter of debate. Length and risks of surgery are decreased, but some patients have persistent pain or other problems with the remaining bladder.

In the 2014 and 2022 literature four articles described cohorts who underwent diversion with the bladder left *in situ*.<sup>229, 231, 237, 238</sup> Cohort sizes ranged from 8 to 22 patients (total 70). Most diversions were ileal conduits. After the initial diversion, 16 patients (23%) had secondary cystectomy: two for pyocystis and 14 for persistent pain. Of those 14, four patients (all without Hunner lesions) still had pain after cystectomy including one who died by suicide. Capacity under anesthesia also appeared to affect outcome: in Redmond's series of 8 patients with capacity < 200 ml, all had pain resolved or markedly improved after ileal conduit diversion.<sup>231</sup>

Four articles described cohorts who underwent primary cystectomy + conduit.<sup>229, 238, 245, 246</sup> Of 26 total patients, 20 (77%) had complete pain relief and one was moderately improved. All five of the failures were patients without Hunner lesions.

For cystectomy + continent diversion, two studies had contrasting results. Lotenfoe et al. noted a 73% success rate for 22 patients who underwent cystourethrectomy and Florida pouch.<sup>194</sup> Predictors of success were capacity under anesthesia < 400 mL and absence of neuropathic pain. In contrast, Webster et al. noted a 75% failure rate after cystectomy and Kock pouch: 6 of 8 patients had persistent pain, including 4 with pain in the pouch.<sup>192</sup>

## Conclusions

The Panel notes that major surgery should be performed only by surgeons with extensive experience in IC/BPS and dedication to long-term care for the patient. Diligent patient selection, to ensure bladder-centric pain, is the most important factor affecting outcome. The best-documented predictors of success are presence of Hunner lesions and small bladder capacity under anesthesia. In contrast, the following features indicate pain sources outside the bladder and a higher risk of failure:

- Large capacity under anesthesia
- Absence of Hunner lesions,
- Lack of relief with local anesthetic bladder instillations,
- Pelvic muscle tightness/tenderness,
- Genital hyperesthesia,
- Pain beyond the pelvis, such as the presence of widespread pain, and, most important,
- Polysymptomatic or polysyndromic presentation. In the latter group, IC/BPS surgery is not recommended.

## Treatments that Should Not be Offered

The treatments below appear to lack efficacy and/or appear to be accompanied by unacceptable AE profiles.

### Guideline Statement 23

**Long-term oral antibiotic administration should not be offered. Standard (Evidence Strength: Grade B)**

One RCT reported that an 18 week protocol of sequential antibiotic administration resulted in 20% of the treatment group reporting 50% or greater symptom improvement compared to 16% of the placebo group – a nonsignificant difference.<sup>247</sup> AEs were typical of long-term antibiotic administration (e.g., GI disturbances, vaginal infections, nausea, dizziness). Using less intensive protocols, two observational studies reported higher efficacy rates of 45% and 47%.<sup>248, 249</sup> Given the non-significant findings from the RCT and the potential hazards associated with long-term antibiotic administration in general (e.g., fostering of antibiotic resistant

organisms), the Panel judged that antibiotic treatment is contraindicated in patients who have previously been administered antibiotics without efficacy and who present with a negative urine culture. This Standard is not intended to prevent antibiotic administration to antibiotic-naïve patients; it is focused on preventing repeated or chronic antibiotic administration to patients for whom no relief was obtained in an initial course. This Standard also is not intended to prevent prophylactic antibiotic administration (e.g., nightly for several months) to patients who present with recurrent UTIs and symptoms suggestive of IC/BPS between infections.

## Guideline Statement 24

**Intravesical instillation of bacillus Calmette-Guerin should not be offered outside of investigational study settings. Standard (Evidence Strength: Grade B)**

Intravesical instillation of BCG is associated with efficacy only non-significantly greater than placebo in the context of potentially serious AEs with long-term follow-up data indicating no differences between BCG- and placebo-treated patients; this treatment should not be offered. This Standard is based on the results of two RCTs reported in four papers. One RCT reported a non-significantly higher response rate in 15 BCG-treated patients compared to 15 placebo-treated patients (60% versus 27%) at eight months of follow-up with all patients reporting one or more AE(s).<sup>250</sup> The second RCT reported in a much larger sample (131 BCG patients, 134 placebo patients) no differences in response rate between treatment arms (21% in the BCG group compared to 12% in the placebo groups) at seven months with 95% of patients in each group reporting at least one AE.<sup>251</sup> Non-responders from both groups were then offered open-label BCG and both groups experienced an 18% response rate at seven months.<sup>252</sup> BCG and placebo responders were followed for 17 months; 86% of BCG responders and 75% of Placebo responders reported themselves to remain improved – a nonsignificant difference.<sup>253</sup> The Panel interpreted these data to indicate that BCG treatment is not reliably more effective than placebo treatment in the context of potentially significant AEs. Life-threatening AEs are possible with exposure to BCG and have been detailed in the bladder cancer literature (e.g., sepsis and other serious AEs, including death).<sup>254-257</sup> For these reasons, the Panel judged that the risks/burdens of BCG outweigh its benefits for IC/BPS patients in routine clinical care situations; BCG administration in this patient group should be restricted to investigational settings.

## Guideline Statement 25

**High-pressure, long-duration hydrodistension should not be offered. Recommendation (Evidence Strength: Grade C)**

High-pressure, long-duration Hydrodistension (.). High-pressure (e.g., greater than 80 to 100 cm H<sub>2</sub>O), long-duration (e.g., greater than 10 minutes) hydrodistension is associated with increased frequency of serious AEs (e.g., bladder rupture, sepsis) without a consistent increase in benefit; this form of hydrodistension should not be offered. This Recommendation is based on results of three observational studies that used high-pressure (e.g., systolic blood pressure, mean arterial pressure) and/or long duration (e.g., repeated intervals of 30 minutes, 3 hours continuously).<sup>258-260</sup> The efficacy rates from these studies ranged from 22% to 67% and all reported at least one case of ruptured bladder. Given the lack of predictable efficacy in the context of serious AEs, the risks/ burdens of this type of hydrodistension outweigh benefits; the Panel recommends that this treatment not be offered.

## Guideline Statement 26

**Systemic (oral) long-term glucocorticoid administration should not be offered. Recommendation (Evidence Strength: Grade C)**

Systemic long-term glucocorticoid administration should not be offered as the primary treatment for IC/BPS symptoms. This Recommendation is based on the findings from two observational studies.<sup>261, 262</sup> Although high rates of efficacy were reported (47 to 64%), given the extremely small combined sample size of fewer than 30 patients, the relatively serious AEs (e.g., new diabetes onset, exacerbation of existing diabetes, pneumonia with septic shock, increased blood pressure), and the known risks of systemic long-term glucocorticoid use, risks/burdens clearly outweigh benefits and the Panel recommends that this therapy not be used long-term. This Recommendation does not preclude the use of short-term glucocorticoid therapy to manage symptom flares.

## Future Research

Patients with IC/BPS constitute a previously under-recognized and underserved population in need of adequate medical management. Over the last 20 years, there have been significant efforts directed at understanding the etiology and the therapeutic challenges of this disease. These efforts were spearheaded by US patient support groups that have urged the National Institutes of Health to fund research studies to better understand IC/BPS pathophysiology and to fund clinical studies to identify valid treatment approaches.

Treating IC/BPS patients presents a significant challenge in clinical practice. Treatment approaches may be local (directed to the bladder) or systemic, range from behavioral to pharmacological, and may include many types of adjunctive therapy approaches intended to optimize quality of life. Although there are evidenced-based data supporting certain treatment approaches for patients in clinical studies, the unsolved question in clinical practice remains: "Who is the ideal patient for a given treatment approach?" Thus, treatment of IC/BPS often requires a trial-and-error approach.

IC/BPS, which was originally considered to be a bladder disease, has now been recognized as a chronic pain syndrome.<sup>214-263-265</sup> There is a growing body of literature demonstrating that different visceral pain syndromes, as well as pain syndromes in other body regions, and other systemic diseases often occur together in the same patient. Thus, efforts to understand the pathophysiology and to design therapeutic modalities have recently shifted from an organ-based approach to a more global approach. Reflecting this new paradigm, the NIDDK has funded the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network ([www.mappnetwork.org](http://www.mappnetwork.org)). The MAPP network is focused on a broader approach to the study of IC/BPS and CP/CPPS than previously undertaken. A wide range of scientific discovery projects, moving beyond the previous traditional bladder- and prostate-focused efforts, are being conducted at six Discovery Sites. Investigations include the relationship between IC/BPS, CP/CPPS and other chronic pain conditions (fibromyalgia, chronic fatigue syndrome, and IBS), innovative epidemiological studies, search for clinically important biomarkers, investigation of bacterial, viral and other infectious causative/exacerbating agents, novel brain imaging studies and animal studies to better understand the pathophysiology of these often disabling syndromes.

As the definition of IC/BPS has expanded, clinical trial design for this condition is becoming more complex and challenging. Early clinical trials have enrolled participants based on NIDDK research criteria for IC.<sup>266</sup> However, this approach resulted in two-thirds of potential subjects being excluded at the outset.<sup>3, 33</sup>

Further, IC/BPS patients with comorbidities have typically been excluded in clinical trials.<sup>267</sup> While there is a need in clinical research to enroll a more homogeneous patient population, this approach raises concerns about the clinical relevance of such studies for the truly heterogeneous IC/BPS population. Two strategies may be useful to move the field forward. First, entry criteria for these trials could be as broad as possible to both improve the ability to generalize the results and permit subgroup analysis.<sup>247</sup> Second, clinically-important subgroups could be identified a priori and evaluated for treatment responses. In future trials it will be important to keep track of comorbidities for clinical trial design, either for the purpose of post hoc subgroup analysis or a priori subgroup recruitment, since the neurophysiological mechanisms in IC/ BPS patients with different co-morbidities are likely to be different.<sup>24, 39, 40, 268, 269</sup>

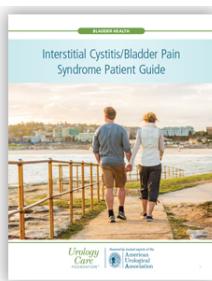
A key issue for future clinical trial design will be to identify clinically relevant objective criteria for patient enrollment, and this remains a challenge, which has delayed a more aggressive approach of the pharmaceutical industry to identifying new treatment avenues for this condition. A validated urine marker for IC/BPS would be a major advantage in this disorder since it would provide an objective criterion for participant enrollment and allow subclassification of various subgroups of BPS.

The second major challenge in clinical trial design remains the selection of outcome measures.<sup>267</sup> Many patients have periods of flares and remission. In other patients, symptoms become more severe and frequent over time. Thus it is difficult to establish a baseline for the symptoms over a longer observation period. It has been suggested by some investigators to circumvent this problem by evaluating the response to an evoked painful visceral stimulus, such as bladder distension, either in normal volunteers, or in subjects with visceral pain.<sup>218</sup> Conceptually, however, it is not clear, if studies evaluating the response to an evoked visceral stimulus can be used to predict the response to spontaneous visceral pain, since the neurophysiological mechanisms are likely to be different. In the past questionnaires have been used to assess a global response or individual symptoms related to IC/BPS. However, as the definition of IC/BPS appears to be expanding from a bladder disease to a chronic pain syndrome, reliable new outcome measures will have to be developed. Again, a biomarker would be an ideal outcome measure, if it would measure the presence of IC/BPS and changes in the biomarker would reflect a response to treatment. Many IC/BPS patients suffer from other chronic pain conditions as well. Outcome measures in clinical trials will have to track these comorbidities, so that different subgroups of IC/BPS patients can be identified and responders versus non-responders categorized appropriately.

IC has only been recognized as a highly prevalent health problem in the last 20 years. Data regarding disease progression, remission, and prevention are very limited and we know very little about risk factors for development of associated symptoms over time. Patients are currently treated with a variety of different medications and other treatment interventions on an empirical basis by different clinicians. There is an urgent need for a long-term registry for these patients following them over several decades prospectively. Such a registry will provide information about the natural course of the disease and information about treatment interventions found to be effective could provide a basis for future clinical trials.<sup>219</sup>

Although progress in developing specific IC/BPS treatments has been slow, these are exciting times for the development of new treatment targets.<sup>270</sup> Modulation of visceral nociceptive pathways can occur at peripheral, spinal and supraspinal sites and a wide variety of potential drug targets exists. Compounds that hit several targets might be the best option for a successful approach in the short term, carefully evaluating the benefits of each sequentially. However, there is emerging evidence that a more refined approach may be achievable.<sup>271</sup>

# Tools & Resources



## [IC/BPS Patient Guide](#)

# Abbreviations

AE	Adverse events
AUA	American Urological Association
BCG	Bacillus calmette-guerin
BTX-A	Onabotulinumtoxin A
COPCs	Chronic overlapping pain conditions
CISC	Clean intermittent self-catheterization
CP/CPPS	Chronic prostatitis/chronic pelvic pain syndrome
DO	Detrusor overactivity
DMSO	Dimethylsulfoxide
fMRI	Functional magnetic resonance imaging
GAR	Global assessment response
GTM	Global therapeutic massage
GUPI	Genitourinary pain index
IBS	Irritable bowel syndrome
IC/BPS	Interstitial cystitis/bladder pain syndrome
ICPI	Interstitial cystitis problem index
ICSI	Interstitial cystitis symptom index
LSS	Lumbar spinal stenosis
MAPP	Multidisciplinary approach to the study of chronic pelvic pain
MCC	Maximal cystometric capacity
MPT	Myofascial physical therapy
NHANES III	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHS	US Nurses Health Study
NSAIDs	Non-steroidal anti-inflammatory drugs
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
OAB	Overactive bladder syndrome
PST	Potassium sensitivity test
PUF	Pelvic pain and urgency/frequency
PNE	Percutaneous nerve evaluation
PPS	Pentosan polysulfate
PSPS	Poly-symptomatic, poly-syndromic
QoL	Quality of life
RCT	Randomized controlled trials
RICE	RAND interstitial cystitis epidemiology
SUFU	Society for Urodynamics and Female Urology
TUF	Transurethral fulguration
TWI	Urinary tract infection
VAS	Visual analog scale

# References

1. Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: A review and analysis of evidence reporting and grading; the recommendations of the american urological association. *BJU Int* 2009; **104**: 294.
2. Hanno P and Dmochowski R: Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. *Neurourol Urodyn* 2009; **28**: 274.
3. Hanno PM, Landis JR, Matthews-Cook Y et al: The diagnosis of interstitial cystitis revisited: Lessons learned from the national institutes of health interstitial cystitis database study. *J Urol* 1999; **161**: 553.
4. Leppilahti M, Tammela TL, Huhtala H et al: Prevalence of symptoms related to interstitial cystitis in women: A population based study in finland. *J Urol* 2002; **168**: 139.
5. Clemens JQ, Meenan RT, Rosetti MC et al: Prevalence and incidence of interstitial cystitis in a managed care population. *J Urol* 2005; **173**: 98.
6. Clemens JQ, Link CL, Eggers PW et al: Prevalence of painful bladder symptoms and effect on quality of life in black, hispanic and white men and women. *J Urol* 2007; **177**: 1390.
7. Lifford KL and Curhan GC: Prevalence of painful bladder syndrome in older women. *Urology* 2009; **73**: 494.
8. Temml C, Wehrberger C, Riedl C et al: Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. *Eur Urol* 2007; **51**: 803.
9. Berry SH, Bogart LM, Pham C et al: Development, validation and testing of an epidemiological case definition of interstitial cystitis/painful bladder syndrome. *J Urol* 2010; **183**: 1848.
10. Berry SH, Elliott MN, Suttorp M et al: Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the united states. *J Urol* 2011; **186**: 540.
11. Suskind AM, Berry SH, Ewing BA et al: The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the rand interstitial cystitis epidemiology male study. *J Urol* 2013; **189**: 141.
12. Curhan GC, Speizer FE, Hunter DJ et al: Epidemiology of interstitial cystitis: A population based study. *J Urol* 1999; **161**: 549.
13. Roberts RO, Bergstrahl EJ, Bass SE et al: Incidence of physician-diagnosed interstitial cystitis in olmsted county: A community-based study. *BJU Int* 2003; **91**: 181.
14. Porru D, Politanò R, Gerardini M et al: Different clinical presentation of interstitial cystitis syndrome. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; **15**: 198.
15. Warren JW, Brown J, Tracy JK et al: Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. *Urology* 2008; **71**: 444.
16. Warren JW, Diggs C, Brown V et al: Dysuria at onset of interstitial cystitis/painful bladder syndrome in women. *Urology* 2006; **68**: 477.
17. Driscoll A and Teichman JM: How do patients with interstitial cystitis present? *J Urol* 2001; **166**: 2118.
18. Sutcliffe S, Bradley CS, Clemens JQ et al: Urological chronic pelvic pain syndrome flares and their impact: Qualitative analysis in the mapp network. *Int Urogynecol J* 2015; **26**: 1047.
19. Peters KM, Carrico DJ, Kalinowski SE et al: Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. *Urology* 2007; **70**: 16.
20. Buffington CA: Comorbidity of interstitial cystitis with other unexplained clinical conditions. *J Urol* 2004; **172**: 1242.
21. Warren JW, Howard FM, Cross RK et al: Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology* 2009; **73**: 52.
22. Talati A, Ponniah K, Strug LJ et al: Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. *Biol Psychiatry* 2008; **63**: 594.
23. Weissman MM, Gross R, Fyer A et al: Interstitial cystitis and panic disorder: A potential genetic syndrome. *Arch Gen Psychiatry* 2004; **61**: 273.

24. Clauw DJ, Schmidt M, Radulovic D et al: The relationship between fibromyalgia and interstitial cystitis. *J Psychiatr Res* 1997; **31**: 125.
25. Krieger JN, Stephens AJ, Landis JR et al: Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: Baseline evaluation of the mapp study. *J Urol* 2015; **193**: 1254.
26. Lai HH, Jemielita T, Sutcliffe S et al: Characterization of whole body pain in urological chronic pelvic pain syndrome at baseline: A mapp research network study. *J Urol* 2017; **198**: 622.
27. Naliboff BD, Stephens AJ, Lai HH et al: Clinical and psychosocial predictors of urological chronic pelvic pain symptom change in 1 year: A prospective study from the mapp research network. *J Urol* 2017; **198**: 848.
28. Kutch JJ, Ichesco E, Hampson JP et al: Brain signature and functional impact of centralized pain: A multidisciplinary approach to the study of chronic pelvic pain (mapp) network study. *Pain* 2017; **158**: 1979.
29. Harte SE, Schrepf A, Gallop R et al: Quantitative assessment of nonpelvic pressure pain sensitivity in urologic chronic pelvic pain syndrome: A mapp research network study. *Pain* 2019; **160**: 1270.
30. Schrepf A, Bradley CS, O'Donnell M et al: Toll-like receptor 4 and comorbid pain in interstitial cystitis/bladder pain syndrome: A multidisciplinary approach to the study of chronic pelvic pain research network study. *Brain Behav Immun* 2015; **49**: 66.
31. Schrepf A, O'Donnell M, Luo Y et al: Inflammation and inflammatory control in interstitial cystitis/bladder pain syndrome: Associations with painful symptoms. *Pain* 2014; **155**: 1755.
32. Bade J, Ishizuka O and Yoshida M: Future research needs for the definition/diagnosis of interstitial cystitis. *Int J Urol* 2003; **10 Suppl**: S31.
33. Payne CK, Terai A and Komatsu K: Research criteria versus clinical criteria for interstitial cystitis. *Int J Urol* 2003; **10 Suppl**: S7.
34. Homma Y, Ueda T, Tomoe H et al: Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. *Int J Urol* 2009; **16**: 597.
35. Philip J, Willmott S and Irwin P: Interstitial cystitis versus detrusor overactivity: A comparative, randomized, controlled study of cystometry using saline and 0.3 m potassium chloride. *J Urol* 2006; **175**: 566.
36. Naliboff BD, Stephens AJ, Afari N et al: Widespread psychosocial difficulties in men and women with urologic chronic pelvic pain syndromes: Case-control findings from the multidisciplinary approach to the study of chronic pelvic pain research network. *Urology* 2015; **85**: 1319.
37. Lai HH, North CS, Andriole GL et al: Polysymptomatic, polysyndromic presentation of patients with urological chronic pelvic pain syndrome. *J Urol* 2012; **187**: 2106.
38. Rothrock NE, Lutgendorf SK, Hoffman A et al: Depressive symptoms and quality of life in patients with interstitial cystitis. *J Urol* 2002; **167**: 1763.
39. Rothrock N, Lutgendorf SK and Kreder KJ: Coping strategies in patients with interstitial cystitis: Relationships with quality of life and depression. *J Urol* 2003; **169**: 233.
40. Clemens JQ, Brown SO and Calhoun EA: Mental health diagnoses in patients with interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome: A case/control study. *J Urol* 2008; **180**: 1378.
41. Nickel JC, Payne CK, Forrest J et al: The relationship among symptoms, sleep disturbances and quality of life in patients with interstitial cystitis. *J Urol* 2009; **181**: 2555.
42. Nickel JC, Tripp DA, Pontari M et al: Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome: A case control study. *J Urol* 2010; **183**: 167.
43. Michael YL, Kawachi I, Stampfer MJ et al: Quality of life among women with interstitial cystitis. *J Urol* 2000; **164**: 423.
44. Nickel JC, Parsons CL, Forrest J et al: Improvement in sexual functioning in patients with interstitial cystitis/painful bladder syndrome. *J Sex Med* 2008; **5**: 394.
45. Peters KM, Killinger KA, Carrico DJ et al: Sexual function and sexual distress in women with interstitial cystitis: A case-control study. *Urology* 2007; **70**: 543.
46. Tincello DG and Walker AC: Interstitial cystitis in the uk: Results of a questionnaire survey of members of the interstitial cystitis support group. *Eur J Obstet Gynecol Reprod Biol* 2005; **118**: 91.

47. Nickel JC, Tripp D, Teal V et al: Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. *J Urol* 2007; **177**: 1832.
48. Sairanen J, Leppilahti M, Tammela TL et al: Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. *Scand J Urol Nephrol* 2009; **43**: 212.
49. Clemens JQ, Meenan RT, Rosetti MC et al: Costs of interstitial cystitis in a managed care population. *Urology* 2008; **71**: 776.
50. Payne CK, Joyce GF, Wise M et al: Interstitial cystitis and painful bladder syndrome. *J Urol* 2007; **177**: 2042.
51. Clemens JQ, Markossian T and Calhoun EA: Comparison of economic impact of chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/painful bladder syndrome. *Urology* 2009; **73**: 743.
52. Wu EQ, Birnbaum H, Mareva M et al: Interstitial cystitis: Cost, treatment and co-morbidities in an employed population. *Pharmacoeconomics* 2006; **24**: 55.
53. Fitzgerald MP, Koch D and Senka J: Visceral and cutaneous sensory testing in patients with painful bladder syndrome. *Neurourol Urodyn* 2005; **24**: 627.
54. Warren JW, Meyer WA, Greenberg P et al: Using the international continence society's definition of painful bladder syndrome. *Urology* 2006; **67**: 1138.
55. Sirinian E and Payne CK: Correlation of symptoms between 2 instruments among interstitial cystitis patients. *Urology* 2001; **57**: 124.
56. Diggs C, Meyer WA, Langenberg P et al: Assessing urgency in interstitial cystitis/painful bladder syndrome. *Urology* 2007; **69**: 210.
57. Greenberg P, Tracy JK, Meyer WA et al: Short interval between symptom onset and medical care as an indication of rapid onset of interstitial cystitis/painful bladder syndrome. *BJU Int* 2007; **100**: 599.
58. Lai HH, Krieger JN, Pontari MA et al: Painful bladder filling and painful urgency are distinct characteristics in men and women with urological chronic pelvic pain syndromes: A mapp research network study. *J Urol* 2015; **194**: 1634.
59. Hand JR: Interstitial cystitis; report of 223 cases (204 women and 19 men). *J Urol* 1949; **61**: 291.
60. Forrest JB and Vo Q: Observations on the presentation, diagnosis, and treatment of interstitial cystitis in men. *Urology* 2001; **57**: 26.
61. Wennevick GE, Meijlink JM, Hanno P et al: The role of glomerulations in bladder pain syndrome: A review. *J Urol* 2016; **195**: 19.
62. Forrest JB and Schmidt S: Interstitial cystitis, chronic nonbacterial prostatitis and chronic pelvic pain syndrome in men: A common and frequently identical clinical entity. *J Urol* 2004; **172**: 2561.
63. Krieger JN, Nyberg L, Jr. and Nickel JC: NIH consensus definition and classification of prostatitis. *JAMA* 1999; **282**: 236.
64. Litwin MS, McNaughton-Collins M, Fowler FJ, Jr. et al: The national institutes of health chronic prostatitis symptom index: Development and validation of a new outcome measure. Chronic prostatitis collaborative research network. *J Urol* 1999; **162**: 369.
65. Miller JL, Rothman I, Bavendam TG et al: Prostatodynia and interstitial cystitis: One and the same? *Urology* 1995; **45**: 587.
66. Nickel JC: Interstitial cystitis: A chronic pelvic pain syndrome. *Med Clin North Am* 2004; **88**: 467.
67. Johnson JE and Johnson KE: Ambiguous chronic illness in women: Community health nursing concern. *J Community Health Nurs* 2006; **23**: 159.
68. Striker GE: Kuh notes. *J Urol* 1989; **142**: 139.
69. Sant GR and Hanno PM: Interstitial cystitis: Current issues and controversies in diagnosis. *Urology* 2001; **57**: 82.
70. Stanford EJ, Mattox TF, Parsons JK et al: Prevalence of benign microscopic hematuria among women with interstitial cystitis: Implications for evaluation of genitourinary malignancy. *Urology* 2006; **67**: 946.
71. Tissot WD, Diokno AC and Peters KM: A referral center's experience with transitional cell carcinoma misdiagnosed as interstitial cystitis. *J Urol* 2004; **172**: 478.
72. van de Merwe JP, Nordling J, Bouchelouche P et al: Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An eSSIC proposal. *Eur Urol* 2008; **53**: 60.

73. Weiss JM: Pelvic floor myofascial trigger points: Manual therapy for interstitial cystitis and the urgency-frequency syndrome. *J Urol* 2001; **166**: 2226.
74. Barocas DA, Boorjian SA, Alvarez RD et al: Microhematuria: Aua/sufu guideline. *J Urol* 2020; **204**: 778.
75. Mazurick CA and Landis JR: Evaluation of repeat daily voiding measures in the national interstitial cystitis data base study. *J Urol* 2000; **163**: 1208.
76. Humphrey L, Arbuckle R, Moldwin R et al: The bladder pain/interstitial cystitis symptom score: Development, validation, and identification of a cut score. *Eur Urol* 2012; **61**: 271.
77. Clemens JQ, Calhoun EA, Litwin MS et al: Validation of a modified national institutes of health chronic prostatitis symptom index to assess genitourinary pain in both men and women. *Urology* 2009; **74**: 983.
78. O'Leary MP, Sant GR, Fowler FJ, Jr. et al: The interstitial cystitis symptom index and problem index. *Urology* 1997; **49**: 58.
79. Melzack R: The short-form mcgill pain questionnaire. *Pain* 1987; **30**: 191.
80. Irwin PP, Takei M and Sugino Y: Summary of the urodynamics workshops on ic kyoto, japan. *Int J Urol* 2003; **10 Suppl**: S19.
81. Parsons CL, Greenberger M, Gabal L et al: The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998; **159**: 1862.
82. Teichman JM and Nielsen-Omeis BJ: Potassium leak test predicts outcome in interstitial cystitis. *J Urol* 1999; **161**: 1791.
83. Sairanen J, Tammela TL, Leppilahti M et al: Potassium sensitivity test (pst) as a measurement of treatment efficacy of painful bladder syndrome/interstitial cystitis: A prospective study with cyclosporine a and pentosan polysulfate sodium. *Neurourol Urodyn* 2007; **26**: 267.
84. Gupta SK: Re: Daha lk, riedl cr, lazar d, hohlbrugger g, pfluger h. Do cystometric findings predict the results of intravesical hyaluronic acid in women with interstitial cystitis? *Eur urol* 2005; 47: 393-7. *Eur Urol* 2005; **48**: 534.
85. HUNNER GL: A rare type of bladder ulcer: Further notes, with a report of eighteen cases. *Journal of the American Medical Association* 1918; **70**: 203.
86. Doiron RC, Tolls V, Irvine-Bird K et al: Clinical phenotyping does not differentiate hunner lesion subtype of interstitial cystitis/bladder pain syndrome: A relook at the role of cystoscopy. *J Urol* 2016; **196**: 1136.
87. Lai HH, Newcomb C, Harte S et al: Comparison of deep phenotyping features of ucpps with and without hunner lesion: A mapp-ii research network study. *Neurourol Urodyn* 2021; **40**: 810.
88. Nigro DA, Wein AJ, Foy M et al: Associations among cystoscopic and urodynamic findings for women enrolled in the interstitial cystitis data base (icdb) study. *Urology* 1997; **49**: 86.
89. Ronstrom C and Lai HH: Presenting an atlas of hunner lesions in interstitial cystitis which can be identified with office cystoscopy. *Neurourol Urodyn* 2020; **39**: 2394.
90. Chung MK, Chung RP and Gordon D: Interstitial cystitis and endometriosis in patients with chronic pelvic pain: The "evil twins" syndrome. *J Sls* 2005; **9**: 25.
91. Paulson JD and Delgado M: Chronic pelvic pain: The occurrence of interstitial cystitis in a gynecological population. *J Sls* 2005; **9**: 426.
92. Waxman JA, Sulak PJ and Kuehl TJ: Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol* 1998; **160**: 1663.
93. Turner KJ and Stewart LH: How do you stretch a bladder? A survey of uk practice, a literature review, and a recommendation of a standard approach. *Neurourol Urodyn* 2005; **24**: 74.
94. FitzGerald MP, Bresnighan C, Brubaker L et al: What is the pain of interstitial cystitis like? *Int Urogynecol J Pelvic Floor Dysfunct* 2006; **17**: 69.
95. Shear S and Mayer R: Development of glomerulations in younger women with interstitial cystitis. *Urology* 2006; **68**: 253.
96. Kuo HC, Chang SC and Hsu T: Urodynamic findings in interstitial cystitis. *J Formos Med Assoc* 1992; **91**: 694.
97. Holm-Bentzen M, Jacobsen F, Nerstrøm B et al: A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. *J Urol* 1987; **138**: 503.

98. Kirkemo A, Peabody M, Diokno AC et al: Associations among urodynamic findings and symptoms in women enrolled in the interstitial cystitis data base (icdb) study. *Urology* 1997; **49**: 76.
99. Steinkohl WB and Leach GE: Urodynamic findings in interstitial cystitis. *Urology* 1989; **34**: 399.
100. Lai HH, Pickersgill NA and Vetter JM: Hunner lesion phenotype in interstitial cystitis/bladder pain syndrome: A systematic review and meta-analysis. *J Urol* 2020; **204**: 518.
101. Ueda T, Nakagawa M, Okamura M et al: New cystoscopic diagnosis for interstitial cystitis/painful bladder syndrome using narrow-band imaging system. *Int J Urol* 2008; **15**: 1039.
102. Van Moh F, Vetter J and Lai HH: Comparison of urologic and non-urologic presentation in interstitial cystitis/bladder pain syndrome patients with and without hunner lesions. *Neurourol Urodyn* 2018; **37**: 2911.
103. Watanabe D, Akiyama Y, Niimi A et al: Clinical characterization of interstitial cystitis/bladder pain syndrome in women based on the presence or absence of hunner lesions and glomerulations. *Low Urin Tract Symptoms* 2021; **13**: 139.
104. Ronstrom C and Lai HH: Presenting an atlas of hunner lesions in interstitial cystitis which can be identified with office cystoscopy. *Neurourol Urodyn* 2020; **39**: 2394.
105. Gross J, Vetter J and Lai HH: Clinical presentation of urologic chronic pelvic pain syndrome (ucpps) varies with presenting age - implication on patient evaluation. *Urology* 2021; **158**: 66.
106. Ueda M, Sengiku A, Kono J et al: Low bladder capacity is an important predictor for comorbidity of interstitial cystitis with hunner's lesion in patients with refractory chronic prostatitis/chronic pelvic pain syndrome. *Int J Urol* 2019; **26 Suppl 1**: 53.
107. Link CL, Pulliam SJ, Hanno PM et al: Prevalence and psychosocial correlates of symptoms suggestive of painful bladder syndrome: Results from the boston area community health survey. *J Urol* 2008; **180**: 599.
108. Propert KJ, Schaeffer AJ, Brensinger CM et al: A prospective study of interstitial cystitis: Results of longitudinal followup of the interstitial cystitis data base cohort. The interstitial cystitis data base study group. *J Urol* 2000; **163**: 1434.
109. Rovner E, Propert KJ, Brensinger C et al: Treatments used in women with interstitial cystitis: The interstitial cystitis data base (icdb) study experience. The interstitial cystitis data base study group. *Urology* 2000; **56**: 940.
110. Carrico DJ, Peters KM and Diokno AC: Guided imagery for women with interstitial cystitis: Results of a prospective, randomized controlled pilot study. *J Altern Complement Med* 2008; **14**: 53.
111. Foster HE, Jr., Hanno PM, Nickel JC et al: Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. *J Urol* 2010; **183**: 1853.
112. Hsieh TF, Yu KJ and Lin SY: Possible application of raman microspectroscopy to verify the interstitial cystitis diagnosis after potassium sensitivity test: Phenylalanine or tryptophan as a biomarker. *Dis Markers* 2007; **23**: 147.
113. Shorter B, Lesser M, Moldwin RM et al: Effect of comestibles on symptoms of interstitial cystitis. *J Urol* 2007; **178**: 145.
114. Lai HH, Vetter J, Song J et al: Management of symptom flares and patient-reported flare triggers in interstitial cystitis/bladder pain syndrome (ic/bps)-findings from one site of the mapp research network. *Urology* 2019; **126**: 24.
115. Rothrock NE, Lutgendorf SK, Kreder KJ et al: Stress and symptoms in patients with interstitial cystitis: A life stress model. *Urology* 2001; **57**: 422.
116. Sengupta JN: Visceral pain: The neurophysiological mechanism. *Handb Exp Pharmacol* 2009; 31.
117. Lutgendorf SK, Kreder KJ, Rothrock NE et al: Stress and symptomatology in patients with interstitial cystitis: A laboratory stress model. *J Urol* 2000; **164**: 1265.
118. Anderson RU, Wise D, Sawyer T et al: Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. *J Urol* 2005; **174**: 155.
119. Clemens JQ, Nadler RB, Schaeffer AJ et al: Biofeedback, pelvic floor re-education, and bladder training for male chronic pelvic pain syndrome. *Urology* 2000; **56**: 951.
120. Cornel EB, van Haarst EP, Schaarsberg RW et al: The effect of biofeedback physical therapy in men with chronic pelvic pain syndrome type iii. *Eur Urol* 2005; **47**: 607.
121. Fitzgerald MP, Anderson RU, Potts J et al: Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. *J Urol* 2009; **182**: 570.

122. Oyama IA, Rejba A, Lukban JC et al: Modified thiele massage as therapeutic intervention for female patients with interstitial cystitis and high-tone pelvic floor dysfunction. *Urology* 2004; **64**: 862.
123. FitzGerald MP, Payne CK, Lukacz ES et al: Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. *J Urol* 2012; **187**: 2113.
124. FitzGerald MP and Kotarinos R: Rehabilitation of the short pelvic floor. II: Treatment of the patient with the short pelvic floor. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14**: 269.
125. Wesselmann U: Interstitial cystitis: A chronic visceral pain syndrome. *Urology* 2001; **57**: 32.
126. Dowell D, Haegerich TM and Chou R: Cdc guideline for prescribing opioids for chronic pain—united states, 2016. *JAMA* 2016; **315**: 1624.
127. van Ophoven A, Pokupic S, Heinecke A et al: A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol* 2004; **172**: 533.
128. van Ophoven A and Hertle L: Long-term results of amitriptyline treatment for interstitial cystitis. *J Urol* 2005; **174**: 1837.
129. Hanno PM, Buehler J and Wein AJ: Use of amitriptyline in the treatment of interstitial cystitis. *J Urol* 1989; **141**: 846.
130. Thilagarajah R, Witherow RO and Walker MM: Oral cimetidine gives effective symptom relief in painful bladder disease: A prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001; **87**: 207.
131. Dasgupta P, Sharma SD, Womack C et al: Cimetidine in painful bladder syndrome: A histopathological study. *BJU Int* 2001; **88**: 183.
132. Seshadri P, Emerson L and Morales A: Cimetidine in the treatment of interstitial cystitis. *Urology* 1994; **44**: 614.
133. Sant GR, Propert KJ, Hanno PM et al: A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol* 2003; **170**: 810.
134. Theoharides TC: Hydroxyzine in the treatment of interstitial cystitis. *Urol Clin North Am* 1994; **21**: 113.
135. Mulholland SG, Hanno P, Parsons CL et al: Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. *Urology* 1990; **35**: 552.
136. Parsons CL, Benson G, Childs SJ et al: A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. *J Urol* 1993; **150**: 845.
137. Parsons CL and Mulholland SG: Successful therapy of interstitial cystitis with pentosanpolysulfate. *J Urol* 1987; **138**: 513.
138. Sairanen J, Tammela TL, Leppilahti M et al: Cyclosporine a and pentosan polysulfate sodium for the treatment of interstitial cystitis: A randomized comparative study. *J Urol* 2005; **174**: 2235.
139. Fritjofsson A, Fall M, Juhlin R et al: Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: A multicenter trial. *J Urol* 1987; **138**: 508.
140. Pearce WA, Chen R and Jain N: Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology* 2018; **125**: 1793.
141. Hanif AM, Armenti ST, Taylor SC et al: Phenotypic spectrum of pentosan polysulfate sodium-associated maculopathy: A multicenter study. *JAMA Ophthalmol* 2019; **137**: 1275.
142. Jain N, Li AL, Yu Y et al: Association of macular disease with long-term use of pentosan polysulfate sodium: Findings from a us cohort. *Br J Ophthalmol* 2020; **104**: 1093.
143. FDA: <https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?Event=searchdetail.Page&drugnameid=2277>, 2020.
144. Forsell T, Ruutu M, Isoniemi H et al: Cyclosporine in severe interstitial cystitis. *J Urol* 1996; **155**: 1591.
145. Sairanen J, Forsell T and Ruutu M: Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine a. *J Urol* 2004; **171**: 2138.
146. Forrest JB, Payne CK and Erickson DR: Cyclosporine a for refractory interstitial cystitis/bladder pain syndrome: Experience of 3 tertiary centers. *J Urol* 2012; **188**: 1186.
147. Ehrén I, Hallén Grufman K, Vrba M et al: Nitric oxide as a marker for evaluation of treatment effect of cyclosporine a in patients with bladder pain syndrome/interstitial cystitis type 3c. *Scand J Urol* 2013; **47**: 503.

148. Crescenze IM, Tucky B, Li J et al: Efficacy, side effects, and monitoring of oral cyclosporine in interstitial cystitis-bladder pain syndrome. *Urology* 2017; **107**: 49.
149. Perez-Marrero R, Emerson LE and Feltis JT: A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol* 1988; **140**: 36.
150. Peeker R, Haghsheno MA, Holmäng S et al: Intravesical bacillus calmette-guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: A prospective, randomized double-blind study. *J Urol* 2000; **164**: 1912.
151. Barker SB, Matthews PN, Philip PF et al: Prospective study of intravesical dimethyl sulphoxide in the treatment of chronic inflammatory bladder disease. *Br J Urol* 1987; **59**: 142.
152. Biggers RD: Self-administration of dimethyl sulfoxide (dmso) for interstitial cystitis. *Urology* 1986; **28**: 10.
153. Rössberger J, Fall M and Peeker R: Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: Discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol* 2005; **39**: 73.
154. Gafni-Kane A, Botros SM, Du H et al: Measuring the success of combined intravesical dimethyl sulfoxide and triamcinolone for treatment of bladder pain syndrome/interstitial cystitis. *Int Urogynecol J* 2013; **24**: 303.
155. Gallego-Vilar D, García-Fadrique G, Povo-Martin I et al: Maintenance of the response to dimethyl sulfoxide treatment using hyperbaric oxygen in interstitial cystitis/painful bladder syndrome: A prospective, randomized, comparative study. *Urol Int* 2013; **90**: 411.
156. Hung MJ, Chen YT, Shen PS et al: Risk factors that affect the treatment of interstitial cystitis using intravesical therapy with a dimethyl sulfoxide cocktail. *Int Urogynecol J* 2012; **23**: 1533.
157. Shalom DF, Klapper A, Lin S et al: Use of the pain urgency frequency (puf) questionnaire to measure response of patients with interstitial cystitis/painful bladder syndrome to a treatment regimen of intravesical dmso and 1% lidocaine solution. *Female Pelvic Medicine & Reconstructive Surgery* 2009; **15**: 5.
158. Stav K, Beberashvili I, Lindner A et al: Predictors of response to intravesical dimethyl-sulfoxide cocktail in patients with interstitial cystitis. *Urology* 2012; **80**: 61.
159. Parsons CL, Housley T, Schmidt JD et al: Treatment of interstitial cystitis with intravesical heparin. *Br J Urol* 1994; **73**: 504.
160. Kuo HC: Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. *J Formos Med Assoc* 2001; **100**: 309.
161. Parsons CL: Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. *Urology* 2005; **65**: 45.
162. Butrick CW, Sanford D, Hou Q et al: Chronic pelvic pain syndromes: Clinical, urodynamic, and urothelial observations. *Int Urogynecol J Pelvic Floor Dysfunct* 2009; **20**: 1047.
163. Parsons CL, Zupkas P, Proctor J et al: Alkalinized lidocaine and heparin provide immediate relief of pain and urgency in patients with interstitial cystitis. *J Sex Med* 2012; **9**: 207.
164. Nomiya A, Naruse T, Niimi A et al: On- and post-treatment symptom relief by repeated instillations of heparin and alkalinized lidocaine in interstitial cystitis. *Int J Urol* 2013; **20**: 1118.
165. Nickel JC, Moldwin R, Lee S et al: Intravesical alkalinized lidocaine (psd597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. *BJU Int* 2009; **103**: 910.
166. Henry R, Patterson L, Avery N et al: Absorption of alkalinized intravesical lidocaine in normal and inflamed bladders: A simple method for improving bladder anesthesia. *J Urol* 2001; **165**: 1900.
167. Welk BK and Teichman JM: Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. *Urology* 2008; **71**: 67.
168. Davis EL, El Khoudary SR, Talbott EO et al: Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: A randomized double-blind clinical trial. *J Urol* 2008; **179**: 177.
169. Parsons CL, Koziol JA, Proctor JG et al: Heparin and alkalinized lidocaine versus alkalinized lidocaine for treatment of interstitial cystitis symptoms. *Can J Urol* 2015; **22**: 7739.
170. Offiah I, Dilloughery E, McMahon SB et al: Prospective comparative study of the effects of lidocaine on urodynamic and sensory parameters in bladder pain syndrome. *Int Urogynecol J* 2019; **30**: 1293.

171. Cole EE, Scarpero HM and Dmochowski RR: Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? *Neurourol Urodyn* 2005; **24**: 638.
172. Erickson DR, Kuselman AR, Bentley CM et al: Changes in urine markers and symptoms after bladder distention for interstitial cystitis. *J Urol* 2007; **177**: 556.
173. Ottem DP and Teichman JM: What is the value of cystoscopy with hydrodistension for interstitial cystitis? *Urology* 2005; **66**: 494.
174. Aihara K, Hirayama A, Tanaka N et al: Hydrodistension under local anesthesia for patients with suspected painful bladder syndrome/interstitial cystitis: Safety, diagnostic potential and therapeutic efficacy. *Int J Urol* 2009; **16**: 947.
175. Hsieh CH, Chang WC, Huang MC et al: Hydrodistention plus bladder training versus hydrodistention for the treatment of interstitial cystitis. *Taiwan J Obstet Gynecol* 2012; **51**: 591.
176. Hoke TP, Goldstein H, Saks EK et al: Hydrodistention of the bladder for the treatment of bladder pain syndrome/interstitial cystitis (bps/ic). *Neurourol Urodyn* 2017; **36**: 784.
177. Kirk PS, Santiago-Lastra Y, Qin Y et al: The effects of cystoscopy and hydrodistention on symptoms and bladder capacity in interstitial cystitis/bladder pain syndrome. *Neurourol Urodyn* 2018.
178. Walker SJ, Blair A, Hemal K et al: Bladder hydrodistention does not result in a significant change in bladder capacity for interstitial cystitis/bladder pain syndrome patients. *Urology* 2019.
179. Malloy TR and Shanberg AM: Laser therapy for interstitial cystitis. *Urol Clin North Am* 1994; **21**: 141.
180. Hillelsohn JH, Rais-Bahrami S, Friedlander JI et al: Fulguration for hunner ulcers: Long-term clinical outcomes. *J Urol* 2012; **188**: 2238.
181. Payne RA, O'Connor RC, Kressin M et al: Endoscopic ablation of hunner's lesions in interstitial cystitis patients. *Can Urol Assoc J* 2009; **3**: 473.
182. Rofeim O, Hom D, Freid RM et al: Use of the neodymium: Yag laser for interstitial cystitis: A prospective study. *J Urol* 2001; **166**: 134.
183. Shanberg AM, Baghdassarian R and Tansey LA: Treatment of interstitial cystitis with the neodymium-yag laser. *J Urol* 1985; **134**: 885.
184. Cox M, Klutke JJ and Klutke CG: Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of hunner's ulcer subtype interstitial cystitis. *Can J Urol* 2009; **16**: 4536.
185. Otsuka A, Suzuki T, Aki R et al: Clinical characteristics of self-reported nocturia in patients with interstitial cystitis, and effects of bladder hydrodistention (with fulguration of hunner lesions) on nocturia. *Low Urin Tract Symptoms* 2018.
186. Chennamsetty A, Khourdaji I, Goike J et al: Electrosurgical management of hunner ulcers in a referral center's interstitial cystitis population. *Urology* 2015; **85**: 74.
187. Jhang JF, Hsu YH and Kuo HC: Characteristics and electrocauterization of hunner's lesions associated with bladder pain syndrome. *Urological Science* 2013; **24**: 51.
188. Ryu J, Pak S, Song M et al: Elimination of hunner's ulcers by fulguration in patients with interstitial cystitis: Is it effective and long lasting? *Korean J Urol* 2013; **54**: 767.
189. Kajiwara M, Inoue S, Kobayashi K et al: Therapeutic efficacy of narrow band imaging-assisted transurethral electrocoagulation for ulcer-type interstitial cystitis/painful bladder syndrome. *Int J Urol* 2014; **21 Suppl 1**: 57.
190. Niimi A, Nomiya A, Yamada Y et al: Hydrodistension with or without fulguration of hunner lesions for interstitial cystitis: Long-term outcomes and prognostic predictors. *Neurourol Urodyn* 2016; **35**: 965.
191. Tomoe H and Yamashita K: Does repeated hydrodistension with transurethral fulguration for interstitial cystitis with hunner's lesion cause bladder contraction? *Arab J Urol* 2019; **17**: 77.
192. Funaro MG, King AN, Stern JNH et al: Endoscopic injection of low dose triamcinolone: A simple, minimally invasive, and effective therapy for interstitial cystitis with hunner lesions. *Urology* 2018; **118**: 25.
193. Rittenberg L, Morrissey D, El-Khwand D et al: Kenalog injection into hunner's lesions as a treatment for interstitial cystitis/bladder pain syndrome. *Curr Urol* 2017; **10**: 154.
194. Mateu L, Izquierdo L, Franco A et al: Pain relief after triamcinolone infiltration in patients with bladder pain syndrome with hunner's ulcers. *Int Urogynecol J* 2017; **28**: 1027.

195. Jiang T, Zhou X, Chen Z et al: Clinical efficacy of submucosal injection of triamcinolone acetonide in the treatment of type ii/iii interstitial cystitis/bladder pain syndrome. *BMC Urol* 2020; **20**: 36.
198. Crescenze IM, Gupta P, Adams G et al: Advanced management of patients with ulcerative interstitial cystitis/bladder pain syndrome. *Urology* 2019.
199. Liu HT and Kuo HC: Intravesical botulinum toxin a injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 2007; **70**: 463.
200. Giannantoni A, Costantini E, Di Stasi SM et al: Botulinum a toxin intravesical injections in the treatment of painful bladder syndrome: A pilot study. *Eur Urol* 2006; **49**: 704.
201. Ramsay AK, Small DR and Conn IG: Intravesical botulinum toxin type a in chronic interstitial cystitis: Results of a pilot study. *Surgeon* 2007; **5**: 331.
202. Giannantoni A, Porena M, Costantini E et al: Botulinum a toxin intravesical injection in patients with painful bladder syndrome: 1-year followup. *J Urol* 2008; **179**: 1031.
201. Kuo HC: Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis. *Urol Int* 2005; **75**: 170.
202. Kuo HC and Chancellor MB: Comparison of intravesical botulinum toxin type a injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. *BJU Int* 2009; **104**: 657.
204. Kuo HC: Repeated onabotulinumtoxin-a injections provide better results than single injection in treatment of painful bladder syndrome. *Pain Physician* 2013; **16**: E15.
205. Kuo HC: Repeated intravesical onabotulinumtoxina injections are effective in treatment of refractory interstitial cystitis/bladder pain syndrome. *Int J Clin Pract* 2013; **67**: 427.
206. Lee CL and Kuo HC: Intravesical botulinum toxin a injections do not benefit patients with ulcer type interstitial cystitis. *Pain Physician* 2013; **16**: 109.
206. Pinto R, Lopes T, Frias B et al: Trigonal injection of botulinum toxin a in patients with refractory bladder pain syndrome/interstitial cystitis. *Eur Urol* 2010; **58**: 360.
207. Pinto R, Lopes T, Silva J et al: Persistent therapeutic effect of repeated injections of onabotulinum toxin a in refractory bladder pain syndrome/interstitial cystitis. *J Urol* 2013; **189**: 548.
208. Chung SD, Kuo YC and Kuo HC: Intravesical onabotulinumtoxina injections for refractory painful bladder syndrome. *Pain Physician* 2012; **15**: 197.
209. Giannantoni A, Mearini E, Del Zingaro M et al: Two-year efficacy and safety of botulinum a toxin intravesical injections in patients affected by refractory painful bladder syndrome. *Curr Drug Deliv* 2010; **7**: 1.
210. Shie JH, Liu HT, Wang YS et al: Immunohistochemical evidence suggests repeated intravesical application of botulinum toxin a injections may improve treatment efficacy of interstitial cystitis/bladder pain syndrome. *BJU Int* 2013; **111**: 638.
211. Pinto RA, Costa D, Morgado A et al: Intratrigonal onabotulinumtoxina improves bladder symptoms and quality of life in patients with bladder pain syndrome/interstitial cystitis: A pilot, single center, randomized, double-blind, placebo controlled trial. *J Urol* 2018; **199**: 998.
212. Akiyama Y, Nomiya A, Niimi A et al: Botulinum toxin type a injection for refractory interstitial cystitis: A randomized comparative study and predictors of treatment response. *Int J Urol* 2015; **22**: 835.
213. Pinto R, Lopes T, Costa D et al: Ulcerative and nonulcerative forms of bladder pain syndrome/interstitial cystitis do not differ in symptom intensity or response to onabotulinum toxin a. *Urology* 2014; **83**: 1030.
214. Wang HJ, Yu WR, Ong HL et al: Predictive factors for a satisfactory treatment outcome with intravesical botulinum toxin a injection in patients with interstitial cystitis/bladder pain syndrome. *Toxins (Basel)* 2019; **11**.
215. Peters KM, Feber KM and Bennett RC: A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. *BJU Int* 2007; **100**: 835.
216. Comiter CV: Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: A prospective study. *J Urol* 2003; **169**: 1369.

217. Steinberg AC, Oyama IA and Whitmore KE: Bilateral s3 stimulator in patients with interstitial cystitis. *Urology* 2007; **69**: 441.
218. Gajewski JB and Al-Zahrani AA: The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. *BJU Int* 2011; **107**: 1258.
219. Ghazwani YQ, Elkeli MS and Hassouna MM: Efficacy of sacral neuromodulation in treatment of bladder pain syndrome: Long-term follow-up. *Neurourol Urodyn* 2011; **30**: 1271.
220. Marinkovic SP, Gillen LM and Marinkovic CM: Minimum 6-year outcomes for interstitial cystitis treated with sacral neuromodulation. *Int Urogynecol J* 2011; **22**: 407.
221. Powell CR and Kreder KJ: Long-term outcomes of urgency-frequency syndrome due to painful bladder syndrome treated with sacral neuromodulation and analysis of failures. *J Urol* 2010; **183**: 173.
222. Zhang P, Wang JY, Zhang Y et al: Results of sacral neuromodulation therapy for urinary voiding dysfunction: Five-year experience of a retrospective, multicenter study in china. *Neuromodulation* 2019; **22**: 730.
223. Marinkovic SP: Improving clinical outcomes with lower motor voltage ( $\leq 3$  v) during stage 1 sacral neuromodulation for interstitial cystitis or bladder pain syndrome. *Neurourol Urodyn* 2019; **38**: 2233.
224. Elhilali MM, Khaled SM, Kashiwabara T et al: Sacral neuromodulation: Long-term experience of one center. *Urology* 2005; **65**: 1114.
225. Peters KM and Konstandt D: Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. *BJU Int* 2004; **93**: 777.
226. Mowafy ZME, Mohammed AH, Moharam AAE et al: Effect of transcutaneous electrical nerve stimulation on interstitial cystitis/painful bladder syndrome. *International Journal of PharmTech Research* 2016; **9**: 59.
227. Fall M and Lindström S: Transcutaneous electrical nerve stimulation in classic and nonulcer interstitial cystitis. *Urol Clin North Am* 1994; **21**: 131.
228. Ragab MM, Tawfik AM, Abo El-enen M et al: Evaluation of percutaneous tibial nerve stimulation for treatment of refractory painful bladder syndrome. *Urology* 2015; **86**: 707.
229. Norus T, Fode M and Nordling J: Ileal conduit without cystectomy may be an appropriate option in the treatment of intractable bladder pain syndrome/interstitial cystitis. *Scand J Urol* 2014; **48**: 210.
230. Nielsen KK, Kromann-Andersen B, Steven K et al: Failure of combined suprarectal cystectomy and mainz ileoceccystoplasty in intractable interstitial cystitis: Is histology and mast cell count a reliable predictor for the outcome of surgery? *J Urol* 1990; **144**: 255.
231. Redmond EJ and Flood HD: The role of reconstructive surgery in patients with end-stage interstitial cystitis/bladder pain syndrome: Is cystectomy necessary? *Int Urogynecol J* 2017; **28**: 1551.
232. Linn JF, Hohenfellner M, Roth S et al: Treatment of interstitial cystitis: Comparison of subtrigonal and suprarectal cystectomy combined with orthotopic bladder substitution. *J Urol* 1998; **159**: 774.
233. Rössberger J, Fall M, Jonsson O et al: Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: Subtyping is imperative. *Urology* 2007; **70**: 638.
234. Hughes OD, Kynaston HG, Jenkins BJ et al: Substitution cystoplasty for intractable interstitial cystitis. *Br J Urol* 1995; **76**: 172.
235. Webster GD and Maggio MI: The management of chronic interstitial cystitis by substitution cystoplasty. *J Urol* 1989; **141**: 287.
236. Lotenoe RR, Christie J, Parsons A et al: Absence of neuropathic pelvic pain and favorable psychological profile in the surgical selection of patients with disabling interstitial cystitis. *J Urol* 1995; **154**: 2039.
237. Andersen AV, Granlund P, Schultz A et al: Long-term experience with surgical treatment of selected patients with bladder pain syndrome/interstitial cystitis. *Scand J Urol Nephrol* 2012; **46**: 284.
238. Brandt SB, Kirkeby HJ, Brandt ASV et al: Urinary diversion in the treatment of refractory bladder pain syndrome. *Scand J Urol* 2019; **53**: 424.
239. Peeker R, Aldenborg F and Fall M: The treatment of interstitial cystitis with suprarectal cystectomy and ileoceccystoplasty: Difference in outcome between classic and nonulcer disease. *J Urol* 1998; **159**: 1479.
240. Downey AP and Osman NI: What is the role of surgery in bladder pain syndrome? *Eur Urol Focus* 2019; **5**: 317.

241. Chakravarti A, Ganta S, Somani B et al: Caecocystoplasty for intractable interstitial cystitis: Long-term results. *Eur Urol* 2004; **46**: 114.
242. van Ophoven A, Oberpenning F and Hertle L: Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. *J Urol* 2002; **167**: 603.
243. Christmas TJ, Holmes SA and Hendry WF: Bladder replacement by ileocystoplasty: The final treatment for interstitial cystitis. *Br J Urol* 1996; **78**: 69.
244. Kim HJ, Lee JS, Cho WJ et al: Efficacy and safety of augmentation ileocystoplasty combined with suprarectal cystectomy for the treatment of refractory bladder pain syndrome/interstitial cystitis with Hunner's lesion. *Int J Urol* 2014; **21 Suppl 1**: 69.
245. Mateu Arrom L, Gutiérrez Ruiz C, Mayordomo Ferrer O et al: Long-term follow-up after cystectomy for bladder pain syndrome: Pain status, sexual function and quality of life. *World J Urol* 2019; **37**: 1597.
246. Peters KM, Jaeger C, Killinger KA et al: Cystectomy for ulcerative interstitial cystitis: Sequelae and patients' perceptions of improvement. *Urology* 2013; **82**: 829.
247. Warren JW, Horne LM, Hebel JR et al: Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. *J Urol* 2000; **163**: 1685.
248. Parziani S, Costantini E, Petroni PA et al: Urethral syndrome: Clinical results with antibiotics alone or combined with estrogen. *Eur Urol* 1994; **26**: 115.
249. Weinstock LB, Klutke CG and Lin HC: Small intestinal bacterial overgrowth in patients with interstitial cystitis and gastrointestinal symptoms. *Dig Dis Sci* 2008; **53**: 1246.
250. Peters K, Diokno A, Steinert B et al: The efficacy of intravesical tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: A double-blind, prospective, placebo controlled trial. *J Urol* 1997; **157**: 2090.
251. Mayer R, Propert KJ, Peters KM et al: A randomized controlled trial of intravesical bacillus Calmette-Guerin for treatment of refractory interstitial cystitis. *J Urol* 2005; **173**: 1186.
252. Propert KJ, Mayer R, Nickel JC et al: Did patients with interstitial cystitis who failed to respond to initial treatment with bacillus Calmette-Guerin or placebo in a randomized clinical trial benefit from a second course of open label bacillus Calmette-Guerin? *J Urol* 2007; **178**: 886.
253. Propert KJ, Mayer R, Nickel JC et al: Followup of patients with interstitial cystitis responsive to treatment with intravesical bacillus Calmette-Guerin or placebo. *Journal of Urology* 2008; **179**: 552.
254. Izes JK, Bahrle W, 3rd and Thomas CB: Corticosteroid-associated fatal mycobacterial sepsis occurring 3 years after instillation of intravesical bacillus Calmette-Guerin. *J Urol* 1993; **150**: 1498.
255. Lamm DL, van der Meijden PM, Morales A et al: Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol* 1992; **147**: 596.
256. Nadasy KA, Patel RS, Emmett M et al: Four cases of disseminated *Mycobacterium bovis* infection following intravesical BCG instillation for treatment of bladder carcinoma. *South Med J* 2008; **101**: 91.
257. Trevenzoli M, Cattelan AM, Marino F et al: Sepsis and granulomatous hepatitis after bacillus Calmette-Guerin intravesical installation. *J Infect* 2004; **48**: 363.
258. McCahy PJ and Styles RA: Prolonged bladder distension: Experience in the treatment of detrusor overactivity and interstitial cystitis. *Eur Urol* 1995; **28**: 325.
259. Glemain P, Rivière C, Lenormand L et al: Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: Efficacy at 6 months and 1 year. *Eur Urol* 2002; **41**: 79.
260. Yamada T: Significance of complications of allergic diseases in young patients with interstitial cystitis. *Int J Urol* 2003; **10 Suppl**: S56.
261. Hosseini A, Ehrén I and Wiklund NP: Nitric oxide as an objective marker for evaluation of treatment response in patients with classic interstitial cystitis. *J Urol* 2004; **172**: 2261.
262. Soucy F and Grégoire M: Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. *J Urol* 2005; **173**: 841.
263. Aaron LA and Buchwald D: A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001; **134**: 868.

264. Abrams P, Baranowski A, Berger RE et al: A new classification is needed for pelvic pain syndromes--are existing terminologies of spurious diagnostic authority bad for patients? J Urol 2006; **175**: 1989.
265. Baranowski AP, Abrams P, Berger RE et al: Urogenital pain--time to accept a new approach to phenotyping and, as a consequence, management. Eur Urol 2008; **53**: 33.
266. Gillenwater JY and Wein AJ: Summary of the national institute of arthritis, diabetes, digestive and kidney diseases workshop on interstitial cystitis, national institutes of health, bethesda, maryland, august 28-29, 1987. J Urol 1988; **140**: 203.
267. Propert KJ, Payne C, Kusek JW et al: Pitfalls in the design of clinical trials for interstitial cystitis. Urology 2002; **60**: 742.
268. Fan YH, Lin AT, Wu HM et al: Psychological profile of taiwanese interstitial cystitis patients. Int J Urol 2008; **15**: 416.
269. van de Merwe JP: Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol 2007; **4**: 484.
270. Wesselmann U, Baranowski AP, Börjesson M et al: Emerging therapies and novel approaches to visceral pain. Drug Discov Today Ther Strateg 2009; **6**: 89.
271. Hobson AR and Aziz Q: Modulation of visceral nociceptive pathways. Curr Opin Pharmacol 2007; **7**: 593.

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#### American Urological Association

1000 Corporate Boulevard  
Linthicum, MD 21090  
Phone: 410-689-3700  
Toll-Free: 1-800-828-7866  
Fax: 410-689-3912  
Email: [aua@AUAnet.org](mailto:aua@AUAnet.org)

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