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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

This document was amended in 2014 to reflect literature that was released since the original publication of this guideline.

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Note to the Reader:

As of December 5, 2014, the Panel has updated this Guideline to indicate suggested dosing of triamcinolone, which reflects the expert opinion of the Panel.

American Urological Association (AUA) Guideline

DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

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

Purpose: The purpose of this Guideline is to provide a clinical framework for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome (IC/BPS).

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. Insufficient evidence was retrieved regarding diagnosis; this portion of the guideline, therefore, is based on Clinical Principles and Expert Opinion. 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. This review identified an additional 31 articles relevant to treatment. 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 rule in symptoms that characterize IC/BPS and rule out other confusable disorders (see text for details). *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 as an aid to diagnosis only for complex presentations; these tests are not necessary for making the diagnosis in uncomplicated presentations. *Expert Opinion*

Treatment:

Overall Management:

4. Treatment strategies should proceed using more conservative therapies first, with less conservative therapies employed if symptom control is inadequate for acceptable quality of life; because of their irreversibility, surgical treatments (other than fulguration of Hunner's lesions) are appropriate only after other

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treatment alternatives have been exhausted, or at any time in the rare instance when an end-stage small, fibrotic bladder has been confirmed and the patient's quality of life suggests a positive risk-benefit ratio for major surgery. *Clinical Principle*

5. Initial treatment type and level should depend on symptom severity, clinician judgment, and patient preferences; appropriate entry points into the treatment portion of the algorithm depend on these factors. *Clinical Principle*
6. Multiple, simultaneous treatments may be considered if it is in the best interests of the patient; baseline symptom assessment and regular symptom level reassessment are essential to document efficacy of single and combined treatments. *Clinical Principle*
7. Ineffective treatments should be stopped once a clinically meaningful interval has elapsed. *Clinical Principle*
8. 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*
9. The IC/BPS diagnosis should be reconsidered if no improvement occurs after multiple treatment approaches. *Clinical Principle*

Treatments that may be offered: Treatments that may be offered are divided into first-, second-, third-, fourth-, fifth-, and sixth-line groups based on the balance between potential benefits to the patient, potential severity of adverse events (AEs) and the reversibility of the treatment. See body of guideline for protocols, study details, and rationales.

First-Line Treatments: First-line treatments should be performed on all patients.

10. Patients should be educated about normal bladder function, what is known and not known about IC/ BPS, the benefits v. 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*
11. Self-care practices and behavioral modifications that can improve symptoms should be discussed and implemented as feasible. *Clinical Principle*
12. Patients should be encouraged to implement stress management practices to improve coping techniques and manage stress-induced symptom exacerbations. *Clinical Principle*

Second-line treatments:

13. 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. *Clinical Principle Standard (Evidence Strength- Grade A)*
14. Multimodal pain management approaches (e.g., pharmacological, stress management, manual therapy if available) should be initiated. *Expert Opinion*
15. Amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate may be administered as second-line oral medications (listed in alphabetical order; no hierarchy is implied). *Options (Evidence Strength- Grades B, B, C, and B)*
16. DMSO, heparin, or lidocaine may be administered as second-line intravesical treatments (listed in alphabetical

order; no hierarchy is implied). *Option (Evidence Strength- Grades C, C, and B)*

Third-line treatments:

17. Cystoscopy under anesthesia with short-duration, low-pressure hydrodistension may be undertaken if first- and second-line treatments have not provided acceptable symptom control and quality of life or if the patient's presenting symptoms suggest a more invasive approach is appropriate. *Option (Evidence Strength- Grade C)*
18. If Hunner's lesions are present, then fulguration (with laser or electrocautery) and/or injection of triamcinolone should be performed. *Recommendation (Evidence Strength- Grade C)*

Fourth-line treatment:

BTX-A moved from fifth-line treatments to first fourth-line treatment

19. Intradetrusor botulinum toxin A (BTX-A) may be administered if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. Patients must be willing to accept the possibility that post-treatment intermittent self- catheterization may be necessary. *Option (Evidence Strength- C)*
20. A trial of neurostimulation may be performed and, if successful, implantation of permanent neurostimulation devices may be undertaken if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. *Option (Evidence Strength- C)*

Fifth-line treatments:

21. Cyclosporine A may be administered as an oral medication if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. *Option (Evidence Strength- C)*

Sixth-line treatment:

22. Major surgery (e.g., substitution cystoplasty, urinary diversion with or without cystectomy) may be undertaken in carefully selected patients for whom all other therapies have failed to provide adequate symptom control and quality of life (see caveat above in guideline statement #4). *Option (Evidence Strength- C)*

Treatments that should not be offered: The treatments below appear to lack efficacy and/or appear to be accompanied by unacceptable AE profiles. See body of guideline for study details and rationales.

23. Long-term oral antibiotic administration should not be offered. *Standard (Evidence Strength- B)*
24. Intravesical instillation of bacillus Calmette-Guerin (BCG) should not be offered outside of investigational study settings. *Standard (Evidence Strength- B)*
25. High-pressure, long-duration hydrodistension should not be offered. *Recommendation (Evidence Strength- C)*
26. Systemic (oral) long-term glucocorticoid administration should not be offered. *Recommendation (Evidence Strength- C)*

Introduction

INTRODUCTION**Purpose**

This guideline's purpose is to provide direction to clinicians and patients regarding how to: recognize interstitial cystitis (IC)/bladder pain syndrome (BPS); conduct a valid diagnostic process; and, approach treatment with the goals of maximizing symptom control and patient quality of life (QoL) while minimizing 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. Studies published after July 22, 2009 were not included as part of the original evidence base considered by the Panel from which evidence-based guideline statements (Standards, Recommendations, Options) were derived. However, the guideline is regularly updated by additional systematic review searches conducted as part of the AUA's update literature review process (see below), and the evidence base is regularly updated based on the findings from the update reviews. 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 Appendix 1), therefore, are provided as *Clinical Principles* or as *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.¹ 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 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 and also have been incorporated. The Panel judged that these were a sufficient evidence base from which to construct the majority of the treatment portion of the algorithm. Data on study type (e.g., randomized controlled trial, 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 ICPS, ICSS, VAS scales, as available. In short supply are objective parameters

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and placebo controlled trials.

Quality of Individual Studies and Determination of Evidence Strength. Quality of individual studies that were randomized controlled trials (RCTs) or crossover trials was assessed using the Cochrane Risk of Bias tool.² 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.

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.³ **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.

Table 1: AUA Nomenclature

Linking Statement Type to Level of Certainty and Evidence Strength [Updated Version]	
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

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Limitations of the Literature. The Panel proceeded with full awareness of the limitations of the IC/BPS literature. These limitations 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. With regard to measures, even though the most consistently used measure was some form of patient-rated improvement scale, the scales differed across studies in anchor points, number of gradations, and descriptors. Overall, these difficulties resulted in limited utility for meta-analytic procedures. The single meta-analysis reported here was used to calculate an overall effect size for data from randomized trials that evaluated pentosan polysulfate (PPS). No comparative procedures were undertaken.

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, many with specific identifiable causes. 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."⁴ 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.⁵

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 100,000.⁶ In NHANES III, the prevalence was 470 per 100,000 population, including 60 per 100,000 men and 850 per 100,000 women.⁶ 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%.⁷ 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.⁸ 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 30-79.⁹ 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.¹⁰ In this cohort of women,

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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).¹¹

Further information is provided in three additional papers that reported data from the RAND Interstitial Cystitis Epidemiology (RICE) study.¹²⁻¹⁴ 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.¹² 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.

Berry et al. (2011) used the questionnaire to determine prevalence of IC/BPS among adult females in the US¹³ 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).¹⁴ 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,

Table 2: RICE BPS/IC Case Definitions¹³

High Sensitivity Definition	High Specificity Definition
(sensitivity 81%, specificity 54% for BPS/IC v. endometriosis, vulvodynia and overactive bladder)	(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	

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and 67/100,000 in the NHS II cohort.¹⁵ A subsequent study was performed using administrative billing data from the Kaiser Permanente Northwest managed care population in the Portland, Oregon metropolitan area.⁸ 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 the fourth decade or after, although the diagnosis may be delayed depending upon the index of suspicion for the disease, and the criteria used to diagnose it.¹⁶ 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 UTI can be identified on presentation in 18-36% of women, although subsequent cultures are negative.^{17,18} Initially it is not uncommon for patients to report a single symptom such as dysuria, frequency, or pain, with subsequent progression to multiple symptoms.^{19,20} Symptom flares, during which symptoms suddenly intensify for several hours, days, or weeks, are not uncommon. 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.²¹ 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, irritable bowel syndrome, chronic fatigue syndrome, Sjogren's syndrome, chronic headaches, and vulvodynia.^{22,23} 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.^{24,25}

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 pain disorders such as interstitial cystitis, irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia tended to co-occur.²⁶ He suggested that there might be a common central pathogenesis and pathophysiology for these disorders. Self-report data collected by the Interstitial Cystitis Association corroborated Clauw's findings and showed an association between IC/BPS and other chronic pain disorders.²⁷ Aaron and Buchwald (2001) analyzed a co-twin control study and supported the findings previously reported by Clauw and colleagues (1997).²⁸ Additional epidemiologic studies support these data and suggest that if the IC patient is properly assessed during the diagnostic evaluation, many of these somatic symptoms are also present.

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.^{29,30} An additional hypothesis is that IC/BPS might be just a part of the continuum of painful v. non-painful overactive bladder syndrome (OAB).^{31,32}

Challenge to Patient and Clinician: Impact on Psychosocial Functioning and Quality of Life (QoL). 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.⁹ QoL is poorer in IC/BPS patients than in controls.^{9,33,34} Rates of depression are also higher.³³⁻³⁵ 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.^{36,37} The impact of IC/BPS on QoL is as severe as that of rheumatoid arthritis and end-stage renal disease.^{9,38} Health-related QoL in women with IC/BPS is worse than that of women with

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endometriosis, vulvodynia or overactive bladder.³⁹ Given that IC/BPS causes considerable morbidity over the course of a patient's life and loss of work during the most productive years of work and family life significant negative psychological and QoL impacts are not surprising.⁹

Sexual dysfunction has an especially important impact on the QoL of IC/BPS patients. In IC/BPS patients, sexual dysfunction is moderate to severe⁴⁰ and occurs at high rates compared with controls.^{41,42} In women with treatment-refractory IC/BPS, poor sexual function is a primary predictor of poor mental QoL.⁴³ 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.⁴¹ 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.⁴⁴ In addition, response to therapy is associated with improved sexual function and sleep, with concomitant improvements in QoL.^{36,40}

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.⁴⁵ They are also more consistent across geographic regions of the United States than other urologic conditions.⁴⁶ 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, National Health and Nutrition Examination Survey, 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).⁴⁶ 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.⁴⁶ 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.⁴⁶ 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.⁴⁶ 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.⁴⁶ 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.^{45,46} 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.^{45,47} 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.⁴⁶ 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

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nearly twice that amount.⁴⁷ 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.⁴⁷ Although clearly substantial, these additional costs fail to reflect the economic burden associated with commonly occurring coexisting conditions.⁴⁸

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—in the urethra, vulva, vagina, rectum—and in extragenital locations such as the lower abdomen and back.^{18,42,49} Warren and colleagues (2006) found that by using “pelvic pain” as the key descriptor that 100% of his population fit the case definition.⁵⁰ 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.^{49,51} 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.¹⁸

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),⁴² 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),⁴² but urgency is considered to be the characteristic symptom of overactive bladder and thus it can actually confound the diagnosis. There may, however, be 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 ICS definition of a “compelling need to urinate which is difficult to postpone.”^{52,53} 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.²⁰ Median time to the development of a full symptom complex of frequency, urgency, and pain was reported to be two years in one study.²⁰

Presentation of Male IC Patients. Historically, IC/BPS in men has been considered relatively unusual with a female to male ratio of 10:1.^{54,55} However, uncontrolled clinical series over the past two decades have suggested the incidence of male IC/BPS may be higher than previously observed.^{8,56} 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, he can be assumed to have the disorder. Early clinical symptoms may begin with mild dysuria or urinary urgency. Mild symptoms may progress to severe voiding frequency, nocturia, and suprapubic pain. The presence or absence of glomerulations on endoscopy can be considered supporting information, but is too nonspecific to make the diagnosis of the disease in anyone who does not fit the symptom complex as defined.

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.⁵⁶ Some data suggest that Hunner’s ulcers are more common in male IC/BPS patients.⁵⁷

Male IC/BPS v. Chronic Prostatitis. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), or NIH Type III prostatitis⁵⁸ is characterized by pain in the perineum, suprapubic region, testicles or tip of the penis.⁵⁹ 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. However, it is also quite clear that certain men have symptoms which meet criteria for both conditions (IC/BPS and CP/CPPS).

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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.⁶⁰ Additionally, empiric IC/BPS strategies in those CP/CPPS patients have demonstrated clinical symptomatic improvement.^{57,60,61}

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.⁶² 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 NIDDK diagnostic criteria (note that the NIDDK diagnostic criteria are not appropriate for use outside of clinical trials).^{63,64} 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

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*

Discussion. 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 Appendix 1: Diagnostic and Treatment Algorithm).⁶⁵⁻⁶⁸ 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 focusing on areas of tenderness. 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 source of pain or infection is important. For a more detailed discussion, please see Weiss 2001.⁶⁹ A trial of antibiotic therapy is appropriate when infection is suspected; if symptoms resolve one might consider a course of antibiotic suppression 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. If the patient reports a history of smoking and/or presents with unevaluated microhematuria, then cytology may be considered given the high risk of bladder cancer in smokers. 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*

Discussion. 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

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characteristic of IC/BPS.⁷⁰ These values can then be used to determine if a clinically significant response to treatment has occurred. Similarly, self-report instruments such as the O'Leary-Sant Symptom and Problem questionnaire and the Pelvic Pain and Urgency/Frequency (PUF) questionnaire can be used to establish a standardized symptom profile baseline for later evaluation of treatment response.²⁹ 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. The O'Leary-Sant ICSI/ICPI is useful to gather comprehensive symptom information, including symptoms in addition to those of pain or discomfort.⁷¹ A 1 to 10 Likert-style visual analog scale (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. 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).⁷² Patients also should be queried regarding factors known to worsen or improve pain or discomfort.

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. 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.⁷³ 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.⁷⁴ 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.⁷⁴ Another proposed role for the PST is to identify the subset of patients who have urothelial dysfunction.⁷⁴ 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 pentosanpolysulfate⁷⁴ or with combined heparinoid and tricyclic antidepressant treatment.⁷⁵ PST findings also did not predict success in a randomized trial of PPS v. cyclosporine A.⁷⁶ Findings from a modified PST predicted response to intravesical hyaluronic acid in one study⁷⁷ but this treatment is not used in the US and unpublished data from two large multicenter randomized controlled trials 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 agreed 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

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Discussion. Cystoscopy and urodynamic testing are appropriate as part of the diagnostic approach when the basic assessment results are in doubt about the IC/BPS diagnosis, or when information that would be gained 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's lesion. Identification of entities such as bladder cancer, vesical 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 (1918).⁷⁸ These lesions may be identified in an acute phase (as an inflamed, friable, denuded area) or a more chronic phase (blanched, non-bleeding area).⁷⁹ Glomerulations (pinpoint petechial hemorrhages) may be detected on cystoscopy and can be consistent with IC/BPS but these lesions 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.^{80,81} Glomerulations may also be present in asymptomatic patients undergoing cystoscopy for other conditions.⁸² 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 on survey analysis.⁸³ Given the differing approaches, the finding of glomerulations on hydrodistension (less than 80 cm H₂O, less than 5 minutes) is variable and not consistent with clinical presentation.^{84,85} 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.⁸⁶ 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's 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).⁸⁷ There is evidence that Hunner's lesions are more common in IC/BPS patients of age over 50 years.⁸⁸ When responses to first- and second-line treatments are inadequate to achieve acceptable quality of life, it is appropriate to proceed to cystoscopy in order to assess for the presence of Hunner's lesions and rule out potential other pathologies that may be causing symptoms.

Similar to 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.⁸⁹ 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.⁸⁹ 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.⁹⁰ 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, and other conditions that could explain

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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.

Treatment Statements

Issues to Consider. 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.⁹¹⁻⁹³ 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 v. 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 quality of life. 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.

Overall Management. The information presented on *Overall Management* of IC/BPS in this section is based on Clinical Principles or Expert Opinion with consensus achieved using a modified Delphi technique. This section is offered to provide clinicians and patients with a framework and strategy for determining optimal treatment approaches (see Appendix 1); it is not intended to replace the judgment and experience of the individual clinician faced with a particular patient. The framework for overall management includes the following:

Guideline Statement 4.

Treatment strategies should proceed using more conservative therapies first with less conservative therapies employed if symptom control is inadequate for acceptable quality of life; because of their irreversibility, surgical

treatments (other than fulguration of Hunner's lesions) are generally appropriate only after other treatment alternatives have been exhausted or at any time in the rare instance when an end-stage small, fibrotic bladder has been confirmed and the patient's quality of life suggests a positive risk-benefit ratio for major surgery. *Clinical Principle*

Discussion. The available treatments for IC/BPS vary considerably in: invasiveness; the probability, duration, severity and reversibility of AEs; and reversibility of the treatment itself. Treatment strategies should proceed from conservative therapies to less conservative therapies. Please see the Treatment section for detailed discussion of this principle.

Guideline Statement 5.

Initial treatment type and level should depend on symptom severity, clinician judgment, and patient preferences; appropriate entry points into the treatment portion of the algorithm depend on these factors. Counseling patients with regard to reasonable expectations for treatment outcomes is important. *Clinical Principle*

Discussion. Effective management of IC/BPS patients requires tailoring of treatments to symptom type and severity as well as ensuring that patients have reasonable expectations for treatment benefits. Please see the Treatment section and patient education section (Statement 10) for more discussion of these issues.

Guideline Statement 6.

Multiple, concurrent treatments may be considered if it is in the best interests of the patient; baseline symptom assessment and regular symptom level reassessment are essential to document efficacy of single and combined treatments. *Clinical Principle*

Discussion. Some patients may benefit from the use of concurrent treatments or may require the use of concurrent treatments to optimize quality of life. Documenting treatment progress achieved with single and multiple treatment approaches is critical to ensure that ineffective treatments are ceased (see discussion under Statement 7) and that only effective treatments (singly and/or in combination) are continued. Please see

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the Treatment section for details on available treatments.

Guideline Statement 7.

Ineffective treatments should be stopped once a clinically-meaningful interval has elapsed.

Clinical Principle

Discussion. IC/BPS treatment alternatives are characterized by the fact that most treatments may benefit a subset of patients that is not identifiable pre-treatment 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. See Treatment section for details.

Guideline Statement 8.

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*

Discussion. 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 quality of life and, particularly for complex patient presentations, may require a multidisciplinary approach. Please see Statement 14 on pain management for a thorough discussion of pain management.

Guideline Statement 9.

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

Discussion. If clinically-meaningful trials of multiple therapies have been conducted without efficacy, 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 Levels 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 (randomized trials, 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 risks/ burdens in terms of the invasiveness of the treatment, the duration and severity of potential AEs, and the reversibility of potential AEs. With regard to treatment invasiveness, oral treatments were judged to be less invasive than intravesical treatments and intravesical treatments were judged to be less invasive than surgical treatments. With regard to duration of AEs, some AEs either diminish over time and/or readily cease upon cessation of the treatment (e.g., medication side effects). 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 BTX-A treatment). With regard to the severity of AEs, potential AEs vary in the extent to which they can compromise QoL. For example, medication side effects can be mild (e.g., pentosan polysulfate) or severe enough to constitute the major reason for study withdrawal (e.g., amitriptyline). Further, some procedures and substances have the potential for rare but life-threatening AEs (e.g., sepsis with intravesical BCG administration). AEs also vary in their reversibility. Most medication side effects cease upon discontinuation of the substance and are completely reversible. Surgical treatments, however, are irreversible.

Treatment alternatives were then categorized as clinical principles, expert opinion, or evidence-based statements

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and divided into first-, second-, third-, fourth-, fifth-, and sixth- line groups. This hierarchy was derived by balancing the potential benefits to the patient with the invasiveness of the treatment, the duration and severity of potential AEs, and the reversibility of potential AEs. Note that the hierarchy was not established based on evidence strength. For example, first- line treatments (composed of Clinical Principles) in the Panel's judgment present essentially no risks to patients and should be offered to all patients. Second-line treatments vary in evidence strength but have in common that they appear to benefit at least a subset of patients, pose the least risk to patients in terms of invasiveness and AE duration/ severity, and are readily reversible. For treatments with a sufficient evidence base, judgments regarding evidence strength and the balance between benefits and risks/burdens then were used to determine statement type (Standard, Recommendation, or Option).

Each set of treatments is presented below. Most treatments are designated as Options with the exception of fulguration of Hunner's lesions (this treatment is designated as a 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 pentosan polysulfate), 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 quality of life, 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's 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.

First-Line Treatments: The first-line treatment approaches presented below are based on Clinical Principles; insufficient literature was available to guide an evidence-based version. The Panel believes that all patients should be offered these treatments. As with other sections of the guideline, this information is presented as a suggested framework for the clinical approach; it is not intended to replace the judgments of individual clinicians and patients regarding the optimal components of treatment.

Guideline Statement 10.

Patients should be educated about normal bladder function, what is known and not known about IC/BPS, the benefits v. 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*

Discussion. The first-line treatment approach should include patient education regarding normal bladder function and what is known and not known about IC/BPS and the fact that it is typically a chronic disorder requiring continual and dynamic management. Patients also should be educated regarding the available treatment alternatives, the fact that no single treatment has been found to be effective for a majority of patients, and that 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 11.

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

Discussion. Clinical experience and a limited literature suggest that modifying certain behaviors can improve symptoms in some IC/ BPS patients.⁹⁴ 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., neutraceuticals, calcium glycerophosphates, pyridium); 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.⁹⁵⁻⁹⁸ 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.

The National Institute of Diabetes and Digestive and Kidney Diseases 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.⁹⁶

Guideline Statement 12.

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

Discussion. Psychological stress is associated with heightened pain sensitivity in general.^{99,100} In laboratory studies, stress increases IC/BPS symptoms.¹⁰¹ 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 irritable bowel syndrome (IBS), endometriosis, recurrent vaginitis/vestibulitis, severe predictable flares occurring with phase of menstrual cycle, panic attacks, depression, etc.

Second-line Treatments:

Guideline Statement 13.

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. [*Clinical Principle*] *Standard*

Discussion. (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.^{21,69} 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

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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.¹⁰²⁻¹⁰⁷ 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 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.¹⁰⁸ 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 14.

Multimodal pain management approaches (e.g., pharmacological, stress management, manual therapy if available) should be initiated. Expert Opinion

Discussion. 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.^{23,109,110} 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.

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.

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 non-narcotic medications used for chronic pain which have been "borrowed" from the treatment of depression, epilepsy, arrhythmias, etc. The use of narcotics presents the risks of tolerance and dependence (although very rarely addiction) but it is clear that many patients benefit from narcotic analgesia as part of a comprehensive program to manage pain. 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

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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.

Guideline Statement 15.

Amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate may be administered as second-line oral medications (listed in alphabetical order; no hierarchy is implied). Options

Discussion. 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.¹¹¹ 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.^{112,113} AEs were extremely common (up to 79% of patients) and, although not life-threatening, had substantial potential to compromise quality of life (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 quality of life, it was designated as an Option. The 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 ITT analysis indicated that at three months the proportion of successes in each group defined by a GRA as moderate or marked improvements 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.¹¹⁴

Discussion. Cimetidine (Evidence Strength – Grade B). One randomized controlled trial 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

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of treatment.¹¹⁵ 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.^{116,117} 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 (40 patients, 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.

Discussion. 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).¹¹⁸ 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.¹¹⁹ 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.

Discussion. Pentosanpolysulfate (PPS; Evidence Strength – Grade B). PPS 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 cyclosporine A), 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% v. 49%, respectively).⁸⁷ 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% v. Placebo 13%).¹¹⁸ 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).^{120,121} 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.¹²² 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 cyclosporine A and reported that CyA patients experienced a statistically significantly higher rate (83%) of clinically significant improvement compared to PPS patients (21%).¹²³ 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 www.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%).

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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's lesions.¹²⁴

Guideline Statement 16.

DMSO, heparin, or lidocaine may be administered as second-line intravesical treatments (listed in alphabetical order; no hierarchy is implied). Option

Discussion. 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").¹²⁵ 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.¹²⁶ 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%.¹²⁷⁻¹²⁹ 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.¹³⁰⁻¹³⁴ 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.

Discussion. Heparin (Evidence Strength – Grade C).

Three observational studies reported findings from the use of intravesical heparin. Using 10,000 IU heparin in 10cm³ sterile water three times a week for three months with retention of one hour, at three months 56% of patients reported clinically significant improvement.¹³⁵ 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.¹³⁶ 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

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triamcinolone (20,000 units heparin, 20 ml 2% lidocaine, 40 mg triamcinolone; see Butrick [2009] under intravesical lidocaine).^{137,138} Two new studies retrieved as part of the update literature review process reported findings from instillation of heparin in combination with alkalized lidocaine.^{139,140} 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.¹³⁹ The observational study (Nomiya et al., 2013) administered instillations weekly for 12 weeks and followed patients for 6 months.¹⁴⁰ 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.

Discussion. Lidocaine (Evidence Strength – Grade B). One randomized multi-center trial reported that 3 and 10 days after treatment (10 ml PSD597; patented combination of 200 mg lidocaine alkalized 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 10.¹⁴¹ 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.^{137,142,143} Alkalinization 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 alkalization. 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.¹³⁸ Heparin or PPS may be added. In one study comparing lidocaine plus PPS v. lidocaine alone, some outcome measures were better in the lidocaine plus PPS group.¹⁴⁴ 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%.¹³⁷ 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.

Third-Line Treatments:**Guideline Statement 17.**

Cystoscopy under anesthesia with short-duration, low-pressure hydrodistension may be undertaken if first- and second- line treatments have not provided acceptable symptom control and quality of life or if the patient's presenting symptoms suggest a more invasive approach is appropriate. Option

Discussion. Cystoscopy under anesthesia with hydrodistension (Evidence Strength – Grade C). If first- and second-line treatments have not provided acceptable symptom control and quality of life or if the patient's initial symptoms suggest that a more invasive approach is appropriate, then cystoscopy under anesthesia with low-pressure (60 to 80 cm H₂O), short duration (less than 10 minutes) hydrodistension may be undertaken. Note that the procedure is intended to serve three purposes. First, before distension, the bladder is inspected for other potential symptom causes (e.g., stones, tumors) and for Hunner's lesions. If these are found, then they are treated appropriately (see below for treatment of Hunner's lesions). Second, if no bladder abnormalities or ulcers are found, then the

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distension may proceed and serve as a treatment. Hunner's lesions can be easier to identify after distention 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.

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%.¹⁴⁵⁻¹⁴⁷ No AEs were reported. Two additional studies identified in the update literature review reported improvement rates for various symptoms that ranged from 65% to >90% at 6 to 9 months of follow-up.^{148,149} 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's lesions are detected, then their treatment is recommended (see below).

Guideline Statement 18.

If Hunner's lesions are present, then fulguration (with laser or electrocautery) and/or injection of triamcinolone should be performed.
Recommendation

Discussion. Hunner's lesion fulguration (Evidence strength – Grade C). If Hunner's lesions are found, then the Panel recommends that fulguration (with laser, cautery) and/or injection of triamcinolone be undertaken. 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.¹⁵⁰ Three additional observational studies were retrieved in the update literature review. Two studies used primarily fulguration; one used electrocautery.^{88,151,152} 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.^{153,154} 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. Patients should be counseled that periodic retreatment is likely to be necessary when symptoms recur. In the experience of the Panel, patients undergoing laser therapy for Hunner's lesions also should be forewarned of the possibility of forward scatter and delayed bowel perforation. 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.¹⁵⁵ While Cox et al. saw improvement using a total dose of up to 400mg, it is the opinion of this panel that in the absence of substantial safety data for this dose, the dose should be limited to a total injection of 60mg in divided aliquots using either a 10mg/cc concentration or 40mg/cc concentration, depending upon the area of tissue requiring injection.¹⁵⁶

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 benefits of Hunner's lesion treatment outweigh risks/burdens and recommend that it be offered.

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Fourth-Line Treatments:**Guideline Statement 19.**

Intradetrusor botulinum toxin A (BTX-A) may be administered if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. The patient must be willing to accept the possibility that intermittent self-catheterization may be necessary post-treatment. Option

Discussion. Intradetrusor Botulinum toxin A (BTX-A) (Evidence Strength – Grade C). Six observational studies reported on the use of BTX-A to treat IC/BPS symptoms. One study reported efficacy of 69% but did not indicate whether this occurred at one, three, or six months of follow up.¹⁵⁷ Two studies reported high initial efficacy rates of 74% and 86% at three months.^{158,159} One study reported that BFLUTS and KHQ scores and frequency improved significantly at 3.5 months.¹⁶⁰ Effectiveness diminished over time, however, and at one year symptoms were indistinguishable from baseline values.¹⁶¹ One study reported a low efficacy rate at three months with only 20% of patients exhibiting improvement.¹⁶²

The update literature review retrieved ten new studies, including one randomized controlled trial¹⁶³ 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.¹⁶⁴⁻¹⁶⁸ 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 U 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: The RCT (Kuo & Chancellor 2009) compared three groups: BTX-A 200 U in the posterior and lateral bladder walls with hydrodistension two weeks later; BTX-A 100 U 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 U dose did not exert a greater effect than the 100 U dose. Rates of AEs were much higher and more serious in the 200 U 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 that the remaining patients that had been randomized to receive 200 U instead were treated with 100 U, accounting for the imbalance in group size.

Chung (2012) also combined BTX-A (100 U 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.¹⁶⁹ About one-third of patients had dysuria but there were no cases of urinary retention and no need for CISC.

Re-treatment with BTX-A: Giannantoni, Mearini (2010) treated patients with 200 U in the lateral bladder walls and trigone with re-treatment when benefits began to decline (mean re-treatment interval 5.25 months).¹⁷⁰ 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 (note this is the 200 U 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 U into the trigonal wall with retreatment upon symptom return and followed patients for up to three years.^{167,168} 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 post treatment 2 (but not after the other treatments); there was no urinary retention or CISC required.¹⁶⁷ In Pinto (2013), a similar pattern of AEs was reported.¹⁶⁸

Shie (2012) injected 100 U in the posterior and lateral bladder walls with re-treatment every six months

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regardless of symptom status for a total of four treatments.¹⁷¹ 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 U into the posterior and lateral bladder walls followed by hydrodistension.¹⁶⁴⁻¹⁶⁶ 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's ulcers 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 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. BTX-A treatment was considered a fifth-line treatment in the original guideline because of the seriousness and particularly the duration of AEs associated with the 200U dose. Common AEs included dysuria, the need for abdominal straining to void, large post-void residuals (greater than 100 ml), and the need for intermittent self-catheterization that persisted for one to three months and in some cases longer. Based on the substantial new evidence retrieved in the update literature review described above, with consistent reports of substantially reduced morbidity with use of the 100U dose, the Panel judged that use of BTX-A at the 100U dose is appropriate as a fourth-line treatment.

The Panel notes that BTX-A should be administered by experienced practitioners and that patients must be

willing to accept the possibility that intermittent self-catheterization 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 20.

A trial of neurostimulation may be performed and, if successful, implantation of permanent neurostimulation devices may be undertaken if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. *Option*

Discussion. Neuromodulation (Evidence Strength – Grade C). Three studies reported findings from permanent implant of sacral or pudendal neurostimulation 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 neurostimulation is approved. One study used a randomized crossover design to test temporary sacral v. pudendal neurostimulation and allowed patients to select the preferred lead for permanent implantation.¹⁷² 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.¹⁷³ 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.¹⁷³ 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).¹⁷⁴

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New evidence retrieved in the update literature review is comprised of four retrospective observational studies reporting on a total of 109 patients.¹⁷⁵⁻¹⁷⁸ All four studies used sacral placement of neurostimulation. 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 (PNE) compared to use of a permanent quadripolar lead in the testing phase.¹⁷⁸ 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.

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.^{179,180}

Fifth-Line Treatments:**Guideline Statement 21**

Cyclosporine A may be administered as an oral medication if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. Option

Discussion. Cyclosporine A (CyA) (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.¹²³ 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 volumes¹⁸¹ and after an average one year of treatment, 87% of patients reporting that they were pain-free with similar improvements in voiding parameters.¹⁸² 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.¹⁸² 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).¹²³ In the observational studies, AE rates ranged from 30% to 55% and included hypertension, gingival hyperplasia, and facial hair growth.^{181,182}

The update literature review retrieved two new observational studies. One retrospective study¹⁸³ pooled findings from three centers (Urologic Specialists of Oklahoma – USO; Stanford University – SU; University of Kentucky – UK; see table below). 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's lesions compared to those without lesions (3/10; 30%). In addition, the authors note that the patients without Hunner's lesions who had improvement did not improve to the same degree as patients with Hunner's 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's 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).

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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's ulcers.¹⁸⁴ These investigators also measured bladder nitric oxide (NO) 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 NO 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 (for UTI; n=1).

Taken together, these data suggest sustained efficacy, particularly in patients with Hunner's 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. Clinicians inexperienced in the use of CyA are strongly encouraged to seek guidance from a clinician expert in CyA dosing and patient monitoring procedures.

Sixth-Line Treatments:**Guideline Statement 22.**

Major surgery (substitution cystoplasty, urinary diversion with or without cystectomy) may be undertaken in carefully selected patients for whom all other therapies have failed to provide adequate symptom control and quality of life (see caveat above in Guideline Statement 4). Option

Discussion. Major Surgery (Evidence Strength – Grade C). IC/ BPS can be a major source of morbidity and compromised quality of life but it also is a non-malignant disorder. Major surgery should be reserved for the small proportion of patients with severe, unresponsive disease, who are motivated to undergo the risks and lifelong changes associated with irreversible major surgery. It can be considered earlier in the course of disease in patients with a severely

limited bladder capacity under anesthesia such that no conservative therapy is likely to significantly improve QoL. Patients must understand that pain relief is not guaranteed, and pain can persist even if the bladder is removed. Patient selection, as described below, can increase the likelihood of good symptom relief but does not guarantee it. For this reason, uncertainty exists in the balance between benefits and risks/ burdens and surgical treatments are Options.

Substitution cystoplasty. There are many potential problems with this procedure, and it is still debated among IC/BPS experts. Removing the trigone increases the risk of urinary retention, requiring intermittent catheterization.¹⁸⁵ However, a preserved trigone may be a source for persistent pain and recurrent ulcers.^{186,187} With regard to patient selection, the patients most likely to fail are those who describe the urethra as the main site of pain,¹⁸⁸ those without Hunner's lesions¹⁸⁹ and those with a larger bladder capacity under anesthesia.^{185,189-191}

Urinary diversion with or without cystectomy. In the properly selected refractory patient, urinary diversion will relieve frequency and nocturia and sometimes can relieve pain. If frequency is perceived as a major problem, then diversion can almost certainly improve quality of life in select patients who have failed to respond to standard and investigational interventions. However, patients must understand that symptom relief is not guaranteed. Pain can persist even after cystectomy, especially in nonulcer IC/BPS.¹⁸⁹ A published report of 14 patients who underwent cystourethrectomy and urinary diversion revealed 10 patients with persistent pelvic pain including four with concurrent pouch pain postoperatively.¹⁹²

The update literature review retrieved an additional retrospective observational study reporting outcomes for 41 patients operated on from 1983 to 2004.¹⁹³ Five patients had cystectomy; the remaining patients had subtotal cystectomy and bladder augmentation (n=16) or supravescical urinary diversion with an intact bladder (n=20). Of note is that thirteen of these 20 patients later had a cystectomy for persisting pain. Overall, 74% of patients reported being pain-free at median follow-up of 66 months. Patients who reported pain were more likely to have a longer symptom history (mean 12.1 years for patients with pain, v. mean 5.4 years for patients without pain).

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The informed consent process for these patients is critical, and careful counseling about possible persistent pain is mandatory. Efforts have been made to predict ahead of time which patients are most likely to have a good response. Small bladder capacity under anesthesia^{185,194} and absence of neuropathic pain¹⁹⁴ are associated with better response.

Additional Comment: Research Trials. Even with appropriate therapy many patients with BPS/IC will not have complete relief of symptoms. Therefore a large percentage of patients are potential candidates for clinical research trials. Clinical research in IC/BPS has been inhibited by the lack of widely accepted, clear diagnostic criteria. The challenges of designing such trials has been reviewed by Probert and colleagues.¹⁹⁵ Nevertheless, cooperative groups supported by the NIDDK have completed trials studying intravesical therapy (BCG), oral therapies (pentosanpolysulfate/hydroxyzine), amitriptyline in treatment naïve patients, and pelvic floor physical therapy. These studies can provide good templates for future research using novel agents. Patients should be encouraged to consider appropriate research trials when standard treatments provide incomplete relief of symptoms.

Treatments that should not be offered: In addition to identifying treatments that appear to benefit a meaningful subset of patients, the Panel also identified treatments that appear to lack efficacy and/or that are accompanied by unacceptable AE profiles or other known negative consequences. In the judgment of the Panel, the risks and burdens of the treatments listed below outweigh their benefits and they should not be offered.

Guideline Statement 23.

Long-term oral antibiotic administration should not be offered. *Standard*

Discussion. Long-term Antibiotics (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.¹⁹⁶ 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%.^{197,198} 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 (BCG) should not be offered outside of investigational study settings. *Standard*

Discussion. Intravesical Bacillus Calmette-Guerin (BCG) (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% v. 27%) at eight months of follow-up with all patients reporting one or more AE(s).¹⁹⁹ 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.²⁰⁰ Non-responders from both groups were then offered open-label BCG and both groups experienced an 18% response rate at seven months.²⁰¹ 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.²⁰² 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

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in the bladder cancer literature (e.g., sepsis and other serious AEs, including death).²⁰³⁻²⁰⁶ 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.

Discussion. High-pressure, long-duration Hydrodistension (Evidence Strength – Grade C).

High-pressure (e.g., greater than 80 to 100 cm H₂O), 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).²⁰⁷⁻²⁰⁹ 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.

Discussion. Systemic long-term glucocorticoid administration (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.^{210,211} 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.

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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.^{28, 212-214} 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.⁹² Reflecting this new paradigm, the NIDDK has funded the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (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,

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CP/CPPS and other chronic pain conditions (fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome), 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.²¹⁵ However, this approach resulted in two-thirds of potential subjects being excluded at the outset.^{5,30} Further, IC/BPS patients with co-morbidities have typically been excluded in clinical trials.¹⁹⁵ 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.¹⁹⁶ 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 co-morbidities for clinical trial design, either for the purpose of *post hoc* subgroup analysis or *a priori* subgroup recruitment, since the neuro-pathophysiological mechanisms in IC/BPS patients with different co-morbidities are likely to be different.^{26,33,35,216,217}

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 sub-classification of various subgroups of BPS.

The second major challenge in clinical trial design remains the selection of outcome measures.¹⁹⁵ 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.²¹⁸ 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 bio- marker 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.

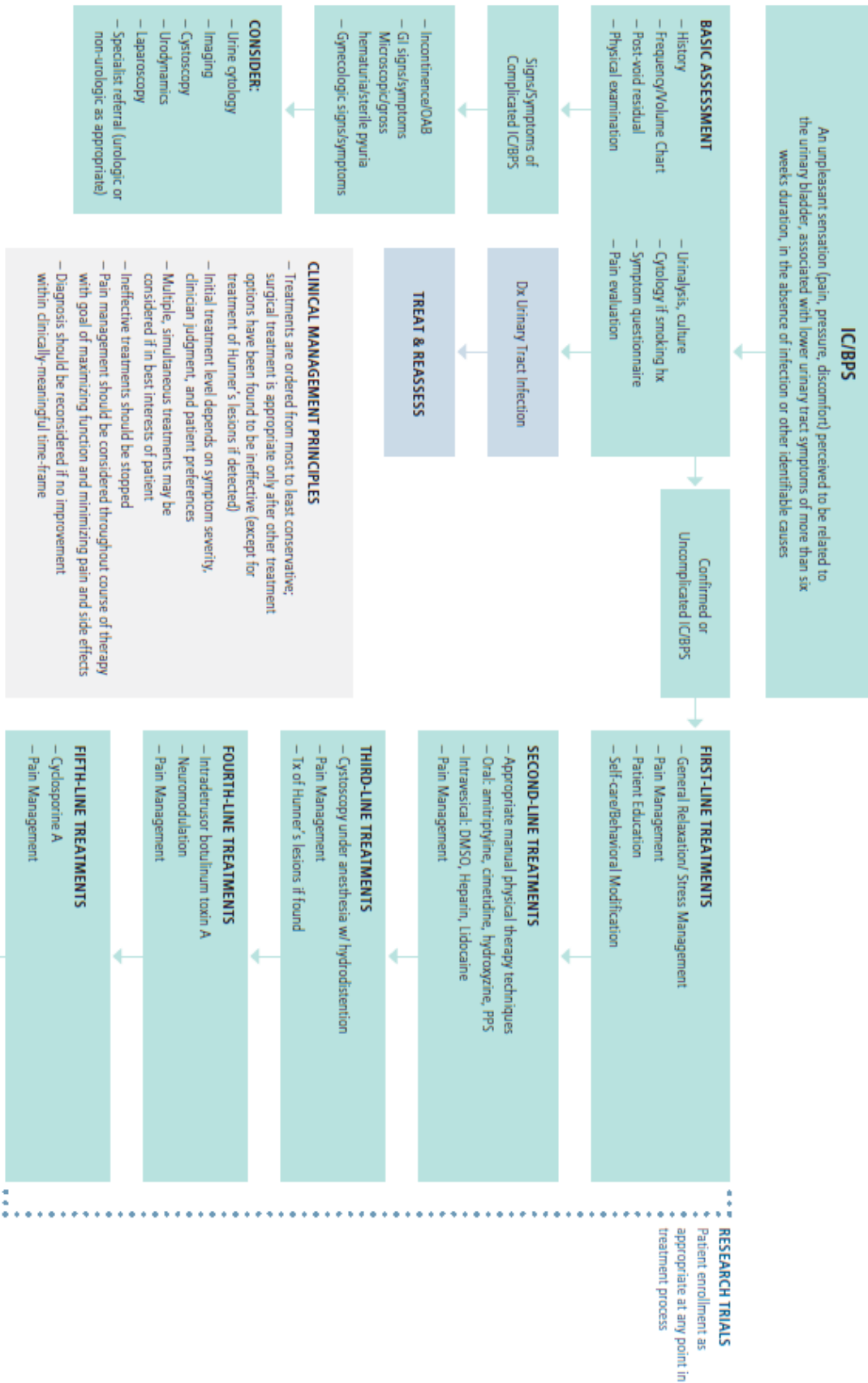
IC has only been recognized as a highly prevalent health problem in the last 20 years. Data regarding disease progression, remission, and prevention are very limited and we know very little about risk factors for development of associated symptoms over time. Patients are currently treated with a variety 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.²¹⁹

Although progress in developing specific IC/BPS treatments has been slow, these are exciting times for the development of new treatment targets.²²⁰ 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.²²¹ In addition, research is needed on antiproliferative factors (APF) as a

possible therapeutic pathway for treatment of IC/BPS. APF is a frizzled 8 protein secreted by the bladder epithelial cells of patients with IC/BPS. It inhibits uroepithelial cell proliferation by decreasing heparin binding epidermal growth factor-like growth factor (HB-EGF).²²² APF has been shown to be a sensitive and specific biomarker for IC/BPS v. controls.²²² It has been speculated that APF suppression of uroepithelial cell proliferation after bladder injury may result in clinical IC/BPS, and inhibition of APF may be an effective treatment or prevention,²²³ but further research is needed.

IC/BPS

Appendix 1



The evidence supporting the use of Neuromodulation, Cyclosporine A, and BTX for IC/BPS is limited by many factors including study quality, small sample sizes, and lack of durable follow up. None of these therapies have been approved by the U.S. Food and Drug Administration for this indication. The panel believes that none of these interventions can be recommended for generalized use for this disorder, but rather should be limited to practitioners with experience managing this syndrome and willingness to provide long term care of these patients post intervention.

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Panel, Consultants, Staff and COI

IC/BPS Panel, Consultants and Staff Panel

Philip M. Hanno, MD, Panel Chair
Division of Urology
Hospital of the University of Pennsylvania
Philadelphia, PA, USA

David Allen Burks, MD, Panel Facilitator
Michigan Institute of Urology
St. Clair Shores, MI, USA

J. Quentin Clemens, MD, MSCI
Associate Professor of Urology
University of Michigan Health System
Ann Arbor, MI, USA

Roger R. Dmochowski, MD
Department of Urologic Surgery
Vanderbilt University
Nashville, TN, USA

Deborah Erickson, MD
University of Kentucky
Lexington, KY, USA

Mary Pat FitzGerald, MD, FACOG, FACS
Loyola University Medical Center
Maywood, IL, USA

John B. Forrest, MD, PGC Representative
Urologic Specialists of Ok, Inc.
Tulsa, OK, USA

Barbara Gordon, MBA, RD
Interstitial Cystitis Association (ICA)
Rockville, MD, USA

Mikel Gray, PhD
Department of Urology
University of Virginia
Charlottesville, VA, USA

Robert Dale Mayer, MD
University of Rochester
Rochester, NY, USA

Diane K. Newman, DNP
University of Pennsylvania
Philadelphia, PA, USA

Leroy Nyberg Jr., MD, PhD

NIH, NIDDK, DKUHD
Bethesda, MD, USA

Christopher K. Payne, MD
Department of Urology
Stanford University Medical School
Stanford, CA, USA

Ursula Wesselmann, MD, PhD
Department of Anesthesiology/Division of Pain
Management
University of Alabama at Birmingham
Birmingham, AL, USA

Consultant

Martha Faraday, PhD

Staff

Heddy Hubbard, PhD., MPH, RN, FAAN
Abid Khan, MHS
Michael Folmer
Carla Foster, MPH
Erin Kirkby, MS
Patricia Lapera, MPH
Del'Rhea Godwin-Brent

CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

Consultant or Advisor: Philip M. Hanno, Astellas (C), Lilly (C), Afferent (C); Robert M. Moldwin, Taris (C)

Scientific Study or Trial: Robert M. Moldwin, Taris (C)

Disclaimer

DISCLAIMER

The original version of this Interstitial Cystitis/Bladder Pain Syndrome Guideline was created in 2011 by a Panel assembled by the Practice Guidelines Committee (PGC) of the American Urological Association Education and Research, Inc. (AUA). This amended Guideline was drafted in 2014 by the original Guideline Panel. This amendment updates the original guideline document to reflect literature released following the original publication.

The mission of the Panel was to develop clinical guideline recommendations based on an in-depth evidence report of the peer-reviewed literature. The recommendations are based on evidence strength, or where evidence is not available, on Delphi-modification consensus statements. The purpose of each guideline is to provide physicians and non-physician providers (primary care and specialists) with a consensus of principles and treatment plans for the management of IC/BPS. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated.

Funding of the original and amendment Panels was provided by the AUA. Panel members receive no remuneration for their work. Panel members' potential conflicts of interest are subject to rigorous and on-going review during the development of the original Guideline and amendment Panel members are screened for conflicts throughout the amendment process.

As medical knowledge expands and technology advances, AUA guidelines are subject to change. Evidence-based guidelines statements are not absolute mandates but thoroughly considered strategies for best practice under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Similarly, conformance with any clinical guideline cannot assure a successful outcome. These guidelines and best practice statements are not intended to provide legal advice.

The guideline text may include information or recommendations about certain drug or device use ('off label') that are not approved by the Food and Drug

Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to understand and carefully follow all available prescribing information about indications, contraindications, precautions and warnings.

Although guidelines are intended to encourage best practices and to reflect available technologies with sufficient data as of the date of close of the literature review, guidelines are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies, pharmaceuticals or management practices, including both those that are FDA-approved, or those which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard emerging technologies or management techniques not addressed by this guideline as manifestly experimental or investigational. These emerging technologies or techniques may simply be too new to be included or fully incorporated in the Panel's evidence-based evaluation at the time the guideline is developed.