Aquinox Pharmaceuticals (Canada), Inc.

ADVISORY COMMITTEE BRIEFING DOCUMENT

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

Meeting on December 7, 2017

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Briefing Document:

Abbreviation or special term	Explanation
AUA	American Urological Association
BRUDAC	Bone, Reproductive and Urologic Drugs Advisory Committee
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
DMSO	Dimethylsulfoxide
EPIC	Events Preceding Interstitial Cystitis
FDA	Food and Drug Administration
GUPI	Genitourinary Pain Index
HR-QOL	Health-Related Quality of Life
IC	Interstitial Cystitis
IC/BPS	Interstitial Cystitis/Bladder Pain Syndrome
ICSI	Interstitial Cystitis Symptoms Index
ICDB	Interstitial Cystitis Data Base
ICPI	Interstitial Cystitis Problem Index
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IND	Investigational New Drug
MAPP	Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain
NIH	National Institutes of Health
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NRS	Numeric Rating Scale
PPS	Pentosan Polysulfate Sodium
PUF	Pelvic Pain and Urgency/Frequency
PRO	Patient Reported Outcome
QOL	Quality of Life
RICE	RAND Interstitial Cystitis Epidemiology Study
SF-12	12-item Short Form Assessment

1. EXECUTIVE SUMMARY

As a holder of an active Investigational New Drug (IND) application for a new chemical entity for the treatment of patients with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS), Aquinox Pharmaceuticals (Canada), Inc. welcomes the opportunity to participate in the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting on December 7, 2017 to discuss clinical development of treatments for this condition.

IC/BPS is an underdiagnosed symptom complex that is defined by the American Urological Association (AUA) as "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." For clarity and consistency in this document, as well as the presentations at the Advisory Committee, we will refer to the symptom complex using the current nomenclature from the AUA, "IC/BPS." This term includes patients presenting with bladder pain and urinary symptoms who have confirmed Hunner lesions as well as those without or those who have not yet been evaluated via cystoscopy.

Patients with IC/BPS present with a set of symptoms, including bladder pain, pressure, or discomfort, that often worsens with bladder filling, resulting in the need to urinate frequently in an attempt to relieve bladder pain. Bladder pain is the hallmark of this symptom complex, and is generally considered by patients to be the most bothersome symptom of IC/BPS. Increased urinary frequency, nocturia, and urgency are also typically observed in patients with IC/BPS but vary in presentation and intensity, and are not specific to this syndrome. Hunner lesions are present in around 12% of patients with IC/BPS, and are thought to identify a cohort of patients for whom underlying disease may differ and early escalation of therapy may be appropriate. That said, initial symptom presentation is generally similar between these two populations.

As IC/BPS is a diagnosis of exclusion, patients are often misdiagnosed and may experience a delay to accurate diagnosis, leading to lags of months to years in patients receiving proper treatment for this debilitating disease. As with other chronic diseases, the stress of associated symptoms, coupled with the unpredictability of bladder pain and lack of effective treatment, can lead to chronic anxiety and depression, and in some patients, suicidal ideation.

It is estimated that 3.3 million females and 2.1 million males in the US are living with IC/BPS. While a wide variety of causes or triggers have been proposed that may lead to IC/BPS, no unifying theory is as yet widely accepted. Multiple pathologies have been identified, including autoimmune phenomena, mast cell dysfunction, bladder wall permeability abnormalities, neurogenic inflammation, and central nervous system changes, among others, and the physiological processes underlying this multiplicity remain unknown.

The treatment approach for IC/BPS is focused on improvements in symptoms, particularly bladder pain, in an effort to improve quality of life (QOL). The AUA guidelines suggest that all patients diagnosed with IC/BPS, regardless of the presence of Hunner lesions, receive first-line and/or second-line treatment approaches that predominately address lifestyle

modifications and offer oral pharmacotherapies. If, on cystoscopy, Hunner lesions are present, the treatment approach may change to include more invasive therapies earlier than otherwise recommended in uncomplicated patients and in those without Hunner lesions.

Treatments approved by the Agency for IC/BPS are limited to a single oral treatment and a single intravesical treatment. Therefore, even with a clinical diagnosis in hand, patients and clinicians are confronted with few effective options for treatment, and of those available, the majority are off-label uses with weak evidence of effectiveness. Thus, there is a clear and pressing need for additional therapies with demonstrated efficacy and safety, and the Sponsor believes the discussion from the BRUDAC meeting will be an invaluable step in allowing industry to develop and bring new treatments forward.

To that end, the Sponsor recommends the following general construct for clinical development of oral medications for chronic therapy for consideration by BRUDAC:

- Enrollment of a broad IC/BPS population, with and without Hunner lesions, if appropriate, based on a compound's mechanism of action
- Stratification by presence of Hunner lesions to enable exploration of potential efficacy and/or safety differences in that subpopulation
- Randomized, Double-blind, Parallel-group, Placebo-controlled study design, allowing for continuation of background treatment if dose remains stable and subject has qualifying residual symptoms
- Approval based on achievement of statistically and clinically meaningful treatment benefit based on alleviation of bladder pain
- Other assessments of concurrent urinary symptoms and/or QOL to be chosen based on proposed mechanism of action and viewed as supportive of the overall benefit-risk assessment of the compound

Additional discussion and detail supporting these recommendations are in Section 6 of this document. We look forward to a productive session on December 7, and thank you in advance for your participation.

2. INTRODUCTION

Aquinox Pharmaceuticals (Canada), Inc. currently holds an active IND application for a new chemical entity in development for patients with IC/BPS, and recognizes the clear medical need for new treatment options and the challenges inherent in IC/BPS drug development. This condition is a syndrome characterized by bladder pain and urinary symptoms (increased voiding frequency, nocturia, and urgency) that adversely impact the lives of patients. [(1)] We, and others working in this field, have chosen to focus on the hallmark symptom of bladder pain. While both industry and academic researchers continue to delve into the etiology of IC/BPS, the profound impact of bladder pain on QOL makes alleviation of bladder pain the highest priority in clinical development. [(2)]

Aquinox is pleased to participate in this Advisory Committee meeting because it is important to provide clear guidance to pharmaceutical researchers in order to make progress towards much-needed treatments for patients with IC/BPS. To broaden the therapeutic options available to treat IC/BPS, an evidence-based path forward must be found. There is a significant unmet need, and it is believed that any outcome from this Advisory Committee meeting should come with the goal of increasing innovation and speeding the development of therapies for this condition. This meeting is a significant step to enhancing the partnership between the US Food and Drug Administration (FDA) and the larger research community towards that end.

IC/BPS is an underdiagnosed symptom complex that is defined by the American Urological Association (AUA) as "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." [(1)] [(3)] Because IC/BPS is a diagnosis of exclusion, patients are often misdiagnosed, and may experience a delay to accurate diagnosis, leading to a lags of months to years in patients receiving proper treatment for this debilitating disease. [(1)]

Variable and evolving terminology surrounding this condition furthers the confusion regarding diagnosis and treatment, and adds to challenges in defining patient populations and study entry criteria. [(4)] For clarity and consistency in this document, as well as the presentations at the Advisory Committee, we will refer to the symptom complex using the current nomenclature from the AUA, "IC/BPS." [(1)] The term IC/BPS includes patients presenting with bladder pain and urinary symptoms who have confirmed Hunner lesions as well as those who do not have Hunner lesions or who have not yet been evaluated via cystoscopy. Patients with Hunner lesions, and those without, present with generally the same symptoms, are seeking relief from bladder pain, and tend to be treated by physicians using the same treatment algorithm. In many cases, patients who are known or discovered to have Hunner lesions may receive fulguration by urologists, [(1)] but will likely still require a chronic medication as part of the recommended multi-modal therapy to address recurrent or persistent symptoms.

We acknowledge the historical view that Hunner lesions define "Interstitial Cystitis" (IC), but find that distinction becomes less clear as the scientific community and the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) project at the National Institutes of Health (NIH) move away from prior National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria towards defining the symptom complex in greater phenotypic detail. [5] However, this evolution is currently academically focused and has not yet made its way into routine clinical practice, and therefore we are not describing it here.

There are, however, some important unintended consequences of migrating away from the use of the IC or IC/BPS terminology. There is a strong patient preference to have their disease referred to as IC, which suggests a true disease etiology, rather than bladder pain syndrome, or a symptom complex which may be perceived as minimizing the validity of their condition. Nonetheless, while being mindful of patient preferences and concerns, we believe that standardizing the terminology will facilitate clarity in our discussions during the Advisory Committee proceedings.

3. DISEASE BACKGROUND AND MEDICAL NEED

IC/BPS is an underdiagnosed symptom complex with presenting symptoms (eg, bladder pain and urinary frequency) that may be shared by other conditions such as urinary tract infections, painful disorders of the internal and external vagina (ie, vaginitis or vestibulitis), urethritis, chronic prostatitis/chronic pelvic pain syndrome, urethral diverticulum, or other potential source of pain or infection (Appendix A). [1] [6] As such, patients with IC/BPS are often misdiagnosed as clinicians work to exclude confounding or confusable causes of symptoms. Even with a clinical diagnosis in hand, patients and clinicians are confronted with few effective options for treatment, with the majority being off-label uses supported by weak evidence. There is a clear and pressing need for additional therapies with demonstrated efficacy and safety. [1] [7]

3.1 Symptoms

Patients with IC/BPS present with a set of symptoms including bladder pain, pressure, or discomfort, often worsening with bladder filling, resulting in the need to urinate frequently to attempt to minimize pain. [1] [8] Bladder pain and the frequent need to void can disrupt personal relationships, impact the patient's social life and psychological well-being, create burden on family and friends, and make participation in the workplace difficult or perhaps impossible. [1] [9] [10] Patients may experience a lack of responsiveness and empathy from healthcare providers, who in turn may be frustrated by limitations in treatment approaches.

As with other chronic diseases, the stress of associated symptoms, coupled with the unpredictability of bladder pain and lack of effective treatment, can lead to chronic anxiety and depression. [11] [12] [13] Based on the 12-item Short Form assessment (SF-12) of health-related quality of life (HR-QOL), the total burden of IC/BPS is comparable to that of other chronic disorders such as irritable bowel syndrome, fibromyalgia, and chronic pancreatitis and, in particular, imparts a considerable mental toll comparable to that of those diseases as

well. [14] [15] [16] [17] Further, patients with IC/BPS tend to have higher rates of depression, anxiety, stress, sleep dysfunction, and suicidal ideation compared to the general population. [9] [18] [19] [20] [21] [22] During a series of four focus groups with patients with IC/BPS, the chronic, unpredictable, and unrelenting nature of bladder pain directly underpinned the fear, depression, anxiety, isolation, and suicidal ideation associated with this condition. [11]

In a case-control study, 207 females with IC/BPS and 117 controls without the condition completed a series of psychosocial questionnaires which assessed presenting symptoms, psychosocial parameters, and QOL. [22] Results from these questionnaires demonstrated that chronic pain and poor QOL are the most relevant parameters that influence the life of a patient with IC/BPS. Participants with IC/BPS reported significantly more bladder pain, sleep dysfunction, depression, anxiety, stress, sexual dysfunction, and social support dysfunction, as well as decreased mental and physical QOL when compared to those without IC/BPS. All of these parameters correlated with general pain, but stress, anxiety, and depression also correlated with IC/BPS specific symptoms and QOL. Through regression modeling, bladder pain was determined to be strongly associated with decreased physical QOL. [22]

3.2 Prevalence

Determining the prevalence of IC/BPS has been historically challenging due to a lack of an objective disease marker. Through a literature review and telephone interviews, the authors of the RAND Interstitial Cystitis Epidemiology (RICE) study established both a high specificity and a high sensitivity definition of IC/BPS, each of which accurately identified patients with IC/BPS over 80% of the time (Table 1). [23] [24] Using the high specificity definition, it is estimated that 3.3 million females and 2.1 million males in the US are living with IC/BPS. [23] [24] In the assessment of females with IC/BPS, based on the high specificity definition, the prevalence of IC/BPS was higher in white females (2.97%) than in black (1.91%) or Hispanic (2.03%) females; and was most prevalent in women between 40 to 59 years of age. [23] Furthermore, 87.1% of these females had consulted a physician about their symptoms, but only 40.4% had seen a urologist and only 9.9% had a diagnosis of IC/BPS. [23]

Table 1 RICE Case Definitions

High Sensitivity Definition Criteria (sensitivity 81%, specificity 54% for IC/BPS v. endometriosis, vulvodynia and overactive bladder)	**High Specificity Definition Criteria (sensitivity 48%, specificity 83% for IC/BPS v. endometriosis, vulvodynia and overactive bladder)**
Pain, pressure, or discomfort in the pelvic area AND Daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, not fear of wetting	Pain, pressure, or discomfort in the pelvic area AND 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, spinal bifida, cyclophosphamide treatment, radiation treatment to pelvic area, tuberculosis affecting the bladder, uterine cancer, ovarian cancer, vaginal cancer, genital herpes, pregnancy

Adapted from (23)

3.3 Pathophysiology

While a wide variety of causes or triggers have been proposed that may lead to IC/BPS, no unifying theory is as yet widely accepted. [8] The etiology of bladder pain related to IC/BPS is thought to be multifactorial, with many patients appearing to have an inflammatory contribution as an inciting or permissive process. [8] [25] [26] Altogether, multiple pathologies have been identified including autoimmune phenomena, mast cell dysfunction, bladder wall permeability abnormalities, neurogenic inflammation, and central nervous system changes, among others, but the physiological processes underlying this multiplicity remain unknown. [1] [8]

Some patients with IC/BPS will be shown to have Hunner lesions, visible lesions that can be identified upon cystoscopy and are thought to represent inflammation. [1] [8] They are seen only in patients with IC/BPS, and data suggest a prevalence rate of 12%. [27] Recent work in the field has noted that patients with Hunner lesions are older and may have more "bladder centric" symptoms than patients who do not have Hunner lesions, but are otherwise similar in symptom presentation. [27] Histopathological examination of the bladders of patients with and without Hunner lesions revealed that non-Hunner specimens were characterized by severe fibrosis and increased mast cell infiltration, while Hunner lesion specimens were characterized by severe inflammation and urothelial denudation in the entire bladder. [28] See Section 4.3.2 for further discussion of Hunner lesions.

Given the uncertainties surrounding the etiology of IC/BPS, current pharmaceutical development efforts are focused on the alleviation of bladder pain, the recognized primary symptom.

3.4 FDA-approved Therapies

There are limited pharmacological treatment options, with only two products being FDA-approved for use in the condition: the oral medication Elmiron® (pentosan polysulfate sodium [PPS]) and the intravesical therapy RIMSO-50® (dimethylsulfoxide [DMSO]).

Elmiron® (PPS) was approved in 1996 and, to date, is the only FDA-approved oral medication for this condition. [(29)] The approved indication is "for the relief of bladder pain or discomfort associated with interstitial cystitis" and was based on two studies using the NIH NIDDK definition of IC (see Appendix B). One study was a 12-week, blinded, randomized, placebo-controlled trial (n=151). In this trial, more subjects treated with PPS 100 mg three times a day for 3 months reported at least a 50% improvement in bladder pain compared to placebo. The second study, a physician's use study, was a prospectively-designed, uncontrolled, open-label retrospective analysis of 2499 patients where the endpoint was subject evaluation of change from baseline in bladder pain/discomfort scores at three month intervals over an up to one year period. [(29)]

RIMSO-50® (DMSO) was approved in 1978 and is currently the only FDA-approved intravesical treatment for this condition. [(30)] The approved indication is "for use in the symptomatic relief of patients with interstitial cystitis." [(30)] In one study, 79 women with IC were treated with instilled DMSO with most patients receiving ten to twenty treatments over a period of one to three years. [(31)] Of these, 54% experienced good to excellent clinical results while another 11% initially had good to excellent responses but relapsed to their baseline symptom levels. [(31)]

4. DIAGNOSIS

4.1 NIDDK and ICDB Criteria

In 1987 and 1988, the NIDDK convened a panel to establish criteria for the diagnosis of IC/BPS (see Appendix B) for use in defining a population for clinical trials. [(32)] [(33)] These criteria required the presence of Hunner lesions or glomerulations during cystoscopy with high pressure hydrodistention under general anesthesia, which in some cases could itself cause bleeding and other visible damage to the bladder, further confounding the interpretation of the findings. [(32)] [(33)] [(34)] While not intended to be used as a definition of the disease in clinical practice, the lack of other diagnostic guidelines led to clinicians using these criteria for that purpose. [(33)]

In the 1990's, the NIDDK sponsored the Interstitial Cystitis Data Base (ICDB) study to establish a patient profile for use in clinical practice. [(33)] [(35)] The entry criteria into the ICDB (see Appendix B) were chosen to be broader than that of the original NIDDK research criteria to more reliably capture patients with IC/BPS. [(35)] Hanno et al compared the criteria set forth

by the NIDDK with that of the ICDB and found that up to 60% of patients clinically believed to have IC/BPS were not identified when using the NIDDK criteria due to a lack of sensitivity and specificity of the original criteria. [36]

A key difference between the NIDDK criteria and the ICDB criteria is the requirement for cystoscopy to identify Hunner lesions or cystoscopy with hydrodistention under anesthesia to identify glomerulations. [33] As part of the ICDB study, the correlation between cystoscopic findings and concurrent IC/BPS symptoms was assessed. [37] In total, 150 women underwent cystoscopy with anesthesia at baseline screening. [37] While the presence of Hunner lesions had a weak association with increased pain (p=0.03), the low prevalence within the general IC/BPS population severely limits the finding as a diagnostic criterion. [27] [37]

4.2 Symptomatic Diagnosis

The AUA guidelines published in 2011, and revised in 2014, recommend an assessment that includes patient history, physical, and laboratory examinations to confirm symptoms of IC/BPS, and to rule out other "confusable diseases." [1] This approach includes gathering information on pain, pressure or discomfort perceived to be in the bladder, frequency, nocturia, urgency, and other urinary symptoms, as well as conducting a thorough pelvic examination to screen for pelvic floor dysfunction or other pelvic pathology which may represent common confounding disease. [1] AUA recommendations note that cystoscopic findings do not generally assist in the diagnosis of IC/BPS, which is symptomatically defined, and therefore the procedure is not required for initial diagnosis in uncomplicated cases. [1]

In cases where a patient has risk factors for other bladder pathology, has a complicated or unclear presentation, or has residual symptoms after receiving first- and second-line treatments per the AUA algorithm, cystoscopy may be beneficial. [1] The procedure can help further rule out confusable diseases or assess for applicability of other treatment strategies such as fulguration if Hunner lesions are present. [1] Patients referred to a urologist or urogynecologist may receive cystoscopy relatively early in their work up with those tertiary care providers.

4.2.1 Bladder Pain

While individual patients may experience multiple urinary symptoms, bladder pain is the hallmark of this symptom complex, [1] is present in up to 97% of patients with IC/BPS, [1] [35] and is generally considered to be the most bothersome symptom of IC/BPS. [11] In a survey of patients with IC/BPS (n=35), conducted by the Interstitial Cystitis Association, participants were asked "what kinds of information about IC/BPS have [they] looked for in the past?" Respondents reported that they are most often seeking information on pain relief or help with symptoms of IC/BPS (40%) and treatment options to address these symptoms (34%). [7]

Patients may describe this bladder pain in many ways, including pressure or discomfort as noted in the AUA guideline, or through pain-related descriptors such as sharp, burning, aching, shooting, or stabbing [1] [35] [38] and may perceive pain not only as suprapubic but throughout the pelvis, lower abdomen, and back. [1] Bladder pain associated with IC/BPS is

generally related to the voiding cycle, increasing in intensity upon bladder filling and decreasing upon bladder emptying. [1]

In the Events Preceding Interstitial Cystitis (EPIC) case-control study, Warren et al investigated bladder pain associated with the voiding cycle by mailing a questionnaire to 209 women with IC/BPS following an initial baseline screening telephone interview. [38] Of those who completed the questionnaire (n=155), 94% reported that bladder pain worsened with bladder filling and/or improved with urination. These findings were confirmed using similar data that were publicly available from the ICDB study, which revealed that 93% of patients reported bladder pain worsening with bladder filling and/or improving with urination. [38] This bladder pain cycle differentiates IC/BPS from other urological conditions with similar urinary symptoms, such as overactive bladder, and from other types of pelvic pain such as endometriosis. [39] [40]

4.2.2 Concomitant Urinary Symptoms

Increased urinary frequency, nocturia, and urgency are symptoms also typically observed in patients with IC/BPS. [1] These symptoms vary among patients in presentation and intensity, and are not specific to this syndrome. [1] [8] Increased urinary frequency ($\geq$8 voids per day) is the most commonly observed secondary urinary symptom in patients with IC/BPS, with studies showing up to 90% of patients experiencing this symptom. [1] The extent to which voiding frequency is due to the pathophysiology of the disease or a combination of other factors is unknown. For example, studies have shown that patients with IC/BPS develop a learned behavior of voiding frequently to relieve or to avoid bladder pain with bladder filling, [1] demonstrating that frequency of urination can be affected by the driving symptom of bladder pain. In some patients with IC/BPS, the need to void frequently is due to limitations in bladder capacity related to fibrosis and loss of bladder elasticity which may accompany extended duration of IC/BPS. [28]

Urinary urgency, defined as the sudden and compelling desire to urinate, and nocturia, nighttime awakening to urinate, are other symptoms often reported among patients with IC/BPS. Similar to voiding frequency, the majority of patients report that these symptoms are in an effort to relieve bladder pain. [38] [41] [42]

4.3 Diagnosis in Clinical Practice

4.3.1 Role of Cystoscopy

The AUA guidelines do not require cystoscopy for initial diagnosis of IC/BPS in uncomplicated cases, where a purely symptomatic diagnosis may be possible. [1] Current clinical practice generally aligns with the 2014 AUA guidelines and reserves cystoscopy for later in the treatment paradigm. However, in patients whose presentation is complicated either by concern of confusable diseases, concurrent pathology, or resistance to treatment, cystoscopy may be employed earlier in the diagnostic and therapeutic journey. [1] It should be noted that cystoscopy is an invasive procedure, places a significant burden on a patient, and any requirement for this procedure should balance the clinical utility of the information gleaned with the pain and discomfort experienced by patient.

4.3.2 Hunner Lesions

A Hunner lesion is a characteristic lesion, seen only in a subset of patients with IC/BPS, which is visible on cystoscopy and thought to represent visible inflammation. [1] Other cystoscopic findings, including petechial bleeding in the bladder mucosa and glomerulations, are not specific for IC/BPS and do not provide specific guidance on treatment. [8] [43] Hunner lesions are present in only about 12% of all patients with IC/BPS, [27] and are thought to identify a cohort of patients for whom underlying disease may differ and where early escalation of therapy may be appropriate. [27] [28] Hunner lesions are not a progressive manifestation of IC/BPS and are generally visible upon initial presentation. [8] This suggests that there is no expectation that a Hunner lesion will develop at a later date if not present during the initial cystoscopy. This supports the use of historical cystoscopy for clinical design stratification by presence or absence of Hunner lesions (See Section 6.1).

Given that an effective treatment (fulguration; See Section 5.3.2) is available for patients with IC/BPS with Hunner lesions, some urologists have moved towards using cystoscopy earlier to identify patients who might benefit from early intervention with this treatment strategy. [27]

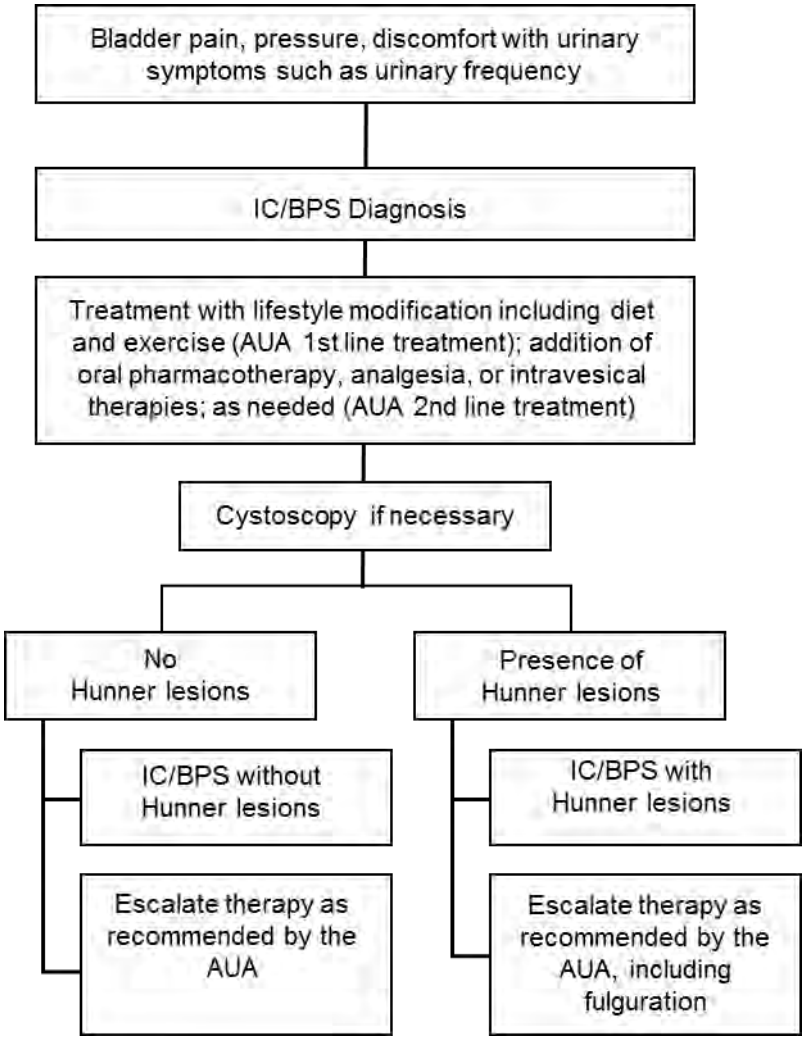
5. CURRENT TREATMENT ALGORITHM

5.1 AUA Algorithm Overview

The treatment approach for IC/BPS is dependent on improvements in symptoms, particularly bladder pain, in an effort to improve QOL. [1] According to the AUA Guidelines, initial treatment strategies should depend on symptom severity, clinical judgement, and patient preference. [1] If needed, multiple, concurrent treatments may be considered to optimize QOL, and bladder pain management should continually be assessed for effectiveness (Figure 1; see also Appendix C).

The AUA guidelines suggest that all patients diagnosed with IC/BPS, regardless of the presence of Hunner lesions, receive first-line and/or second-line treatment approaches. [1] First-line therapies include patient education related to IC/BPS and normal bladder function, self-care and behavioral modification (change in diet or fluid intake, application of heat or cold compress to the bladder, pelvic floor muscle relaxation, or bladder training), stress management, pain management, and physical therapy.

Figure 1 Algorithm and Time Course of Diagnosis and Treatment of IC/BPS



Adapted from AUA Guideline (1)

5.2 Pharmacological Options

Included as second-line treatments are oral medications such as amitriptyline, cimetidine, or Elmiron® (PPS). Evaluation of a broad range of oral medications for IC/BPS using the Oxford criteria shows the limitations of supporting data (Table 2). [8] Of note, no treatment is judged to be supported by Grade A evidence (demonstrating consistent results across high quality/Level 1 studies). Review of the available data for these off-label treatments shows a lack of efficacy based on generally limited, poor quality evidence. [8] This further highlights the medical need for the development of new therapies.

Table 2 Oral therapies for IC/BPS rated with the Oxford system

Medication	Grade Recommendation[a]	Level of Evidence[b]
Amitriptyline	B	2
Analgesics	C	4
Cimetidine	C	3
Cyclosporine	C	3
Antihistamine	D	1
Suplatast tosilate	D	1
Aziothioprine	D	4
Chloroquine derivatives	D	4
Corticosteroids	D	4
Pentosan polysulfate (Elmiron® -- FDA approved 1996)	D	1
Quercetin	D	4
Antibiotics	D	4
Methotrexate	D	4
Montelukast	D	4
Nifedicpine	D	4
L Arginine	Not recommended	1

Adapted from (8)

Level of Evidence and Grade Recommendation ratings according to the Oxford Centre for Evidence-based Medicine (44).

a Grades of Recommendation range from A to D, with A indicating "consistent Level 1 studies," and D indicating "Level 5 evidence or troublingly inconsistent or inconclusive studies of any level."

b Levels of Evidence range from 1 to 5 with higher numbers indicating lower levels of assurance. Level 1 is "Systematic review with homogeneity of randomised clinical trials;" Level 5 is "Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'."

A recent survey of patients with IC/BPS found that patient perception of treatments was misaligned with the AUA recommendations. (45) Approximately 66% of patients reported opioids as providing symptomatic improvement while only about 2% reported worsening. Alkalinizing agents were reported as beneficial for approximately 55% of patients, with about 2% reporting worsening. (45) The only FDA-approved oral treatment, Elmiron® (PPS), was reported as giving improvement by approximately 51% and as resulting in worsening by approximately 35%. (45)

5.3 Intravesical Treatments

5.3.1 Pharmacological Agents

Included as second-line treatments are intravesical therapies such as RIMSO-50® (DMSO), heparin, and lidocaine, and these have been important options for IC/BPS treatment for a number of years. [(1)] As a class, these treatments involve instillation of the medication directly into the bladder with the aim of relieving symptomatic bladder pain. [(46)] The major challenges of intravesical therapy for IC/BPS include the short duration of action, lack of permeability of the bladder epithelium, and lack of bladder uptake of drugs. Data on the efficacy of intravesical therapies are lacking, with very few double-blind, randomized, placebo-controlled clinical trials.

Table 3 Intravesical therapy for IC/BPS rated with the Oxford system

Medication	Grade Recommendation[a]	Level of Evidence[b]
RIMSO-50® (DMSO)	B	2
Lidocaine	C	3
Heparin	C	3
Hyaluronic Acid	C	1
Chondroitin Sulfate	C	1
Hyaluronic Acid + Chondroitin Sulfate	C	2
Pentosan Polysulfate	D	4
Oxybutynin	D	4

Adapted from (8)
Level of Evidence and Grade Recommendation ratings according to the Oxford Centre for Evidence-based Medicine (44).
a Grades of Recommendation range from A to D, with A indicating "consistent Level 1 studies," and D indicating "Level 5 evidence or troublingly inconsistent or inconclusive studies of any level."
b Levels of Evidence range from 1 to 5 with higher numbers indicating lower levels of assurance. Level 1 is "Systematic review with homogeneity of randomised clinical trials;" Level 5 is "Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'."

5.3.2 Fulguration

If Hunner lesions are present upon cystoscopy, fulguration by laser or electrocautery is recommended by the AUA. [(1)] While many patients experience near complete relief from bladder pain and urinary frequency following fulguration, duration of relief varies. Observational studies of patients receiving fulguration report relief of IC/BPS symptoms between 2 months to 22.3 months, depending on the population, with high likelihood that that the bladder pain would return and the procedure would need to be repeated in the future. [(1)] [(47)] [(48)] [(49)] These patients would also be expected to benefit from the availability of a chronic, non-invasive treatment targeting bladder pain and symptom relief as ongoing background therapy.

6. CLINICAL DEVELOPMENT RECOMMENDATIONS

The following design features are recommended for clinical trials of oral medications to demonstrate safety and efficacy of chronic treatments in patients with IC/BPS:

Study Population	• IC/BPS diagnosis using AUA criteria • Cystoscopy within last 36 months
Inclusion criteria	• Females & males ≥18 and ≤80 years of age • ≥3-month history of symptoms • Moderate or severe bladder pain associated with voiding cycle as assessed using an 11-point numerical rating scale (NRS) • Frequent urination (≥8 voids per day)
Exclusion criteria	• Confounding infection, non-bladder pelvic pain, or tumors • History of recent hydrodistention, instillation, or fulguration which might confound endpoint measures • Opioid dependency, cyclosporine use, or non-stable concurrent treatment use which might confound endpoint measures
Experimental design	• Randomized, Double-blind, Parallel-group, Placebo-controlled • On stable background therapy with qualifying residual symptoms • Hunner lesion/non-Hunner lesion stratification via cystoscopy without hydrodistention in the prior 36 months • 12-week dosing duration
Primary endpoint	• Change from baseline in daily maximum bladder pain rated on an 11-point numerical rating scale
Secondary endpoints (may vary by mechanism of action of compound being studied)	• Change from baseline: o Average daily bladder pain o Urinary frequency o Nocturia o Global response ratings o Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) or equivalent o HR-QOL o Opioid use o Rescue medications

6.1 Study Populations

The scientific community views patients with and without Hunner lesions as similar in regards to initial symptom presentation (eg, bladder pain and urinary symptoms), while increasingly recognizing that patients with Hunner lesions may represent a distinct population with respect to underlying pathophysiology and treatment selection. [8] [27] When the treatment goal of a compound being evaluated for effect in patients with IC/BPS is relief of bladder pain, studying the populations together has clear rationale as it reflects the unifying features of the disease based on symptom presentation. However, if the objective is something other than symptom relief (eg, addressing the underlying mechanism of disease with an endpoint of time to recurrence of Hunner lesion), or if existing data for a specific compound reflects differential safety or efficacy between these populations, then there is rationale for studying the two entities separately.

In clinical trials that enroll the broad IC/BPS population, inclusive of patients with and without Hunner lesions, the design should control for the presence or absence of Hunner lesions so that any differential effects of safety and efficacy can be detected. This can be accomplished by stratifying subjects at randomization based on cystoscopy at screening or within the past 36 months, and would be an efficient way to evaluate the potential common symptomatic benefit. Based on the specific mechanism of action of a compound in development, or data from previous studies, sponsors may choose to narrow subsequent trials to a single population if data does not support inclusion of both.

Additionally, with only 12% of patients with IC/BPS having Hunner lesions, [27] requiring them to be studied independently in adequately powered trials would mean that these trials would take years to enroll, and thus dramatically lower the likelihood of new innovations for this cohort of patients. If symptom benefit in both cohorts can be demonstrated in combined trials, controlling for presence or absence of Hunner lesions, then new potential treatments could be studied more efficiently.

6.2 Use of Concomitant medications

Since patients with IC/BPS have limited effective treatment options, [8] and moderate-to-severe bladder pain has such a significant impact on QOL, [9] [18] [19] [20] [21] [22] studies should allow subjects to remain on current therapies if their residual symptom burden meets the threshold for entry and their drug regimen is stable. Investigators have seen resistance from patients to enrolling in placebo-controlled studies if they are required to wash out of their current therapies from which they are deriving some level of benefit. Thus, the enrolled population would include a combination of patients on concomitant medications, others that may proceed with lifestyle modifications alone, and some that may continue both. That said, patients with recent changes to their treatment regimens or who are adequately controlled with their current therapies would be excluded from clinical trials.

Furthermore, to allow for adequate pain management, patients should be allowed pre-specified levels of rescue medication for bladder pain. The use of these therapies must be recorded for

proper analysis, and note taken if thresholds are exceeded. Patients using opioids chronically should be excluded from clinical trials in IC/BPS.

6.3 Outcome Assessments

For a disease such as IC/BPS, characterized by a defining hallmark symptom (bladder pain) and multiple secondary symptoms (eg, urinary frequency and nocturia), [1] it is important to use discrete Patient Reported Outcome (PRO) measures to show an impact on the areas of greatest importance to the patient population being studied. This can be approached in numerous ways but a simple, well-precedented assessment strategy is to use single-item questionnaires. The 11-point pain NRS, used universally to assess pain outcome in chronic pain studies, [50] and counts of urinary frequency, also widely accepted as a simple and valid measure in incontinence studies, appear to be robust assessments for use in the IC/BPS population given the presenting symptomatology.

6.3.1 Bladder Pain Assessment

As bladder pain is the hallmark symptom of IC/BPS, [1] and generally what brings patients to their healthcare providers for assessment and treatment, it is important that interventions for this condition be successful at improving bladder pain and that it be measured in a way that the patient can easily and accurately recall. The FDA recommends that the instrument used to measure changes in pain be appropriate for the type of pain studied, with the assessment occurring at the same time each day, and asks the patient to recall his/her worst pain over a short period of time. [51] [52] Retrospective ratings, such as pain intensity recall, are affected by the "peak-and-end" rule in which patients being asked to recall average pain over the course of a day are influenced by the most intense pain they have felt near the time of report. [53] As such, it is most appropriate and robust to study change in maximum (or worst) bladder pain, over a short recall period, as the primary endpoint for clinical trials in IC/BPS as opposed to average bladder pain.

In 2003, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)-II convened to review measures that could be used in trials of chronic pain conditions. [50] Members of this consensus meeting included physicians specializing in pain conditions, government officials from the US NIH and FDA, and individuals from the pharmaceutical industry. Appropriateness of content, reliability, validity, responsiveness, and participant burden were given greatest weight when considering various measures to assess pain. Based on these criteria, the 11-point NRS measure of pain intensity was recommended as a core outcome measure. The 11-point NRS is a widely used instrument to measure pain intensity, with 0 being "no pain" and 10 being "pain as bad as it could be" or "worst possible pain" [51] and generally, the recall period is "in the last 24 hours." [50] [54]

To date, randomized, controlled, clinical trials evaluating subjects with IC/BPS have utilized the 11-point NRS to assess improvements in pain. [17] [55] [56] In future IC/BPS clinical trials, the 11-point NRS could be adapted to specifically mention bladder pain, with 0 being "no bladder pain" and 10 being "bladder pain as bad as it could be" or "worst possible bladder pain."

6.3.2 Urinary Symptom Assessment

Urinary symptoms, such as frequency, nocturia, and urgency are commonly investigated as endpoints in treatment interventions for IC/BPS. [17] [55] [56] Urinary frequency and nocturia can be captured quantitatively by asking the patient to record in a bladder diary the number of times per day they urinate or the number of times they awake from sleep to urinate. However, irritative urinary voiding symptoms in this patient population vary in presentation, perception, and intensity, which makes assessing the impact of a therapy on urinary symptoms challenging. [1] [38] [42] For instance, some patients with IC/BPS will complain more of urinary frequency, while others will find feelings of urgency most bothersome. However, given that urgency is more subjective in nature, it is more challenging to measure reliably than frequency symptoms. Therefore, assessing quantitative counts of urinary episodes may be more appropriate, especially in clinical trials.

Urinary symptoms can also be captured as part of a questionnaire such as the BPIC-SS, the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), the Genitourinary Pain Index (GUPI), or the Pelvic Pain and Urgency/Frequency (PUF). However, many questionnaires that encompass multiple domains of the disease state and provide a single composite score may not provide robust enough information on the specific impacts of treatment. [57] Nonetheless, if properly evaluated and accepted per FDA PRO Guidance, some multi-symptom instruments have the potential to serve as endpoints.

6.3.3 Endpoint Hierarchy Options

Chronic bladder pain is considered the most debilitating symptom for patients with moderate-to-severe IC/BPS. [8] In addition to bladder pain, the associated symptom complex includes a combination of one or more urinary symptoms such as frequency, nocturia, and urgency, which are varied in presentation, intensity, and degree to which they are a concern to patients.

Below, three approaches to endpoint selection are proposed, each of which contain bladder pain, the hallmark symptom of IC/BPS, as the primary endpoint.

1. **Bladder pain as the primary endpoint and one urinary symptom or a symptom composite as a key secondary:** Since bladder pain is the hallmark symptom in this disease state or symptom complex, and is most bothersome and debilitating symptom to patients, this approach aligns endpoint selection with the patients' and clinicians' treatment focus. The choice of a single urinary symptom as a key secondary, or alternatively a multi-symptom questionnaire, allows for further support of a therapy's clinical effect, and can be supportive of overall benefit without displacing focus from the pathognomonic symptom of IC/BPS. A composite questionnaire, such as the BPIC-SS, could be used to assess effects on IC/BPS urinary symptoms. While bladder pain would still be considered the primary endpoint, if properly designed to detect change in symptoms, a PRO measure can assess bladder pain, the need to urinate driven by bladder pain, and the impact of daytime and nighttime frequency. Selection of the secondary symptom or composite tool may vary based on a compound's mechanism of action.

2. **Bladder pain and one urinary symptom as coprimary endpoints:** Demonstration of benefit through coprimary endpoints, using bladder pain and one additional bothersome urinary symptom. Although bladder pain is substantial in IC/BPS, the complex nature of the coexisting urinary symptoms creates variability both qualitatively (ie, subjects do not consistently display the same combination of symptoms) and quantitatively (ie, symptom severity will vary from none-to-severe within each of the symptoms). Urinary symptoms also vary among subjects with IC/BPS and wax and wane over time. Changes in urinary symptoms may vary with the reduction of bladder pain, with some subjects modifying voiding behavior in response to bladder pain relief, while others will not. Independent factors such as decreased bladder capacity may impact urinary frequency and may not be modifiable by many potential therapies. This variability confounds the utilization of a urinary symptom coprimary endpoint.

3. **Bladder pain as primary endpoint with patient identification of key secondary:** In addition to bladder pain, patients could prospectively identify their most bothersome IC/BPS urinary symptom. Using this approach, the primary endpoint would be a demonstrated drug effect on bladder pain and the key secondary endpoint would be a demonstrated effect on the next most bothersome IC/BPS-associated symptom for that individual patient. Regardless of the urinary symptom identified as most bothersome, all important individual symptoms of the IC/BPS symptom complex would be assessed as secondary endpoints. While this approach has worked well in some highly prevalent conditions, such as migraine, the IC/BPS population is significantly smaller. Thus, this approach would dramatically increase the required sample size to have each additional most bothersome symptom adequately powered.

Considering these potential approaches, it is the Sponsor's position that the most appropriate approach for the endpoint hierarchy for clinical trials in IC/BPS is to specify change in bladder pain as the primary endpoint, consistent with Approach #1 above. With a statistically significant and clinically meaningful result, using endpoint measures discussed and agreed upon with the Division and the Clinical Outcome Assessments staff at FDA, this standalone primary endpoint would be sufficient for review and approval. As discussed previously, urinary frequency would be selected as a key secondary endpoint. Due to potential limitations on the ability to reliably change learned behavior in the short term, or the presence of unmodifiable factors affecting bladder size, this secondary endpoint would not be required for approval. Additional urinary symptoms and composite questionnaires may serve as additional secondary or exploratory endpoints.

7. SUMMARY/RECOMMENDATIONS

- IC/BPS is an underdiagnosed symptom complex that is described as pain, pressure, or discomfort perceived to be related to the urinary bladder and associated with lower urinary tract symptoms for which there is no other plausible explanation.
- The hallmark symptom of IC/BPS is bladder pain that is generally associated with the voiding cycle. The concomitant symptoms of increased urinary frequency, nocturia, and urgency are also typically observed, although at varying degrees of severity, and in many cases, may reflect mechanisms to relieve or avoid bladder pain.
- For the purpose of this briefing document and discussion at BRUDAC, the term IC/BPS is used inclusively to refer to patients presenting with bladder pain and urinary symptoms who have confirmed Hunner lesions as well as those who do not have Hunner lesions or who have not been evaluated via cystoscopy.
- The AUA guidelines do not require cystoscopy for initial diagnosis of IC/BPS in uncomplicated cases, where a purely symptomatic diagnosis may be possible.
- Patients with Hunner lesions, and those without, present with generally the same symptoms, are seeking relief from bladder pain, and tend to be treated by physicians using the same treatment algorithm
- IC/BPS represents a significant unmet medical need, and products that provide benefit to the broad IC/BPS population are needed.
- Hunner lesions, while relatively uncommon, may identify a cohort of patients for whom underlying disease and early escalation of treatment may differ. While treatment of these patients may include fulguration, these patients are also expected to have a continuing need for background therapy to control residual symptoms.
- The broad and inclusive IC/BPS population is recommended for clinical studies. A randomized, stratified treatment design would enable evaluation of potential differences in treatment effects between those with and without Hunner lesions.
- The threshold for FDA approval should be achievement of statistically and clinically meaningful treatment benefit based on alleviation of bladder pain, assessed as a standalone primary endpoint.
- Other assessments of concurrent urinary symptoms could be considered according to an endpoint hierarchy as key secondary or exploratory endpoints, viewed as supportive of the overall benefit risk assessment of the compound.
- Clear communication and guidance from the BRUDAC membership and the Agency will be invaluable in allowing industry to develop and bring new treatments forward to address the unmet patient need.

8. REFERENCES

1. Hanno PM, Burks DA, Clemens JQ, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. American Urological Association (AUA) Guideline. American Urological Association. 2014: p. 1-45.

2. McKernan LC, Walsh CG, Reynolds WS, Crofford LJ, Dmochowski RR, Williams DA. Psychosocial co-morbidities in interstitial systitis/bladder pain syndrome (IC/BPS): A systematic review. Neurourol Urodyn. 2017; https://doi.org/10.1002/nau.23421: p. 1-16.

3. Hanno P, Dmochowski R. Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. Neurol Urodyn. 2009; 28: p. 274.

4. Doggweiler R, Whitmore KE, Meijlink JE, Drake MJ, Frawley H, Nordling J. A standard for terminology in chronic pelvic pain syndromes: a report from the chronic pelvic pain working group of the International Continence Society. Neurol Urodyn. 2017; 36: p. 984-1008.

5. MAPP. MAPP Network. [Online].; 2008 [accessed 30 October 2017]. Available from: http://www.mappnetwork.org.

6. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. European Urology. [Online].; 2008 [accessed 27 October 2017]. Available from: http://www.europeanurology.com/article/S0302-2838(07)01165-7/fulltext#section0030.

7. ICA. Interstitial Cystitits Association. [Online].; 2017 [accessed 27 October 2017]. Available from: https://www.ichelp.org.

8. Hanno P, Cervigni M, Dinis P, Lin A, Nickel JC, Nordling J, et al. Bladder pain syndrome. In Abrams P, Cardozo L, Wagg A, Wein A, editors. Incontinence. 6th ed.: International Continence Society; 2017.

9. Rothrock NE, Lutgendorf SK, Kreder KJ. Coping strategies in patients with interstitial cystitis: relationships with quality of life and depression. J Urol. 2003; 169: p. 233.

10. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, McKinlay JB. Prevalence of painful bladder symptoms and effect on quality of life in black, hispanic and white men and women. J Urol. 2007; 177: p. 1390-4.

11. Kanter K, Volpe KA, Dunivan GC, et al. The important role of physicians in addressing the psychological aspects of interstitial cystitis/bladder pain syndrome (IC/BPS): a qualitative analysis. Int Urogynecol J. 2017; 28: p. 249-56.

12. ADAA. Anxiety and Depression Association of America. [Online].; 2016 [accessed 27 October 2017]. Available from: https://adaa.org/understanding-anxiety/related-illnesses/other-related-conditions/chronic-pain.

13. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. Med J Australia. 2009; 190(7 Suppl): p. S54-S60.

14. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States. Gastroenterology. 2012; 143: p. 1179-87.

15. Shaver JL, Wilbur J, Robinson FP, Wang E, Buntine MS. Women's health issues with fibromyalgia syndrome. J Women's Health. 2006; 15: p. 1035-45.

16. Pezzilli R, Morselli-Labate AM, Frulloni L, Cavestro GM, Ferri B, Comparato G, et al. The quality of life in patients with chronic pancreatitis evaluated using the SF-12 questionnaire: a comparative study with the SF-36 questionnaire. Dig Liv Dis. 2006; 38: p. 109-15.

17. Nickel JC, Egerdie B, Davis E, Evans R, Mackenzie L, Shrewsbury SB. A phase II study of the efficacy and safety of the novel oral SHIP1 activator AQX-1125 in subjects with moderate to severe interstitial cystitis/bladder pain syndrome. J Urol. 2016; 196: p. 747-54.

18. Rothrock NE, Lutgendorf SK, Hoffman A, et al. Depressive symptoms and quality of life in patients with interstitial cystitis. J Urol. 2002; 167: p. 1763.

19. Clemens JQ, Brown SO, Calhoun EA. Mental health diagnoses in patients with interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome: A case/control study. J Urol. 2008; 180: p. 1378-82.

20. Hepner KA, Watkins KE, Elliott MN, Clemens JQ, Hilton LG, Berry SH. Suicidal ideation among patients with bladder pain syndrome/interstitial cystitis. Urology. 2012; 80: p. 280–5.

21. Nickel JC, Christopher KP, John F, et al. The relationship among symptoms, sleep disturbances and quality of life in patients with interstitial cystitis. J Urol. 2009; 181: p. 2555.

22. Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK, et al. Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome: A case control study. J Urol. 2010; 183: p. 167-72.

23. Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the united states. J Urol. 2011; 186: p. 540-4.

24. Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND interstitial cystitis epidemiology male study. J Urol. 2013; 189: p. 141-5.

25. Grover S, Srivastava A, Lee R, Tewari AK, Te AE. Role of inflammation in bladder function and interstitial cystitis. Ther Adv Urol. 2011; 3: p. 19-33.

26. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci. 2005; 6: p. 521-32.

27. Doiron RC, Tolls V, Irvine-Bird K, et al. Clinical phenotyping does not differentiate hunner lesion subtype of interstitial cystitis/bladder pain syndrome: a relook at the role of cystoscopy. J Urol. 2016; 196: p. 1136-1140.

28. Kim A, Han JY, Ryu CM, Yu HY, Lee S, Kim Y, et al. Histopathological characteristics of interstitial cystitis/bladder pain syndrome without Hunner lesion. Histopathology. 2017; 71: p. 415-24.

29. ELMIRON® [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals. 2012.

30. RIMSO-50® [Package Insert]. Canonsburg, PA: Mylan Pharmaceuticals. 1978.

31. Shirley SW, Stewart BH, Mirelman S. Dimethyl sulfoxide in treatment of inflammatory genitourinary disorders. Urology. 1978; 11: p. 215-20.

32. Gillenwater JY, Wein AJ. Summary of the national institute of arthritis, diabetes, digestive and kidney diseases workshop on interstitial cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol. 1988; 140: p. 203-6.

33. Hanno PM. Interstitial cystitis-epidemiology, diagnostic criteria, clinical markers. Rev Urol. 2002; 4 Suppl 1: p. S3-8.

34. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. J Urol. 1998; 160: p. 1663-1667.

35. Simon LJ, Landis JR, Erickson DR, Nyberg LM. The interstitial cystitis data base study: concepts and preliminary baseline descriptive statistics. Urology. 1997; 49(5A Suppl): p. 64-75.

36. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L. The diagnosis of interstitial cystitis revisited: Lessons learned from the national institutes of health interstitial cystitis database study. J Urol. 1999; 161: p. 553-7.

37. Messing E, Pauk D, Schaeffer A, Nieweglowski M, Nyberg LM, Landis JR, et al. Associations among cystoscopic findings and symptoms and physical examination findings in

women enrolled in the interstitial cystitis data base (ICDB) study. Urology. 1997; 49(5A Suppl): p. 81-5.

38. Warren JW, Brown V, Jacobs S, Tracy JK, Langenberg P, Wesselmann U, et al. Evidence-based criteria for the pain of interstitial cystitis/painful bladder syndrome in women. Urology. 2008; 71: p. 444-8.

39. Humphrey L, Arbuckle R, Moldwin R, et al. The bladder pain/interstitial cystitis symptom score: development, validation, and identification of a cut score. European Association of Urology. 2012; 61: p. 271-9.

40. Butrick CW. Patients with chronic pelvic pain: endometriosis or interstitial cystitis/painful bladder syndrome. JSLS. 2007; 11: p. 182-9.

41. Greenberg P, Brown J, Yates T, et al. Voiding urges perceived by patients with interstitial cystitis/painful bladder syndrome. Neurourol Urodyn. 2008; 27: p. 287-290.

42. Clemens JQ, Bogart LM, Liu K, et al. Perceptions of “urgency” in women with interstitial cystitis/bladder pain syndrome or overactive bladder. Neurourol Urodyn. 2011; 30: p. 402-405.

43. Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in bladder pain syndrome - a review. Journal of Urology. 2016.

44. CEBM. Centre For Evidence-Based Medicine. [Online].; 2009 [accessed 15 October 2017]. Available from: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009.

45. Lusty A, Kavaler E, Zakariasen K, Tolls V, Nickel JC. Treatment effectiveness in interstitial cystitis/bladder pain syndrome: Do patient perceptions align with efficacy-based guidelines? J Urol. 2017; 197(Suppl): p. e388.

46. Ha T, Xu JH. Interstitial cystitis invravesical therapy. Transl Androl Urol. 2017; 6(Suppl 2): p. S171-S179.

47. Niimi A, Nomiya A, Yamada Y, Suzuki M, Fujimura T, Fukuhara H, et al. Hydrodistention with or without fulguration of Hunner lesions for interstital cystitis: long-term outcomes and prognostic predictors. Neurol Urodyn. 2016; 35: p. 965-69.

48. Jhang JF, Hsu YH, Kuo HC. Characteristics and electrocauterization of Hunner's lesions associated with bladder pain syndrome. Urological Science. 2013; 24: p. 51-5.

49. Payne RA, O'Connor RC, Kressin M, Guralnick ML. Endoscopic ablation of Hunner's lesions in interstitial cystitis patients. CUAJ. 2009; 3: p. 473-7.

50. Dworkin RH, Turk DC, Farrar J, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. J Neuroimmunol. 2005; 113: p. 9-19.

51. Farrar JT, Young JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001; 94: p. 149-158.

52. FDA. Guidance for industry analgesic indications: Developing drugs and biological products, draft guidance. United States Food and Drug Administration; 2014.

53. Schneider S, Stone AA, Schwartz JE, Broderick JE. Peak and end effects in patients' daily recall of pain and fatigue: a within-subjects analysis. Pain. 2011; 12: p. 228-35.

54. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). Arthritis Care Res. 2011; 63(Suppl 11): p. s240-52.

55. Evans RJ, Moldwin RM, Cossons N, Darekar A, Mills IW, Scholfield D. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. J Urol. 2011; 185: p. 1716-21.

56. Nickel JC, Herschorn S, Whitmore KE, et al. Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: insights from a randomized, double-blind, placebo controlled study. J Urol. 2015; 193: p. 857-62.

57. Griffith JW, Stephens-Shield AJ, Hou X, et al. Pain and urinary symptoms should not be combined into one score: psychometric findings from the multi-disciplinary approach to the study of chronic pelvic pain (MAPP) research network. J Urol. 2016; 195: p. 949-54.

Appendix A ESSIC List of Relevant Confusable Diseases and How They Can Be Excluded or Diagnosed

Confusable diseases	Excluded or diagnosed by
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with:	
Common intestinal bacteria	Routine bacterial culture
Chlamydia trachomatis	Special culture
Ureaplasma urealyticum	Special culture
Mycoplasma hominis	Special culture
Mycoplasma genitalium	Special culture
Corynebacterium urealyticum	Special culture
Mycobacterium tuberculosis	Dipstick if "sterile", pyuria culture for *M. tuberculosis*
Candida species	Special culture
Herpes simplex	Physical examination
Human Papilloma Virus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder neck obstruction	Flowmetry and ultrasound
Neurogenic outlet obstruction	Medical history, flowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or haematuria (→upper urinary tract imaging such as CT or IVP)
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Post-void residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Flowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis
Pelvic floor muscle related pain	Medical history, physical examination

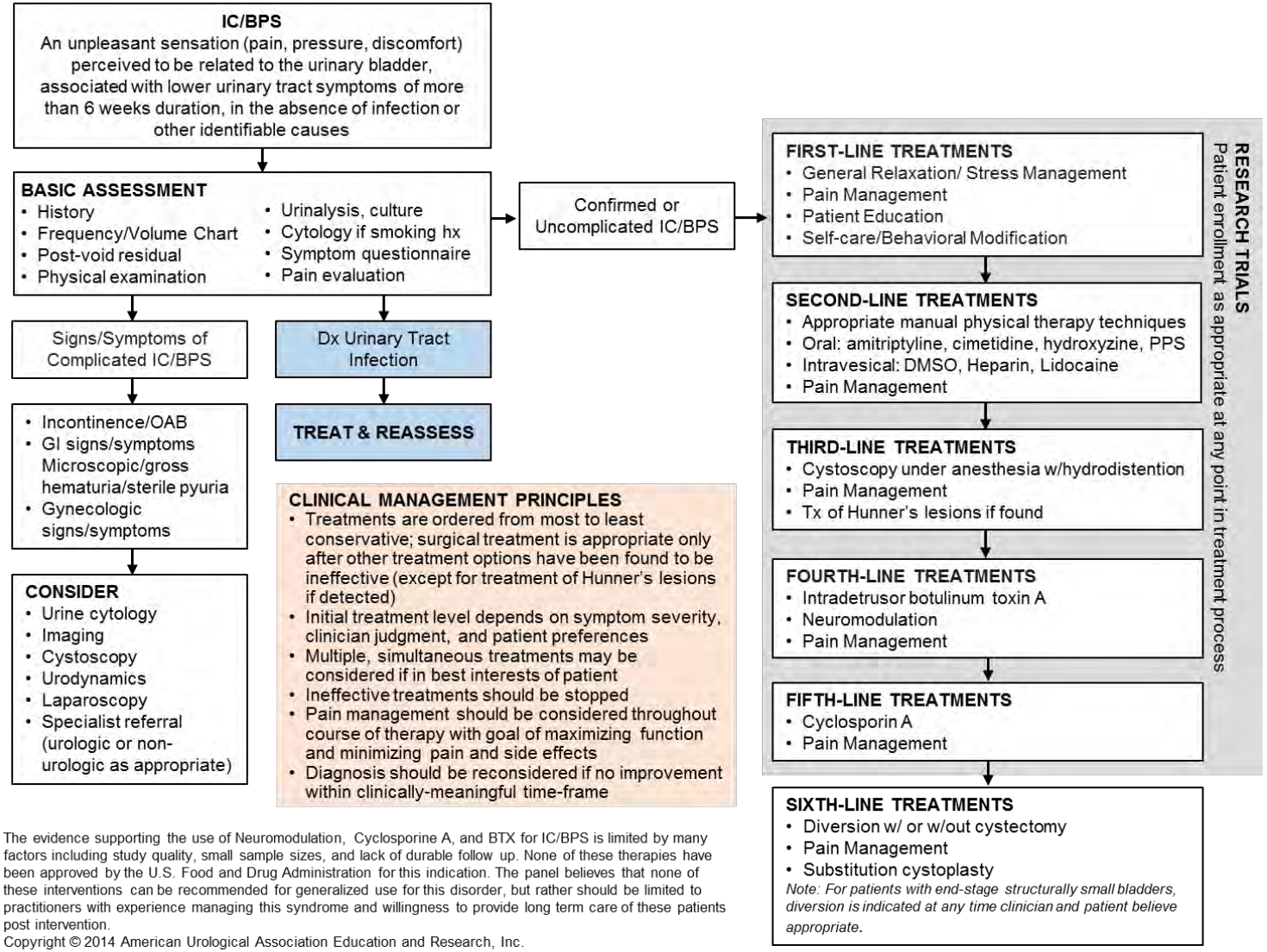
CT = computed tomography; IVP = intravenous pyelogram; PSA = prostate-specific antigen.
Source: European Society for the Study of IC/BPS (ESSIC). Eur.Urol. 2008;53:60-7. Epub 2007 Sep 20.
as cited by: Meijlink JM. Interstitial Cystitis/Bladder Pain Syndrome. Brochure published by the International Painful Bladder Foundation 2017

Appendix B NIDDK and ICDB Diagnostic Criteria

The National Institute of Diabetes and Digestive and Kidney Diseases Consensus Criteria for the Diagnosis of Interstitial Cystitis
To be diagnosed with interstitial cystitis, patients with either:
Glomerulations on cystoscopic examination Or a classic Hunner's ulcer
and either:
Pain associated with the bladder Or urinary urgency
An examination for glomerulations should be undertaken after distension of the bladder under anesthesia to 80-100 cm of water pressure for 1-2 minutes.
The bladder may be distended up to two times before evaluation.
The glomerulations must:
Be diffuse-present in at least 3 quadrants of the bladder
Be present at a rate of at least 10 glomerulations per quadrant
Not be along the path of the cystoscope (to eliminate artifact from contact instrumentation).
The presence of any one of the following criteria excludes the diagnosis of interstitial cystitis:
1. Bladder capacity of greater than 350 cc on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100 cc of gas or 150 cc of water during cystometry, using a fill rate of 30 – 100 cc/min
3. The demonstration of phasic involuntary bladder contractions on cytometry using the fill rate described above
4. Duration of symptoms less than 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics
7. A frequency of urination, while awake, or less than 8 times per day
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period
9. Bladder or ureteral calculi
10. Active genital herpes
11. Uterine, cervical, vaginal, or urethral cancer
12. Urethral diverticulum
13. Cyclophosphamide or any type of chemical cystitis
14. Tuberculous cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumors
17. Vaginitis
18. Age less than 18 years

The Interstitial Cystitis Data Base Study Entry Requirements
1. Providing informed consent to participate in the study
2. Willing to undergo a cystoscopy under general or regional anaesthesia, when indicated, during the course of the study
3. At least 18 years of age
4. Having symptoms of urinary urgency, frequency, or bladder pain for more than 6 months
5. Urinating at least 7 times per day, or having some urgency or bladder pain (measured on linear analog scales)
6. No history of or current genito-urinary tuberculosis
7. No history of urethral cancer
8. No history of or current bladder malignancy, high-grade dysplasia, or carcinoma in situ
9. Males: no history of or current prostate cancer
10. Females: no occurrence of ovarian, vaginal, or cervical cancer in the previous 3 years
11. Females: no current vaginitis, clue cell, trichomonas, or yeast infections
12. No bacterial cystitis in previous 3 months
13. No active herpes in previous 3 months
14. No antimicrobials for urinary tract infections in previous 3 months
15. Never having been treated with cyclophosphamide (Cytoxan)
16. No radiation cystitis
17. No neurogenic bladder dysfunction (eg, due to a spinal cord injury, a stroke, Parkinson's disease, multiple sclerosis, spina bifida, or diabetic cystopathy)
18. No bladder outlet obstruction (determined by urodynamic investigation)
19. Males: no bacterial prostatitis for previous 6 months
20. Absence of bladder, ureteral, or urethral calculi for previous 3 months
21. No urethritis for previous 3 months
22. Not having had a urethral dilation, cystometrogram, bladder cystoscopy under full anaesthesia, or a bladder biopsy in previous 3 months
23. Never having had an augmentation cystoplasty, cystectomy, cystolysis, or neurectomy
24. Not having a urethral stricture of less than 12 French

Appendix C AUA Treatment Algorithm for IC/BPS



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.

Source (1)