Interstitial Cystitis/Bladder Pain Syndrome

Ioana Marcu, MD[1] E. Cristian Campian, MD, PhD[1] Frank F. Tu, MD, MPH[2]

[1] Department of Obstetrics, Gynecology, and Women's Health, St. Louis University, St. Louis, Missouri
[2] Department of Obstetrics and Gynecology, Pritzker School of Medicine, University of Chicago, Evanston, Illinois

Address for correspondence Frank F. Tu, MD, MPH, Department of Obstetrics and Gynecology, North Shore University Health System, Pritzker School of Medicine, University of Chicago, Walgreens 1507, 2650 Ridge Avenue, Evanston, IL 60201 (e-mail: ftu@northshore.org).

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Abstract

Interstitial cystitis/bladder pain syndrome is an uncommon but potentially devastating pelvic pain disorder affecting both women and men. This condition is often confusable and comorbid with other pelvic pain disorders. Although our understanding of the underlying pathophysiology is growing, the exact longitudinal course by which peripheral and central aberrations involving the bladder mucosa, peripheral inflammation, and central dysregulation of bladder sensitivity create painful bladder symptoms remains an area in need of further study. Only a limited number of drugs have been approved for treatment by the Food and Drug Administration, and overall durable efficacy of the many treatments reviewed in recent American Urological Association guidelines remains suboptimal, making awareness, early diagnosis, and use of effective treatments early in the disease course, where neural changes may still be reversible, imperative.

Keywords

- chronic overlapping pain conditions
- cross-organ sensitization
- glycosaminoglycan layer

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic painful bladder condition characterized by pelvic pain and urinary symptoms without another identifiable cause.[1,2] Some cases exhibit visible urothelial changes (glomerulations and Hunner's ulcers). Its diagnostic criteria and ideal name remain fluid as the exact etiology is unknown, resulting in very few consistently reliable treatment options.

Estimates of prevalence of IC/BPS have increased as definitions have changed over time. Previous reports ranged from 10 to 510 per 100,000.[3,4] In a population-based cross-sectional study in Boston, Clemens et al found that the prevalence of IC/BPS varies based on the definition—from a value of 0.83% in women, with a more restrictive definition, to 2.71% in women, with a more inclusive definition.[5] Some studies have suggested that females are more affected than males by a factor of 5:1 to 10:1.[6] Suskind and colleagues, however, using validated case definitions for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and IC/BPS, have shown that IC/BPS may be far more common in men, with 1.9% of men meeting the high specificity definition for IC/BPS and an overlap of 17% of men who meet the high specificity IC/BPS criteria and also the CP/CPPS criteria.[7–9]

Estimates of medical costs and sick leave combined for IC/BPS in the United States alone were $428 million in 1987.[10] This is equivalent to approximately $1.226 billion in 2014 dollars according to the U.S. Department of Labor, Bureau of Labor Statistics.

Diagnostic Criteria

At its heart, BPS is a disorder that results in sensory dysregulation of bladder awareness, both in terms of pain perceived in the organ and an increased sense of urgency and/or frequency. It generally excludes the presence of other known causes of such symptoms: acute or recurrent infection, radiation- or medication-induced injury, malignancy, or nephrolithiasis. Diagnostic criteria for IC/BPS have evolved over the years, without one consensus definition among the relevant stakeholder organizations.

Among the most widely utilized are the European Society for the Study of IC/PBS (ESSIC) and the American Urological Association (AUA) criteria. ESSIC's definition includes symptoms of "chronic pelvic pain (>6 months), pressure or discomfort perceived to be related to the urinary bladder

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accompanied by at least one other urinary symptom like persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioral, emotional, and sexual symptoms should be addressed." Also included components are cystoscopy with hydrodistension findings with normal, glomerulations, and Hunner lesions as categories as well as biopsy results showing histology of inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.[11]

The AUA has likewise stepped away from the requirement of cystoscopy with hydrodistention for the diagnosis of IC. Instead, the AUA, having combined the terms IC/BPS to refer to one disease entity, recommends a clinical approach to diagnosis and requires a far shorter duration of symptoms, defining IC/BPS as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks of duration, in the absence of infection or other identifiable causes."[10] Other organizations including the European Association of Urology, Society of Interstitial Cystitis of Japan, and the International Continence Society have slightly varying definitions, summarized in ►**Table 1**.

Research diagnostic criteria often are referenced by clinicians in identifying patients with these syndromes; so, it is helpful to review their history. However, it is also critical to note that research study designs often have different purposes than identifying clinically significant cases. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was the first to standardize a definition in 1987 for the purposes of uniformity in studies. The NIDDK definition, which was then revised in 1988 to lend more diagnostic importance to glomerulations, requires the presence of either glomerulations or "Hunner ulcers" on cystoscopic examination, and pain associated with either filling of the urinary bladder or urinary urgency with symptoms presents at least for 9 months. A minimum of 10 glomerulations must be present in three of four quadrants after distension of the bladder to 80 to 100 cm water pressure for 1 to 2 minutes.[12] In 1999, Hanno et al found that although 90% of patients meeting research criteria were also diagnosed with IC/BPS on the basis of experienced physicians' clinical judgment, the research definition excluded more than 60% of patients identified by clinicians, prompting debate regarding the clinical applicability of the criteria.[13] Subsequent iterations of this trial network including the multicenter, observational cohort study, Interstitial Cystitis Data Base (ICDB), made cystoscopy with hydrodistention optional but not required for entry.[14] The current Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (mappnetwork.org) has markedly loosened their enrollment criteria to better study the dimensional nature of bladder distress, including any patients reporting the unpleasant sensation of pain, pressure, or discomfort, perceived to be related to the bladder and/or pelvic region, associated with lower urinary tract symptoms,

Table 1 Comparison of contemporary definitions of BPS/IC

Organization	Definition	Duration	Cystoscopy requirement
NIDDK[12]	(a) glomerulations or "Hunner's ulcers" on cystoscopic examination, (b) pain associated with either filling of the urinary bladder or urinary urgency, and (c) not meet extensive exclusion criteria from cystometry, treatment response, other diagnoses	9 mo	Yes
ESSIC[11]	Chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded	6 mo	Yes to exclude other conditions
AUA[10]	An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms, in the absence of infection or other identifiable causes	6 wk	Optional
SICJ[193]	*Symptoms* such as urinary frequency, hypersensitivity, and/or bladder pain, *cystoscopic findings* proving pathologies in the urinary bladder and *exclusion* of other confusable diseases explainable for the symptoms and findings	3 mo	Yes
ICS[194]	PBS: pelvic pain related to bladder filling "accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology IC: if histological findings or cystoscopic features	No duration	Yes (if diagnosing IC)

Abbreviations: AUA, American Urological Association; BPS/IC, bladder pain syndrome/interstitial cystitis; ESSIC, European Society for the Study of Interstitial Cystitis; ICS, International Continence Society; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; SICJ, Society of Interstitial Cystitis of Japan.

as long as they are present for the majority of the time during any 3 months in the previous 6 months. Those criteria should *not* be used to diagnose patients clinically, however. A major shift in thinking about IC/BPS has occurred through systematic studies beginning in 2008, which approached the urologic chronic pelvic pain syndromes (UCPPS, with both IC/BPS and CP/CPPS from only males), in a more systematic manner. The study includes extensive deep phenotyping with brain imaging studies, serological and urological assessments for potential biomarkers, and quantitative sensory testing. The aims of MAPP reflect the current thinking that UCPPS likely represent an overlapping spectrum of bladder and extraurological CNS-centered pathology.[15]

Pathophysiology

There are multiple theories relating to the etiology of the condition, many of which are increasingly influenced by the possibility of common central pathophysiology for IC/BPS's bladder centric symptoms. Possible peripheral etiologies include urothelial and epithelial cell abnormalities.[16] Symptoms of IC/BPS may be due to disruption in the urothelium's apical cell layer, possibly due to disruption of its overlying glycosaminoglycan (GAG) layer, which in a healthy bladder acts to regulate the passage of cations, as well as protect the urothelium from damaging substances and bacteria.[13,14] This in turn may be due to poor differentiation of the urothelium, as supported by a different pattern of biomarkers and GAGs in the urine of patients with IC/BPS compared to controls.[18]

There is debate regarding the significance of pathologic findings, namely, Hunner's lesions and glomerulations, on cystoscopy with hydrodistention. Hunner's lesions are considered distinctive to IC, but are present only in about 4 to 10% of patients with either newly diagnosed IC/BPS or with suspected IC/BPS.[14,19–21] The great improvement following Hunner's lesion resection, combined with a documented association with pain and urgency, and the finding that patients with Hunner's lesions have a statistically significantly higher number of chronic disorders than patients without the lesion have led some to propose two different categories of IC/BPS: ulcerative IC/BPS and a nonulcerative IC.[22,23]

Although the preliminary ICDB findings by Simon et al found that about 90% of patients enrolled in the database had glomerulations, an analysis of the correlation between symptoms and findings on cystoscopy with hydrodistention found that "the presence, density, or diffuseness of glomerulations was not associated with urinary pain or urgency on the analog scales."[14,24] A systematic review by Wennevik and colleagues concluded that there were no convincing data to show that glomerulations on cystoscopy with hydrodistension is specifically related to IC/PBS. They cited studies showing high rates of glomerulations found in diagnosed patients; however, a significant proportion had no glomerulations. They also cited that there are similar observed rates among patients with unrelated pathology such as upper urinary tract stones and normal asymptomatic women.[25–27]

There is some support for the associations between cystoscopic pathology and symptoms. However, different studies have found different correlations between findings on cystoscopy and symptoms, making interpretation of the overall association difficult; a recent study looking at Hunner's ulcers and overall reported symptoms found that they are not predictive of whether a patient is more likely to exhibit bladder centric versus polysyndromic IC/BPS.[20,28–30]

Infection may play a role in initiating some of these morphological changes in IC/BPS,[31] a theory which is supported by the decreased presence of GP51, a urinary antibacterial glycoprotein, in patients with IC/BPS compared to controls.[18] The inflammation resulting from a urinary tract infection (UTI) may be the trigger that leads down the path toward development of IC/BPS.[32] Differentiation of IC/BPS from chronic UTI is especially difficult, given a possible common mechanism as well as the possibility of coexistence of the conditions.[33]

The role of mast cells in IC/BPS has also been examined, with Peeker and colleagues finding evidence of inappropriate mast cell activation.[34] Mast cells have been found in patient with IC/BPS and have been found especially in areas of weakened urothelium or in the presence of Hunner's lesions.[35,36] Increased mast cell presence has also been noted in areas of greater vascularity and inflammatory granulation tissue.[36]

The postulated mechanism of mast cells' role in IC/BPS pain potentially includes hormonally mediated neurogenic inflammation.[37] Estrogen appears to play some role in the development of the IC/BPS phenotype and inflammation. Imamov and colleagues showed that deficiency of estrogen receptor-beta in female mice led to the development of urothelium similar to that found in IC/BPS.[38] Additionally, mast cells, which have been found in greater number in the urothelium of patients with IC, have been found to have estrogen receptors; increase in estrogen may lead to degranulation of histamine from mast cells, and subsequent release of substance P.[39–41]

Other postulated etiologies include deficiency in Tamm-Horsfall protein (an anionic protein which binds to and thereby neutralizes urinary toxins) and antiproliferative factor (APF) which inhibits the normal proliferation of bladder epithelial cells.[42,43] Characterization of the latter factor, which initially received significant attention, has not been proven to be easily replicable of note, and research efforts no longer focus on APF at present.

Cigarette smoking also appears to be involved in the pathophysiology of IC. While some studies have found no association between smoking and IC/BPS,[44,45] Kennedy et al found an odds ratio of 2.33 for current smokers to have IC/BPS by a restrictive definition, but no association using a less restrictive definition.[46] In a twin study, Tettamanti et al found an odds ratio of 1.5 for BPS in former or current smokers, but noted possible familial confounding factors.[47] The theory behind this association may include nicotine's angiogenic properties, both by increasing vascular endothelial growth factor (VEGF) to pigment endothelium-derived factor (PEDF) ratio and by release of factors promoting angiogenesis, such as nitric oxide.[48–51]

Increasingly, evidence supporting a connection between angiogenic factors, vascular changes, and IC/BPS has been identified. Expression of an angiogenic factor, platelet-

derived endothelial cell growth factor/thymidine phosphorylase (PDECGF/TP), was found to be greater in IC/BPS patients with glomerulations than those without glomerulations or asymptomatic patients. Both PDECGF/TP and VEGF were found in 97.4 and 68.4% of patients with glomerulations by immunohistochemical study.[52] VEGF expression was also found to be positively correlated with pain severity in patients with IC/BPS.[53] PDECGF/TP also likely plays a role in long-term inflammation of the bladder due to the role of its coexpressed protein CD44 in enhancing the action of heparin-binding growth factors.[52,54]

Some evidence suggests that platelet-activating factor (PAF), an inflammatory mediator, plays a role in pathophysiology of IC/BPS and may serve as a biomarker.[55,56] PAF has been shown to be upregulated by histamine, which is released by mast cells, and PAF has been shown to activate mast cells.[57,58] Using urothelial cell isolates from normal and IC/BPS patients, Marentette and McHowat demonstrated increased prevalence of the $iPLA_2\beta$ isoform responsible for PAF production in IC/BPS patients. Stimulating the cells with a selective $iPLA_2\beta$ agonist led to greater PAF production and increased tissue adherence of polymorphonuclear leukocytes (PMNs). Pretreating the cells with an $iPLA_2\beta$ antagonist blocked PAF production and PMN adherence.[59] Marentette and colleagues found that human and mice urothelial cells exposed to cigarette smoke extract showed increased PAF accumulation, decreased PAF breakdown by PAF-acetylhydrolase (AH), and increased inflammatory cell adherence compared to controls.[60] Increased PAF due to smoking may exacerbate ongoing IC/BPS inflammatory changes.

Recently, the MAPP research network has identified several urinary solutes which discriminate patients with IC/BPS and BPS with a sensitivity and specificity of 90%, including etiocholan-3α-ol-17-one sulfate (Etio-S), a sulfoconjugated 5-β reduced isomer of testosterone. The clinical and pathophysiological implications of these preliminary findings need further investigation.[61]

As a pain state, IC/BPS exhibits neural pathophysiological mechanisms commonly seen in chronic overlapping pain conditions, including neural mechanisms such as enhanced neuronal excitability[62] and central nervous system alterations.[63] As noted earlier, neurogenic inflammation, whether alone or as part of a more complex inflammatory process, has been increasingly thought to play a role in IC/BPS pathophysiology.[64,65] Patients with IC/BPS have upregulated nerve growth factor (NGF) mRNA transcript and protein expression, which may explain how a urothelial injury induces persistent afferent activity.[66,67] Mechanical injury or inflammation of the bladder, and other pelvic organs, can sensitize afferent nerves, also leading to increased sensation of pain as well as long-term changes precipitated by a neuronal gene expression cascade.[68,69] Multiple studies have shown that this peripheral sensitivity is carried through the level of the dorsal root ganglia and to the level of the brainstem and spinal cord.[64] Pelvic organ cross-sensitization, which has been demonstrated experimentally and clinically (between bladder pain and uterine pain), also may be the consequence of both peripheral and central neural changes.[70–72] Afferent cross-sensitization of hypogastric, splanchnic, pelvic, and pudendal nerves has been shown in animal models to occur, as they course to their corresponding dorsal root ganglia and then to the central nervous system. Noxious activation of afferent signaling then activates reflexive pathways promoting release of neuromodulators and neuropeptides; the resulting inflammation can activate ascending nociceptive tracts to the cerebral cortex, leading to central interpretation of the experience as painful.[72–74] Of note, Hellman and colleagues have recently used noninvasive bladder filling paradigms to identify that many women with heightened dysmenorrhea exhibit silent bladder pain sensitivity; this may be an opportunity to explore for identifying a preclinical phenotype conveying future IC/BPS risk.[75]

Central sensitization is increasingly appreciated as a consequence and cause of bladder pain. Sites in the central nervous system, including the rostral ventromedial medulla (RVM), a suspected key regulator of descending sensory inhibition, are inappropriately activated in pathological pain states and facilitate greater transmission of noxious information through spinal cord tracts from persistently inflamed or previously sensitized viscera.[76] The MAPP research network, which has investigated the central mechanisms of urogenital pain, has identified both fMRI activation differences at multiple sites throughout the brain (notably including key areas involved in valence, emotion, and motor control—right premotor cortex/supplementary motor area, insular cortex, frontal pole/medial orbital frontal cortex, insular cortex, thalamus, and anterior cingulate), and white matter axonal differences (such as the right corticospinal tract and right anterior thalamic radiation).[63,77] Evidence for such CNS changes also extends to circulating levels of mood-related metabolites; patients with IC/BPS have decreased γ-aminobutyric acid (GABA) levels, which is linked to worsened mood and also may enhance central neural excitability.[78] Thus, at every level, it appears that peripheral inflammation and injury leads to neuronal upregulation and sensitization from the level of the bladder to the central nervous system.

Clinical Features

IC/BPS presentation and severity is variable between patients temporally. Typically, it presents mildly and intermittently, with a disease progression toward worsening symptoms. The original NIDDK criteria study for IC/BPS found a majority of patients (89.8%) to be female and Caucasian 94.1%, with mean age of presentation of 53.8 years.[79] However, the average onset of symptoms has been found in many studies to be in the age of 30s.[80–83] Some syndrome features begin to present even in early childhood (irritative voiding) and may be more prevalent than previously thought in men.[7,84] As a result of the syndrome's features evolving over time, the latency between onset of symptoms to diagnosis of IC/BPS is variable and can range from 1 month to 30 years, with an average of about 5 years.[24,83,85–87] Presentation, of note, in older patients may be more bladder irritation, as opposed to pain.

Historically, studies focused on the peripheral mucosal defects of IC/BPS have not been exact in requiring a common body of symptoms. Most patients present with bladder and pelvic pain, but up to 30% may present with no pain initially.[88] IC/BPS pain classically encompasses dysuria, but may be experienced as suprapubic pain, low back pain, or groin pain.[89] In the ICDB study, however, which sought to study patients with clinical signs of IC, 93.6% of patients reported pain. One Japanese retrospective chart review found that almost all patients in the study (98.3%) had urinary frequency, followed by urgency (62%). Only 41.6% had suprapubic pain, echoing others' findings that pain is not a defining factor.[83] In the more recent findings from the NIDDK MAPP research network (which recruited only patients with pain and irritative symptoms), participants were found to have a wide distribution of symptoms, with polysyndromic diagnoses, discussed later.[90]

The differential diagnosis of IC/BPS includes chronic UTIs, urethral diverticula, overactive bladder syndrome, and many other causes of pelvic pain, including endometriosis, vulvodynia, and vaginal candidiasis.[89] IC/BPS can be differentiated from other disorders through careful clinical assessment combined with voiding diaries, with occasional cystoscopy where appropriate (such as persistent hematuria). IC/BPS has been found to exhibit more voiding frequency, smaller volumes, and more consistent frequency even at night compared to overactive bladder.[91]

In surveys of patients meeting strict NIDDK criteria, 30 to 90% of those enrolled in urogenital pain syndromes (both CP/CPPS and IC/BPS) report that certain foods trigger symptoms.[92,93] Foods observed to exacerbate IC/BPS symptoms include citrus fruits, caffeinated beverages, alcoholic beverages, and spicy dishes.[80,94–96] Mechanisms by which certain foods or beverages may trigger IC/BPS include passage of irritative solutes across a disrupted urothelium.[17] Another cause why diet may trigger IC/BPS pain may be due to neuronal "cross-talk" between the gastrointestinal (GI) and urinary tracts, by which inflammation and irritation of the GI tract may lead to urinary tract pain.[97,98] Peripheral or central neuronal upregulation may interact with diet to promote pain experience.[64,94]

Following this logic, Parsons and colleagues proposed the Potassium Sensitivity Test (PST) as a way to assess for potential IC/BPS, theorizing that high levels of potassium, when instilled intravesically, trigger pain when crossing a compromised urothelial mucosa GAG layer.[89,99] Given the lack of specificity, however, the test consequently has largely fallen out of favor. The accompanying Pelvic Pain and Urgency/Frequency (PUF) questionnaire, also developed by Parsons and colleagues, rested on validation with the PST, and as a result is no longer used extensively in clinical practice as a diagnostic tool, but may still have value in tracking symptom improvement over time.[100]

Behavioral factors that aggravate IC/BPS symptoms include stress, constrictive clothes, and sexual intercourse.[96] However, the MAPP study recently found in an analysis of 292 participants that patient symptom trigger, other than sexual activity, seems to be not generalizable and rather is individual specific.[101]

Quality of life for patients with IC/BPS has been repeatedly identified as significantly affected by the disease.[102] Pain management significantly affects quality of life, and therefore has been recognized by the AUA as a cornerstone of IC/BPS management.[10] Effects on sexual function have been found to be related to overall quality of life.[103] Increasingly, symptom questionnaires such as IC/BPS have started to focus on quality of life.[104] MAPP data also suggest that patients who present with a polysymptomatic, polysyndromic presentation, in which IC/BPS coincides with other chronic pain and inflammatory conditions, have higher pain scores and a poorer quality of life.[105] Decreased quality of life not only reflects pain but also stems from comorbid anxiety, poor sleep, catastrophizing, depression, and stress.[103] Stress can then have a vicious cycle effect and worsen IC/BPS symptoms and further decrease quality of life.[86] In line with this multidimensional view of disease-related QOL, Nickel and colleagues have encouraged broader assessment of patients and proposed broad phenotyping across multiple health domains to optimize therapy of IC/BPS, a philosophy they have coined UPOINT (urological, psychosocial, organ specific, infection, neurological, and muscle tenderness). Notably they found in initial analysis of 100 women (mean age: 48) that almost half of women met criteria for other neurological issues, and likewise for associated muscle tenderness.[106]

Several studies have shown that smaller bladder capacity and more inflammatory signs are found in older patients.[24,107] In a study describing 40 patients with painful bladder symptoms, older patients were more likely to fulfill NIDDK criteria of IC/BPS.[108] In a population-based cross-sectional survey of 5,506 subjects, younger patients with IC/BPS were found to have fewer symptoms than older patients.[5] In a retrospective cohort of 349 patient with clinically diagnosed IC/BPS, older patient had a significantly higher rate of intrafascicular fibrosis and a higher mast cell count.[109] A longitudinal observational study of 190 patients has shown that baseline age during the study was significantly associated with severity of symptoms.[14] Hunner's lesions also appear to be found more often in older patients.[81,110,111]

Age-specific trajectories of IC/BPS symptom progression also have been described. Younger patients appear to experience more urgency, frequency, and dysuria and intermittent symptoms such as flaring, whereas older patients have more nocturia and incontinence.[110,112] Earlier age of onset of symptoms has been found to trend positively with severity of IC/BPS.[14] However, plateau of symptoms or even early symptom regression has also been described.[86,113] The natural history is variable from patient to patient and disease course likely is modulated by how aggressively treatment is initiated at onset.[114] Increasingly prognosis for many persistent IC/BPS is mostly thought to be like that of any other chronic disease, where the aim is symptom and pathology management, not cure.[115]

A significant barrier to diagnosis based on mucosal appearance criteria is the relative subjectivity of evaluating glomerulations cystoscopically. According to ESSIC, grades II to III glomerulations are suggestive of IC/BPS, with grades II and III referring to large submucosal bleeding and diffuse

global submucosal bleeding, respectively.[116] In previous studies, consistency in evaluating severity of glomerulations has been difficult. In one study, five blinded urologists were asked to assign grade of glomerulations given cystoscopic images, and only three could be included in the final results as a result of inconsistency among the others.[26]

Researchers have identified significant associations with other extraurological pain syndromes not associated with the bladder, with the comorbid disorders largely falling into two categories: chronic pain disorders and autoimmune disorders. The highest rates of comorbidity are seen with fibromyalgia, chronic fatigue, and irritable bowel syndrome (IBS).[85,103,117] In addition to those associations, IC/BPS has also found to be associated with temporomandibular joint disorder, endometriosis, migraines, asthma, inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE).[85,117] Despite a low percentage of persons with IC/BPS having IBD or SLE, due to the overall low prevalence of these conditions, Alagiri and colleagues showed that participants with IC/BPS were 30 to 50 times more likely to have lupus and 100 times more likely to have IBD when compared with controls.[85]

There is high overlap of IC/BPS with IBS and increasing evidence of similar overlap with upper GI disorders, including functional disorders and gastroesophageal reflux disease (GERD). Between 7 and 48% of patients with IC/BPS or IC-like symptoms were found to have IBS in a MAPP study evaluating for multiple comorbidities of IC/BPS, which also found that 38% had nonurological chronic pain syndromes.[99] In studies where patients with IC/BPS were evaluated for IBS only, 30 to 75% of patients with IC/BPS or IC-like symptoms were found to have IBS or similar symptoms. Nineteen percent to 79% of patients with chronic pelvic pain had IBS or IBS-like symptoms. A mechanism by which IBS could interact with IC/BPS and other pelvic pain syndromes may have to do with neurologically mediated pain "cross-talk," as described earlier.

Additionally, there are similarities in the urothelial pathology of patients with IC/BPS and the epithelial pathology of the esophagus in patients with GERD, such as epithelial dysfunction leading to lack of barrier protection of underlying tissue.[118] Of note, there is also high overlap of IBS and GERD, with a weighted average of 39.3% of patients previously diagnosed with IBS found to have GERD and a weighted mean of 60.5% of patients previously diagnosed with GERD found to have IBS.[119]

The MAPP research network found that participants with UCPPS and nonurological chronic syndromes (polysymptomatic, polysyndromic [PSPS] pattern) reported more severe and widespread pain as well as more severe urologic symptoms.[120] Patients with the PSPS pattern had more genitourinary pain, more frequent pain, and more widespread distribution of pain.[105] Similar findings were corroborated in an external multisite study, where 81% of the 173 women were found to have the "pelvic pain beyond" phenotype, and had more depression, sleep disturbance, physical quality of life, and sensory pain.[121] Female patients were more likely to have PSPS IC/BPS than males, and while overall severity of pain was similar for both men and women with these pelvic pain syndromes, women were likely to report more bladder-focused symptoms such as urgency, frequency, and suprapubic pain.[70,122]

This distinction between IC/BPS with and without comorbidities may be of great prognostic value, given that preexisting chronic pain disorders such as IBS greatly increase the risk of a woman with IC/BPS to undergo hysterectomy.[123] Preexisting comorbidities in women with IC/PBS further increase the risk of ultimately hysterectomy. PSPS IBS has also been found to have poorer outcomes than non-PSPS IBS.[124,125]

Several questionnaires have been developed with the goal of both identifying and following the course of IC/BPS upon afflicted patients. In 1997, O'Leary and Sant developed the interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI), based on the responses of patients who met the stringent NIDDK research criteria and led to the determination of IC/BPS defining characteristic of urgency, frequency, nocturia, and pain. The ICSI/ICPI is short, with only eight questions, and may be helpful to follow treatment response.[126] Alternately, the genitourinary pain index (GUPI) is a validated tool developed as part of the ongoing NIDDK bladder/pelvic pain network trials by modifying the NIH-Chronic Prostatitis Symptom Index. GUPI addresses not only pain and urinary symptoms in both women and men but also addresses quality of life, and has been shown to have discriminant validity (prostatitis vs. IC/BPS, and incontinence vs. IC/BPS) and to be responsive to change in an NIH sponsored trial of physical therapy.[104] A critical point to highlight is that although IC/BPS inherently lumps bladder pain and bladder irritative symptoms together, a MAPP study by Griffith et al identified using exploratory factor analysis of responses on the ICSI/ICPI and the GUPI that these symptoms are psychometrically distinct and concluded they need to be considered separately in individuals to optimize clinical care.[113]

Treatment

Treatment for IC/BPS is targeted at symptom control, ideally attempting to match to possible underlying pathophysiologic causes. Oral medications, intravesical instillations, and cystoscopy with hydrodistension (HD) have variable, usually short-lived effects once the treatment exposure is completed, over the course of 1 year, but occasional patients will go into remission, some permanently (see ►**Table 2**). Surgical interventions other than mucosal fulguration and cystoscopy with HD for some patients can have long-term benefit and high cure rates, up to 80%, but have more associated risks.[6]

The AUA has developed guidelines for the diagnosis and treatment of IC, divided into six tiers.[10] They outline that treatment should start at more conservative levels and then advance as necessary toward more invasive options and often simultaneous treatment. Pain management ought to be regularly reassessed due to the disease's impact on quality of life.

First-line treatment includes conservative management such as behavioral changes, diet alteration, heat or cold packs, pelvic floor exercises, and reduction of psychological stress. Patients can be encouraged to cut out potential noxious food or stimuli one at a time, and assess if avoidance

Table 2 Standard dosages for commonly used treatments for BPS/IC

Medication	Initial dose, taper regimen	Key side effects
Pentosan polysulfate	100 mg TID orally	Hair loss, GI upset
Tricyclic antidepressants[a] Nortriptyline, amitriptyline, imipramine, desipramine	10–25 mg orally once at night, gradually increase every 4–7 d by the same dose to 100–150 mg at night	Sedation, dizziness, dry mouth, constipation, arrhythmias (consider checking blood metabolite level upon exceeding 100 mg daily), may lower seizure threshold in combination with tramadol
Antiepileptics[a] Gabapentin Pregabalin	100–300 mg orally qhs gradually taper every 4–7 d up to 900–1,200 mg three times a day 75 mg BID, gradually taper up every week to a max. of 450 mg/d divided	Sedation, dizziness, ataxia, mood changes, easy bruising
Hydroxyzine	25 mg qhs orally	Sedation
Cimetidine	200 mg TID orally	Dizziness, headache, diarrhea, B12 deficiency (persistent use), watch for confusion in the elderly
Bladder instillations Marcaine, Kenalog, heparin Buffered lidocaine DMSO	M (30 mL) K (40 mg), H (40,000 units), 2 × /wk for 6 wk L (30 mL) + NaHC03 (10 mL) 2 × /wk for 6 wk 50 mL weekly for 6 wk	Urethral irritation, urinary retention (rare), UTI, central effects of local anesthetics (lightheadedness, tongue numbness) *Similar* Worsened pain, garlic odor

Abbreviations: BPS/IC, bladder pain syndrome/interstitial cystitis; DMSO, dimethyl sulfoxide; UTI, urinary tract infection.
[a]If symptoms improve, taper should be stopped, or if side effects persist more than a day or two, the patient should be maintained on the lowest dose previously tolerated for up to 2 weeks to determine maximal benefit.

of certain food and behaviors improves symptoms.[115] Interventions such as pelvic floor exercises and bladder training have also been shown to improve symptoms, increase latency between voids, and increase void volumes, albeit mostly in uncontrolled studies.[127–132] Self-care and stress reduction can improve symptoms and improve patients' sense of control in their treatment strategy.[133,134]

The second line of therapy involves physical therapy; oral medications including tricyclic antidepressants, hydroxyzine, cimetidine, and pentosan polysulfate (PPS) sodium; or bladder intravesical therapy. Pelvic floor physical therapy with myofascial trigger point release, connective tissue release, and muscle coordination training leads to symptom improvement in over 50% of participants, and has shown significant improvement compared to sham therapy in one randomized controlled trial using highly trained therapists.[130–132] Use of amitriptyline, a tricyclic antidepressant, has demonstrated improvement of symptoms in patients with IC/BPS ranging from 50 to 77%, but efficacy is highly dependent on tolerance of dose increases, with many individuals unable to tolerate therapeutic doses due to side effects, including sedation, nausea, and lightheadedness.[10,135,136]

Hydroxyzine is a H1-histamine receptor antagonist that blocks activation of mast cells and has very few side effects beyond sedation.[137] A case series cited significant symptomatic improvement of 40%, but no significant improvement was noted in a recent underpowered randomized clinical study.[138–140] Cimetidine has limited data to support its benefit, which includes only one randomized control trial, but was included in the AUA second-line therapies also due to no serious adverse events.[10,141]

PPS is thought to reduce urothelial permeability by reenforcing the GAG layer. PPS has been approved by the Food and Drug Administration (FDA) for the treatment of IC/BPS and modestly improves urinary, frequency, and pain, especially in patients with ulcerative IC/BPS. The drug is generally well tolerated, with adverse events of nausea, vomiting, diarrhea, and headache, as well as rare reversible alopecia.[137,142–146] However, two randomized control studies showed no improvement with PPS, although one was underpowered.[140,147]

The most common intravesical therapies are dimethyl sulfoxide (DMSO), lidocaine, or heparin; however, other GAGs and intravesical agents have been used.[10] DMSO is the only FDA-approved intravesical IC/BPS treatment; its mechanism is thought to encompass a combination of an anti-inflammatory response, collagen dissolution, and detrusor relaxation, and the drug may be used in "cocktail" combinations with other intravesical instillations.[146,148,149] Intravesical treatment demonstrated a 47 to 93% rate of improvement in symptoms in randomized crossover trials, with greater improvement in patient with ulcerative IC/BPS.[150–152] Treatment relapse is 35 to 40% within 8 weeks, but patients are often responsive to repeat treatment.[151] However, some patients cannot tolerate the side effect profile (including pain after instillation and garlic odor), and there is some evidence that it may cause bladder injury.[153,154]

Lidocaine is a local anesthetic with anti-inflammatory properties that has shown symptomatic improvement both alone and with other intravesical medication.[155,156] Intravesical heparin is part of the GAG family of mucopolysaccharides whose mechanism of action is postulated to promote growth of the urothelium.[146,148] Heparin has also

been shown to improve symptoms of IC/BPS between 56 and 94% and has a benign side effect profile, similar to placebo.[157–159] Although not described in the AUA guidelines, several other intravesical treatments for the management of IC/BPS pain exist. Bacillus Calmette-Guerin (BCG) is believed to work through modulation of an exaggerated immune response and has adverse event profiles comparable to placebo.[148] Instillation of oxybutynin, an anticholinergic used to treat overactive bladder, has also been shown to improve IC/BPS symptoms for some patients.[148] Other intravesical treatments include GAG mucopolysaccharides such as chondroitin sulfate. Steroids are often used in conjunction with other intravesical treatments for their anti-inflammatory effects. While steroids and other intravesical GAGs are not on the AUA treatment guideline, they are commonly used in practice.[10] Less frequently used treatments include capsaicin and resiniferatoxin, which are thought to desensitize neuronal afferents,[160] and disodium cromoglycate, better known for use in allergic reactions, and thought to exert its effects by inhibiting mast cells. These therapies may be considered in refractory cases.[161]

The third-line options include cystoscopy with hydrodistention under anesthesia and fulguration of Hunner's lesions. Hydrodistension with and without instillation additives has been shown to be an effective therapeutic procedure for IC/BPS and is generally a safe procedure other than rare reports of bladder rupture.[162–164] However, relief of symptoms from hydrodistension therapy has been shown to decline over the time scale of months, with a wide variation in efficacy thought to be partly due to many different practices for hydrodistention.[19,80,165,166] Greater duration of therapy has been found in patients with ulcerative IC/PBS and in patients without comorbidities such as IBS.[167] Hunner's lesions are infrequent, but if they are found, fulguration leads to improvement in more than 90% of patients, possibly pointing toward a possible dichotomy of classical ulcerative IC/BPS and nonulcerative IC/BPS.[149,168] However, almost half of patients will require retreatment within the timeframe of 2 to 5 years.[169,170]

The fourth line of treatment is intradetrusor botulinum toxin A (BoNT/A) or neuromodulation. BoNT/A is a neurotoxic protein that can be injected intravesically into the detrusor muscles and has been shown to lead to an improvement in IC/BPS symptoms through flaccid paralysis of the detrusor.[171,172] Observational studies and randomized prospective studies of this off-label use have also supported a high response rate to BoNT/A among IC/BPS patients, but long-term data are lacking, and patients need to be open to performing self-catheterization if they have initial urinary retention.[159,173,174]

While sacral neuromodulation is not specifically FDA indicated for IC/BPS, a significant body of literature supports its effectiveness in some refractory cases. Multiple prospective, nonrandomized studies have found statistically (and clinically) significant improvements in pain, frequency, voided volumes, quality-of-life scores, or opioid usage.[175–178] Long-term success rates from two small studies with average follow-ups of around 5 years are approximately 72 to 78%, but only 50 to 60% of patients were eligible for permanent implantation.[179,180] Explantation rates vary among studies between 0 and 50%.[181] Given high cost, invasiveness, and lack of randomized efficacy data, neuromodulation should be limited to patients with significant symptom burden who have failed multiple conservative treatment options.

The fifth line of treatment is the neuromodulating drug cyclosporine A. Cyclosporine A, a calcineurin inhibitor, is a rarely employed treatment. Several randomized control studies and prospective cohorts have supported improvement in quality of life, decreased pain, and increased bladder capacity.[182–186] Of note, the benefits of the low-dose cyclosporine A reportedly used must be weighed against side effects such as hypertension and renal function impairment, which appear to resolve after discontinuation, at least in the short term.[186–188]

The sixth and final line of therapy is more radical surgical treatment such as diversion with or without cystectomy and substitution cystoplasty. Very few patients will ever progress to this level of treatment, but small studies suggest that this can relieve patients of irritative voiding symptoms and particularly may be useful for those with a fixed small bladder capacity. Unfortunately, some patients will continue to report pain symptoms persisting even after these radical procedures, although one center has described long-term complete pain relief in 28/38 individuals followed up for an average of 5 years in a period spanning two decades.[189] This group was defined using the strict NIDDK research criteria of note.

These guidelines represent a heterogeneous group of treatments, reflecting IC/BPS' multifactorial pathophysiologic causes. Many of the choices result in modest symptom improvement, possible due to the long latency from onset of symptoms to start of treatment. If treatment is instituted soon after onset of symptoms, outcomes may be better; when treated within an average latency of diagnosis of 2½ years, 80% of patients with IC/BPS has significant symptom resolution within 6 months of treatment.[114] Notable also is the heterogeneity of treatments used across practitioners. In a study of the 581 women in the ICDB cohort, 183 different treatments were prescribed by physicians, and there were 90 treatments unique to one participant only.[190] Outside of these guidelines, several complementary medicines have shown benefit in small trials and might also be considered for IC/PBS treatment.[191,192] Oral supplements include naturally occurring GAG mucopolysaccharides such as hyaluronic acid and chondroitin sulfate, and aloe vera, as well as bioflavonoids.

Conclusion

The management of IC/BPS will evolve with improved understanding of this condition that involves both central and peripheral contributors. There is significant promise in identifying central markers in patients who may develop vulnerability for IC/BPS symptoms later in life. It is essential to remember that this is a pain condition and to employ early, multimodal therapies after doing a thorough evaluation for all potential contributing factors, especially given the nature of pelvic cross-organ sensitization.

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