What's New in the Diagnosis and Management of Painful Bladder Syndrome/Interstitial Cystitis?

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Painful bladder syndrome/interstitial cystitis (PBS/IC) is a controversial subject. Despite its many controversies, recent data on diagnostics show that cystoscopy and hydrodistension findings may not be sensitive or specific. Diagnosis is suggested primarily on the basis of history. Antiproliferative factor and Tamm-Horsfall protein are novel tests that may prove to be worthwhile pending future studies. Currently, there is no single diagnostic gold standard. Recent data on therapeutics show that, among oral therapies, amitriptyline and pentosan are efficacious. For best response, pentosan should be initiated early and used for a minimum of 6 months. Immune-modulating agents show promise but are limited by side effects. Intravesical alkalinized lidocaine with heparin may be effective for rapid symptom relief, pending results of prospective randomized trials. Intravesical botulinum toxin A, bacille Calmette-Guérin, and sacral neuromodulation may have a role in select patients.

Introduction

Much has changed in our understanding of the painful bladder syndrome/interstitial cystitis (PBS/IC) over time. For years, clinicians marginalized PBS/IC patients. A 1944 Mayo Clinic report [1] stated that "Patients who have this disease are frequently considered neurotics." In 1979, the 4th edition of *Campbell's Urology* listed IC in a chapter titled, "Psychosomatic Aspects of Urology," recognizing the association between emotional stress and interstitial cystitis [2]. The chapter cited the case of a 29-year-old woman with IC and a chronic history of psychologic abuse, concluding that "her bladder had come to serve as a pathway for the discharge of unconscious hatreds."

Against this backdrop, urologists began to study the disorder. We know that PBS/IC has a pathophysiology, and can be treated effectively. It is now understood (albeit with controversy) that PBS/IC generally involves epithelial dysfunction, mast cell activation, and as the disease becomes more severe, neural activation and upregulation with inappropriate nociceptive pain signaling [3–8]. Several broad themes have emerged. The bladder has a limited and stereotypical repertoire of responses to injury, regardless of the nature of the initial injury [9,10]. It is possible that the initial injury may also reflect a host with limited reserve to protect the bladder [11•]. Some patients may have prior central (limbic system) sensitization, so that their bladder may be an "accident waiting to happen" [12••]. Neural upregulation is also important to understand the clinical manifestations [8,9,13•]. Patients exhibit bladder hypersensitivity and allodynia, particularly as disease progresses over time [14].

Likewise, where no diagnostic criteria existed 30 years earlier, Messing and Stamey [15] proposed a cystoscopy-based diagnostics criteria in 1978. Subsequently, in 1987, the National Institutes of Arthritis Diabetes Digestive and Kidney Diseases (NIDDK) research criteria became widely adopted [16]. More recent data show the NIDDK criteria miss the diagnosis in 60% of patients, which may explain delays from symptom onset to diagnosis of 2–7 years [13•,14,17]. Many clinicians now accept that PBS/IC is diagnosed using symptom-based criteria [18••]. Treatment has also progressed. Where once clinicians had little to offer patients other than cystoscopy with hydrodistension, oral and intravesical therapies have shown efficacy, and increased experience with neuromodulation has raised possibilities. This article discusses recent data and outlines current concepts in the diagnosis and management of PBS/IC.

Diagnosis

Many clinicians rely on the NIDDK criteria. The NIDDK criteria were based on expert consensus to define strict, homogenous criteria for patient recruitment into research trials, and were not based on hard evidence [15]. Some

Table 1. Common symptoms

Symptom	Patients, %
Urinary urgency	57–98
Daytime frequency	84–97
Pain with voiding or dysuria	71–98
Nocturia	44–90
Dyspareunia (women)	46–80
Subjective sensation of bladder spasms	50–74
Pubic pressure	60–71
Suprapubic pain	39–71
Pubic pressure	60–71
Depression	55–67
Perineal pain	25–56
Genital pain (men)	40–50
Rectal pain (men)	30–32

(*Adapted from* Teichman et al. [27], Ito et al. [28], Parsons et al. [29]; Berger et al. [32].)

criteria were established for practical considerations for research trials, for example, excluding diagnosis in children under age 18. In fact, PBS/IC occurs in children [19]. The NIDDK diagnosis mandates cystoscopy findings of Hunner's ulcer, glomerulations, and/or reduced anesthetic capacity. Recent data challenge these criteria [20]. Cystoscopy and hydrodistension criteria are not sensitive or specific [21,22,23••]. Many patients whose clinical symptoms are highly suggestive of PBS/IC do not satisfy strict cystoscopic criteria [16]. Patients diagnosed clinically (without cystoscopy and hydrodistension) seem to be little different from patients with NIDDK criteria, except that NIDDK patients tend to have greater pain [24•]. A recent multicenter report divided subjects with PBS/IC undergoing cystoscopy and hydrodistension into NIDDK criteria and noncriteria patients [23••]. NIDDK criteria subjects had a median anesthetic capacity of 750 mL compared with 1000 mL for noncriteria subjects. Despite these apparent differences, there were no differences in urine marker levels or bladder biopsy features of NIDDK criteria and noncriteria subjects. We infer that cystoscopic criteria define an arbitrary threshold for diagnosis: 39%–60% of patients have minimal reduction in capacity, minimal or scant glomerulations, and no consistent urine marker or bladder biopsy findings [16,21,22,24•,25•]. Positive cystoscopy findings may confirm PBS/IC—and may define quite well an advanced severity of PBS/IC—but negative cystoscopy findings also do not exclude PBS/IC. This statement applies to all diagnostic tests reviewed here: a positive test may indicate PBS/IC, but a negative test does not necessarily exclude it.

In 2003, three separate consensus panels (United States, Europe, and Japan) reviewed diagnostic criteria [26]. The American and Japanese panels could not reach consensus on cystoscopy. In contrast, the European panel felt that cystoscopy and hydrodistension, and bladder biopsy for increased mast cells, were necessary for diagnosis. Bladder biopsy findings are problematic for diagnostics. Mast cell counts are significantly increased primarily in the presence of Hunner's ulcer, which is a rare finding, and thus mast cell counts are not significantly elevated in most patients [5,6]. There is no correlation between cystoscopic findings and any urinary markers or biopsy features reported [23••,25•]. (Again, a positive test may be diagnostic, but most patients suspected of having PBS/IC test negative.)

All three consensus panels concluded that the diagnosis is suspected on the basis of history, physical examination, and laboratory tests, including negative urinalysis, negative urine culture, negative cytology, and possibly cystoscopy findings [25•]. If PBS/IC is essentially a symptom-based diagnosis, it is relevant to appreciate the cardinal symptoms (Table 1). Although pain is commonly present at the time of diagnosis, many patients have urgency, frequency, and nocturia early, and pain often develops later [27,28]. Thus, early on, pain may not be obvious [14,29]. No symptoms listed in Table 1 are specific to PBS/IC.

Some clinicians are reluctant to diagnose PBS/IC in the absence of pain, and undoubtedly, the recent move to rename the disorder from IC to PBS/IC will confirm this reluctance. Given the common features of urgency and frequency with both IC and overactive bladder, it would be convenient to distinguish patients on the presence or absence of bladder pain, respectively [30•]. Regrettably, there is often not a "clean" distinction and differences may be subtle. In the early phase of disease, many PBS/IC patients report no pain, or report pressure or discomfort rather than pain [14,19]. Some patients deny pressure, discomfort, or pain, yet indicate that they do have pain when asked if sex is painful [17]. Thus, clinicians should inquire of "pressure" or "discomfort" when patients deny "pain," in order to elicit early-phase disease, and inquire of specific triggers (sex, food, menses) [14,17,27]. Pain or pressure may not always localize to the bladder, and may instead localize elsewhere in the pelvis [31]. Hand [8] reported that 29% of patients had pain in a neighboring region. Rectal pain occurs in 30%–32% and genital pain in 40%–50% of men with PBS/IC [32,33]. Pain or pressure localization is variable, may wax and wane, and pain character may vary over time [7,14,17,26,34]. Urgency is common to both PBS/IC and OAB. A recent study showed that PBS/IC patients may describe their urgency differently than overactive bladder patients [35]. PBS/IC patients are more likely to link their urgency with relief of pain after they void, rather than urgency as an impending warning sign of incontinence [36••].

Given that patients present with urgency, frequency, nocturia, and dysuria, it is understandable that patients are often misdiagnosed with recurrent bacterial cystitis.

Table 2. Novel diagnostic tests

Proposed tests	Positives	Negatives
APF	High sensitivity; APF abnormalities seen in multiple racial groups	Validated only in NIDDK cases; test not reproduced yet outside original laboratory
THP	Appears sensitive and specific	Test difficult to perform; limited number of patients and controls tested so far
Intravesical anesthetic challenge	Easy to perform	No randomized, published trials published

APF—anti-proliferative factor; NIDDK—National Institute of Diabetes and Digestive and Kidney Diseases; THP—Tamm-Horsfall protein.

In one study, the single most common prior diagnosis was recurrent bacterial cystitis, yet only 1 of 19 patients (5%) diagnosed had a prior positive urine culture [14]. Even among urologists, antibiotics are the most common treatment for PBS/IC [37]. Similarly, it is understandable that patients may be diagnosed with gynecologic disorders. In one study, subjects presented to urogynecologists with chronic pelvic pain and were initially diagnosed with chronic pelvic pain, vestibulitis/vulvodynia, dyspareunia, or endometriosis in 76% of cases, yet 84% were found to have PBS/IC [38]. Premenstrual flares are common, raising endometriosis as a diagnosis [14,17,25•,32]. However, bladder pain and micturition frequency are both increased before and during menses compared with baseline among PBS/IC patients [39•]. Dyspareunia occurs in up to 87% of patients [26,32]. Fear of sex-related pain may impair other aspects of female sexual function [40]. PBS/IC patients fare worse in all domains of the Female Sexual Function Index compared with controls [41,42•]. Thus, patients may present for "gynecologic" pain, dyspareunia, or sexual dysfunction. The nature of symptoms may not be appreciated unless a voiding history or diary are obtained.

An obvious concern is that there is no "hard data"—a reliable diagnostic test—on which to base the diagnosis. Many clinicians feel uneasy to diagnose and "label" a patient, given that the PBS/IC diagnosis connotes a chronic and potentially debilitating condition. Nonetheless, all three consensus panels concluded that diagnosis is suggested mostly from history and physical examination [25•]. All patients should have urinalysis and urine culture to exclude hematuria and infection. Where appropriate, additional studies to exclude bladder cancer (urine cytology, cystoscopy) are warranted. Two cautionary reports validate that bladder cancer can present with irritative voiding complaints suggestive of PBS/IC. However, in nonsmoking women younger than age 40 who do not have occupational or other risks for transitional cell cancer, in the absence of hematuria, the risk of bladder cancer is low. In other patients, the risk is higher and cystoscopy warranted [43,44]. Most urologists would likely feel uncomfortable without excluding obvious bladder pathology by at least performing cystoscopy either with the patient awake or an anesthetic cystoscopy with hydrodistension. Where appropriate, additional studies (imaging) may be considered to exclude other mimicking disorders.

Some novel tests have been described recently: anti-proliferative factor (APF), Tamm-Horsfall protein (THP), and intravesical anesthetic challenge (Table 2). APF is a peptide growth inhibitor. It induces reversible inhibition of heparin-binding epidermal growth factor-like growth factor (HB-EGF) production and normal bladder epithelial cell proliferation. Using NIDDK criteria as a diagnostic gold standard, increased APF activity has a sensitivity and specificity postulated at 94% and 95%, respectively [45]. It may modulate cell permeability [5]. High urinary APF, low HB-EGF, and low epidermal growth factor have been linked to IC patients with many racial backgrounds compared with age-matched asymptomatic women [46]. It is possible that APF can be used to gauge response to therapy [47]. However, in a study of 33 PBS/IC subjects undergoing cystoscopy with hydrodistension under anesthesia, 12 subjects (36%) had symptom improvement ≥ 30% [48•]. Urine APF decreased and urine HB-EGF increased after hydrodistension. However, the APF increased for all subjects, regardless of symptom improvement, and no correlation was seen between postoperative symptoms and change in APF levels. It is not clear if APF is a marker for disease severity, voiding frequency, or some other aspect of PBS/IC. One study of men diagnosed with PBS/IC or chronic pelvic pain syndrome (CPPS) showed abnormal APF findings in the PBS/IC cohort compared with the CPPS cohort, $P = 0.06$ [49]. Based on study findings, the authors report that APF performs well, distinguishing PBS/IC from CPPS. To date, APF has only been measured at the University of Maryland. Further studies are required to determine if it is reproducible. Importantly, APF studies to date have characterized NIDDK-criteria IC subjects. It would be particularly useful for early diagnosis if abnormal APF levels occur with early phase, mild PBS/IC. APF may prove invaluable.

Sialic acid content of THP is a novel finding that awaits further validation [10]. Urine contains low molecular weight cations that could potentially induce mucosal injury. THP is secreted by the renal tubular cells. THP has a surface glycoprotein, sialic acid, that appears to protect bladder urothelium from interaction from chemicals or bacteria [50]. In a study in which THP was isolated from the urine of normals and IC/PBS subjects, THP showed greater activity to protect cultured cells from protamine-induced injury from normals compared with

Table 3. Treatment options

Therapy	Positives	Negatives
Dietary	Easy to do; inexpensive	Patients often unsure which foods trigger symptoms
Stress reduction	Noninvasive	Not easy to reduce many stressors; no proven benefit
Pentosan	Proven efficacy; well-tolerated	Long-term therapy required; expensive
Amitriptyline	Proven efficacy; inexpensive	Side effects
Hydroxyzine	Inexpensive; trend to enhanced efficacy in combination with pentosan	Unproven benefit as monotherapy; side effects
Cyclosporine A	Response better than pentosan	Side effects; symptoms return after cessation of therapy
Intravesical bacille Calmette-Guérin	Readily available; proven efficacy	Low efficacy
Cystoscopy with hydrodistension	Easily performed; one act of motivation for patient	Response typically lasts only 2–3 months
Neuromodulation	May yield dramatic improvement	No randomized trials; long-term data lacking; expensive
Intravesical alkalinized lidocaine (+ heparin)	May yield dramatic improvement; office-based; may be done at home	Randomized trial data pending
Intravesical botulinum A toxin injection	May yield dramatic improvement	Side effects include urinary retention; repeat treatment required

IC/PBS-derived THP [51]. Comparing normals and IC/PBS THP, IC/PBS THP was desialylated and lost its protective activity implying that sialylation is vital to its activity as a protective urinary macromolecule [52]. In this scenario, abnormal THP may fail to neutralize toxins, leaving them more readily able to interact with bladder epithelium, and begin the inciting process.

A more practical (albeit controversial) and older approach has been intravesical administration of potassium to provoke symptoms [4,5]. One advantage of the potassium test is that it can identify early phase (minimally symptomatic) patients, and reproduce or "provoke" their symptoms. Some patients report urgency and not pain when provoked with potassium chloride (KCl) [27]. Newer versions of the test have emerged, using a potassium-based instillation in urodynamics, and seeing if the filling phase has lower capacity compared with water instillation [53]. Even this modified version of potassium testing is controversial [54]. The potassium test and its modified versions appear not to be performed commonly, in part, possibly due to physician reluctance to provoke pain in their patients. Again, a positive test means something, whereas a negative test does not necessarily indicate normal.

Instead, some clinicians advocate testing for bladder hypersensitivity by an intravesical anesthetic challenge [29]. There are several versions. In one version, a 14 mL solution alkalinized lidocaine with heparin is placed via 10 Fr hydrophilic catheter in the bladder, the catheter is removed, and the patient is allowed to walk around the clinic for an hour. If the patient reports that pelvic pain disappears or improves more than 50% from baseline, the test is considered positive. Other versions use similar small volumes of alkalinized lidocaine with or without heparin. (We caution against using bupivacaine due to potential cardiotoxicity if absorbed systemically.) To our knowledge, there is no published data on using this test to diagnose. Having performed the test, it is instructive to patients to see their bladder pain improve dramatically from an instillation, and physicians who are disinclined to perform the KCl test due to fear of causing patient pain would likely find alkalinized lidocaine instillation more palatable. Other versions include performing urodynamics before and after intravesical lidocaine administration to determine if capacity increases [55]. The theme for all test versions is that reduction or elimination of pain with intravesical anesthetic challenge is evidence (conceptually) of bladder origin pain. Patients who have no pain at the time of presentation (but pain intermittently at other times) may test negative to alkalinized lidocaine, and may do better with a KCl test to reproduce their symptoms. KCl testing may still have a role in patients diagnosed with other diagnoses, where rational treatment has failed, and PBS/IC is being considered [28].

Treatment

Study diagnostic criteria and outcomes often are not standardized, thus making treatment comparisons difficult. However, effective therapies have emerged (Table 3). A greater appreciation of dietary triggers has lead clinicians to appropriately counsel their patients to avoid coffee, tea, soda, alcohol, citrus fruit and juices, artificial sweeteners, and hot peppers. Mexican food (particularly salsa) is ranked among the more provocative triggers [56•].

Limited, open-label reports using calcium glycerophosphate show that nearly three quarters of patients report reduced food triggers after taking calcium glycerophosphate [57]. Stress is known to increase pain perception among patients with IC [17]. Stress-induced pain exacerbations may occur via hormonally induced amplification of nociceptive and spinal cord pathways, or via mast cell activation [58,59]. Stress reduction techniques may be helpful, although scientifically they have not been validated [32,60–62]. Complementary approaches (acupuncture, transdermal tibial nerve stimulation) have shown limited success [63,64].

Oral medications show efficacy. Pentosan polysulfate has demonstrated efficacy in prospective, randomized, double-blinded trials. Generally, patients randomly allocated to receive oral pentosan report twice the response rate compared with patients randomly allocated to receive placebo at follow-up after 3 months [65,66]. Duration of therapy is more important than dose. A higher response rate is seen with 6 months compared with 3 months therapy [67••]. A recent trial showed faster response to pentosan if subjects were treated both by oral and intravesical dosing compared with oral dosing alone [68•]. Another recent report showed that subjects treated with pentosan within 3 months of diagnosis (early treatment) had higher response rates compared with subjects treated after being diagnosed 2 years earlier (delayed treatment). Our interpretation is that early initiation of long-term therapy before central sensitization leads to improved outcomes. The presumed mechanism of action is to coat the bladder epithelium, although pentosan has additional effects. In an attempt to enhance clinical response, various authors have suggested multimodal therapy, using drugs for different pathways of PBS/IC pathophysiology (epithelium, mast cells, pain). Hydroxyzine has been tested in combination with pentosan in a randomized, prospective, double-blinded trial [56•]. Regrettably, the study was underpowered. Although patients randomly allocated to receive pentosan had a statistically significant better response than patients receiving double placebo or hydroxyzine plus placebo, the highest response rate was seen with patients randomly allocated to receive combination pentosan and hydroxyzine. It is unlikely that an appropriately powered study will be repeated, and clinicians will have to decide whether combination pentosan and hydroxyzine are better than pentosan alone. We believe combination therapy is better.

Amitriptyline has been used for many years. However, only recently has efficacy been demonstrated in a prospective, randomized, double-blinded trial [69]. Subjects randomly allocated to receive amitriptyline had a significant reduction in symptom and problem index scores. However, anticholinergic side effects occurred in 92% of subjects receiving medication versus 21% receiving placebo. The dropout rate was identical in both groups. In a follow-up, open-label trial, 94 subjects were given amitriptyline and followed for a mean of 19 months. Subjects self-titrated, and the mean dose was 55 mg. Overall response was 64%, with no difference seen whether subjects were NIDDK or non-NIDDK criteria patients. Anticholinergic side effects occurred in 84%. The dropout rate was 31%. Not all antidepressants in this class are effective [70].

The finding of autoantibodies in some patients has generated the idea of using immune-modulating agents. In a randomized comparative study of 64 NIDDK criteria subjects, cyclosporine A was compared with pentosan. The end points included daily micturition frequency, voided volume, number of nocturia episodes, O'Leary-Sant symptom and problem indexes, visual analog scale for pain, and subjective global response assessment. Cyclosporine A was superior in all parameters at 6 months [71•]. However, only 29 subjects completed the full 6-month follow-up and there were more adverse events noted in the cyclosporine arm. In another retrospective analysis of 23 IC subjects treated with cyclosporine A for 1 year, there was decreased number of voids per 24 hours and increased voided volumes and maximal bladder capacities. The therapeutic effect of cyclosporine A was maintained throughout follow-up. However, symptoms recurred after cessation of cyclosporine A [72]. A recent study compared 2 g of mycophenolate daily versus placebo in a randomized, double-blinded trial of refractory PBS/IC patients. The study was terminated early as patients on mycophenolate fared worse than patients on placebo [73].

Surprisingly, cystoscopy with hydrodistension under general anesthesia has received little scrutiny despite being the most widely used surgical treatment for PBS/IC [30•]. In one study, 60% of subjects reported global symptom improvement > 50% with a mean duration of response of 2 months [24•]. Similar data have been reported recently by others.

Several open-label trials using sacral neuromodulation have reported symptom improvement [74]. One study of 21 subjects with mean follow-up of 15 months reported decreased narcotic requirements and subjective pelvic pain after S3 neuromodulation [75]. Of the 18 subjects using narcotics for pain control before neuromodulation, four ceased using narcotics after neuromodulation. Mean narcotic use overall decreased by 36%. In a prospective study of 27 refractory subjects, implantation of sacral nerve stimulator showed improvements in urinary frequency, voided volumes, nocturia, and pain after a mean follow-up of 14 months [76]. One prospective cohort showed particular improvement in the presence of PBS/IC and pelvic floor dysfunction. In a study of 64 subjects, a symptomatic improvement of 50% in symptoms and quality of life was noted in 80% of patients after a mean follow-up of 24 months [77]. Neuromodulation should not be considered a "quick fix." A study reporting on 17 subjects who had sacral neuromodulation with minimum 12 months of follow-up reported that of seven PBS/IC

subjects, the average number of reprogramming sessions was 6.9 per patient [78••]. Another study indicates that the reprogramming burden is not onerous [79•].

An interesting finding is that abnormal APF normalizes in patients who respond to neuromodulation [43]. Sacral neuromodulation is thought to desensitize unmyelinated C-fiber afferents [72]. It raises an interesting possibility that desensitization of sacral nerve afferents leads to decreased expression of bladder epithelium peptides (APF). There likely is some effect on efferent pathways [80]. More research is required. Moreover, a limitation of interpreting neuromodulation data is that there have been no randomized, double-blinded trials for PBS/IC. It is likely that the invasive (and expensive) nature of neuromodulation will preclude such a blinded trial from being conducted. Long-term follow-up of neuromodulation for overactive bladder shows sustained efficacy, but similar long-term follow-up for PBS/IC is lacking. It is critical that patients be selected appropriately from the test stimulation. The stated indication for sacral nerve stimulation is treatment of intractable urge urinary incontinence, refractory urinary urgency–frequency syndrome, nonobstructive retention, and inability to initiate normal micturition.

Intravesical bacille Calmette-Guérin (BCG) showed initial success in early trials. In a double-blind pilot trial, 30 patients were randomly allocated to receive six weekly instillations of BCG or placebo. Using patient-rated assessment, 60% of BCG-treated patients versus 27% of controls had success at a mean follow-up of 8 months [81]. In a larger study, 265 NIDDK criteria subjects were randomly assigned in a double-blinded fashion to intravesical BCG or placebo for 6 weekly instillations [82]. At 34 weeks, patients were assessed for global improvement, and secondarily for voiding diary, pain, urgency, and validated questionnaire results. Response rates for primary outcome measure (global improvement) were 21% for BCG versus 12% for placebo ($P = 0.06$). Secondary outcomes showed some improvement. Among responders, continued response was seen durable to 68 weeks [83]. Among patients who failed a first round of BCG, a second round of BCG achieved an 18% response rate [84]. We view these results as evidence that few PBS/IC patients derive benefit from intravesical BCG.

Recently, open-label trials of intravesical instillations of lidocaine, heparin, and sodium bicarbonate were reported. Alkalinized lidocaine penetrates bladder epithelium, and is safe even with a dosage of up to 5 mg/kg [85]. In an initial open-label trial of patients given instillations of 40,000 U heparin, 3 mL of sodium bicarbonate combined with 8 mL of 1% or 2% lidocaine [86••]. Patients receiving 1% or 2% lidocaine-based instillations reported 75% versus 94% significant symptom relief after a single instillation ($P < 0.01$), respectively. Subjects receiving the 2% lidocaine-based instillations three times weekly for 2 weeks reported sustained relief in 80% of subjects 2 weeks after completion of the instillations. In a separate open-label trial of 23 patients treated with lidocaine, heparin, and sodium bicarbonate instillations three times weekly for 3 weeks, 65% reported global improvement (50% reduction in overall symptoms) and 57% reported resolution of dyspareunia at a follow-up of 8 months [87••]. Subjects responded better if they had bladder tenderness alone versus multiple tender locations. These results are encouraging. In our experience, about two thirds of patients respond favorably, and among responders, improvements are typically dramatic.

The popularity and success of botulinum toxin type A injections for multiple pain disorders has lead to some trials for PBS/IC. A recent trial studied 15 subjects with 1-year follow-up [88•]. Subjects were injected with 200 U Botox (Allergan, Irvine, CA) diluted in 20 mL of 0.9% sodium chloride in a grid-like fashion on the trigone and lateral walls to map the area expected where supravesical nerves might course. Using voiding diary, visual analog scale, and urodynamics before and after treatment, 1-month results showed significant improvement in daytime and nighttime frequency, 87% of subjects had subjective improvement in bladder pain, and mean cystometric capacity increased from 256 mL to 361 mL. Impaired contractility occurred in 60% of subjects. However, at 3 months, the results were similar. At 5 months, bladder pain recurred in 73%. At 1 year, bladder pain recurred in all cases. Clinical and urodynamic parameters reverted to baseline. It would appear that successful, temporary relief of PBS/IC can be achieved through botulinum toxin A injections but at risk of need for clean intermittent catheterization [77].

Conclusions

PBS/IC diagnosis remains controversial. Cystoscopy and hydrodistension are no longer considered necessary or even reliable by many experienced clinicians to diagnose. APF and THP may prove to be helpful biomarkers or diagnostic tests if future studies validate their use. Intravesical alkalinized lidocaine challenge may be a straightforward diagnostic test, but current data are absent. The current trend is to diagnose patients by clinical suspicion in the absence of any competing diagnosis. Management includes patient education, dietary and lifestyle counseling, oral therapy, intravesical therapy, and surgery. Recent data suggest early initiation of therapy (pentosan) may be better than delayed therapy. A minimum of 6 months of therapy should be considered. Amitriptyline is effective. Immunemodulating agents such as cyclosporine A or mycophenolate may be effective, although recent data are contradictory and side effects are a limiting factor. Intravesical therapy with alkalinized lidocaine and heparin is effective for rapid relief of symptoms. Recent experiences with intravesical BCG, botulinum A toxin injection, or neuromodulation show that some, select patients may benefit.

Disclosures

Dr. Teichman is an advisor/consultant to Ortho McNeil, Urigen, and Aculight. No further potential conflicts of interest relevant to this article were reported.

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