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# Chronic pelvic pain syndromes: clinical, urodynamic, and urothelial observations

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#### Abstract

Introduction/methods A cohort of 408 patients with bladder pain syndrome/interstitial cystitis (BPS/IC) was evaluated, and findings were discussed in this retrospective chart review. *Results* Based on the chief complaints, they were divided into four subgroups: BPS/IC (n=157), CPP (n=98), vulvodynia/dyspareunia (n=40), and "other" (n=113). Similar findings were found in all four subgroups: complaints of voiding dysfunction (70%), dyspareunia (54%), mean PUF score of  $15.9\pm6.4$ , and a positive potassium sensitivity test in 83%. Urodynamics revealed a maximal urethral pressure of 131 cm of water and an abnormal uroflow in 80%. Urothelial therapy in the form of intravesical therapeutic anesthetic cocktails provided benefit in all groups (50%, 67%, 73%, and 77% for vulvodynia, CPP, BPS/IC, "other").

*Conclusions* All subgroups had similar findings and response to therapy. Five to 10% of patients with chief complaints of stress or urge incontinence or prolapse were also found to have BPS/IC.

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## Introduction

Chronic pelvic pain (CPP) is a challenging and frustrating problem that affects 10% to 15% of all women [1]. Recent data document that patients with CPP often have multiple causes for their pelvic pain syndromes. The bladder is one of the most common pain generators seen in patients with CPP—both in men and women. In the past, the diagnosis of interstitial cystitis (IC) was thought to be a rare disorder associated with severe bladder pain that often was diagnosed only after years of suffering [2]. We are now shifting toward a newer definition of bladder pain syndrome (BPS)/ IC that expands the diagnosis to patients presenting with symptoms of frequency, urgency, and pain in the absence of infection or other pathology [3].

Exclusive reliance on symptom-based diagnosis increases the prevalence of BPS/IC significantly. Although the precise amount of the increase is uncertain, some authors report the prevalence to be as high as 26% [4]. It is clear that BPS/IC represents a spectrum of bladder and pelvic pain disorders that are quite heterogeneous, yet many clinicians consider this higher symptom-based prevalence to be excessive and worry that the new diagnosis is overly inclusive. Patients who are ultimately diagnosed to have PBS/IC may present with various chief complaints such as recurrent bladder infections, dyspareunia, urinary frequency, or CPP. A bladder component of pain is found in 38-85% of women with CPP [5, 6]. Patients with BPS/IC often have more than one pain generator and can present with chief complaints not related to the bladder at all. They often report multiple pain syndromes that involve not only the pelvis but also other parts of the body. Given our understanding of visceral pain syndromes and the neuropathology of chronic pain, this is exactly what we would expect to find in patients with CPP [7].

The purpose of this report is to characterize a cohort of patients who presented to a referral urogynecologic pain center with complaints of various pain and urogynecologic/ pelvic floor disorders and who, after an initial evaluation, were felt to have symptoms that would suggest BPS/IC based on the newer, expanded symptom-based diagnostic criteria. Through this characterization, we hope to better understand this heterogeneous group of patients who are ultimately diagnosed with BPS/IC and therefore to be better able to manage their bladder pain disorders.

## Materials and methods

This retrospective chart review included 408 patients with symptoms that were suggestive to the lead author of at least a component of their symptoms representing BPS/IC. These patients, identified from 1958 new patients, were seen between January 1, 2004 and December 31, 2006 at The Urogynecology Center—a regional referral center for urogynecologic as well as pain disorders. The reason for their referral may have been related to a complaint of pain or it may have related to more traditional urogynecologic problems such as incontinence or prolapse. The clinical diagnosis of BPS/IC was based on a history of pelvic or bladder pain that worsened with bladder filling and typically was associated with a history of frequency or a functional bladder volume of less than four ounces. Institutional Review Board approval was obtained for this retrospective chart review.

Initial evaluation included history, which was assisted with the use of the pelvic pain and urgency frequency (PUF) questionnaire [8], a general urogynecologic questionnaire, and a bladder diary. A pelvic-pain-directed pelvic examination was done, which emphasizes single-digit examination to localize areas of allodynia. The examiner then determines the areas of greatest tenderness and evaluates whether this reproduces an area associated with the patient's symptoms. This exam targets introtial areas, pelvic floor awareness, and trigger points and all other components of the urogenital tract. A traditional urogynecologic exam to evaluate pelvic floor disorders was also done. Urine analysis and/or culture, vaginal cultures (when indicated), were also done with this initial evaluation. If these preliminary findings suggested a bladder pain component to the patient's complaint, the patient underwent multichannel urodynamics using micro-tip catheters and an office cystoscopy to rule out significant bladder pathology and to assist in the evaluation of her pain disorder. Seven days after this initial evaluation, all patients underwent a potassium sensitivity test (PST) as described by Parsons

[6], which was immediately followed by an anesthetic bladder challenge [9]. The vast majority of patients also had at least three therapeutic anesthetic cocktails (TAC) given 1 week apart based upon the patient's perception of the reduction of pain or urinary urgency/frequency symptoms and/or a PUF score of greater than 13. The TAC involves 20 ml of 2% lidocaine, 20,000 units of heparin, and 40 mg of triamcinolone. Additionally, other therapeutic interventions were initiated at the discretion of the physician.

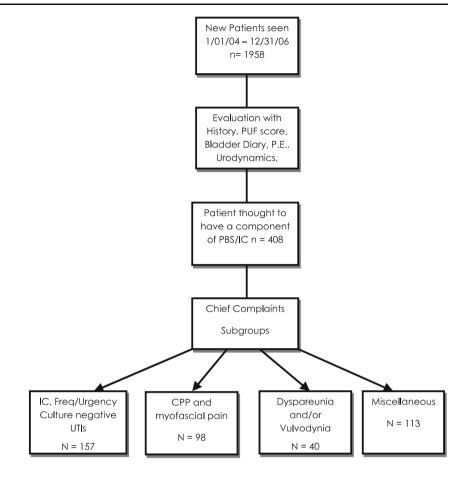
Descriptive statistics were generated for these measures. both overall and within specific subgroups. The Cochrane-Ameritage test for trend was used to assess associations between presence of bladder-based tenderness, pelvic floor tenderness, hypertonic pelvic floor, inflammation found on office cystoscopy, and TAC with PUF scores (<10, 10-20,  $\geq$ 20). ANOVA was used to assess the relationship between urethral pressure and PUF scores. Pearson chi-square tests were performed to assess the bivariate associations of PST pain score ( $\geq 2$  vs. <2), urgency score ( $\geq 2$  vs. <2), positive PST (based on the perception of a noticeable difference between the two solutions used; different vs. no different), abnormal uroflow and maximum urethral pressure (0-<75,75–<120, 120–<165, and  $\geq$ 165) with TAC. We then built a logistic regression model using these factors to assess for multivariable associations with TAC using stepwise selection with p=0.05 to enter and remain in the model.

## Results

The average age of this cohort of patients was  $48.3 \pm 16.1$ (mean $\pm$ SD; range 17–91). The most frequent presenting complaint was related to bladder pain (157 patients) with chief complaints of IC, urinary/frequency, or culturenegative recurrent UTIs. The second most common chief complaint was chronic pelvic pain (98 patients), which included patients who had pelvic myofascial pain disorders. The third was vulvodynia and/or dyspareunia (40 patients). The final group (113 patients) represents patients with miscellaneous chief complaints but included 27 with the chief complaint of stress incontinence, 24 patients with the complaint of urge incontinence, and 21 patients with the complaint of pelvic organ prolapse (see Fig. 1). Additional chief complaints in this miscellaneous group included hematuria, mixed incontinence, fecal incontinence, vesicovaginal fistula, and abnormal vaginal bleeding.

Highlights for the entire cohort include an average PUF score of  $15.9\pm6.4$  with findings of bladder base tenderness in 79% of patients and pelvic floor tenderness in 82%. Hypertonic pelvic floor dysfunction was identified in 70.4% of patients. Urodynamics demonstrated an abnormal uroflow in 80% of patients based on either a non-instrumented study or an instrumented micturition study. An abnormal

Fig. 1 Cohort/Subgroup distributions



uroflow was defined as a "non-Bell curve" appearance in patients with voided volume of over 150 cm<sup>3</sup>. Peak urethral pressures at rest averaged  $131\pm49$  cm H<sub>2</sub>O measured typically at bladder capacity, which averaged  $352\pm140$  cm<sup>3</sup> for this cohort. Of the 321 patients who underwent cystoscopy, 4.4% were found to have Hunner ulcers.

PST was positive in 83% of patients based on the perception of a noticeable difference between the two solutions used, 60% positivity based on the symptom of urgency increased by at least two points, and 59% positivity based on the symptoms of pain increased by at least two points. Therapeutic anesthetic cocktails were felt to be beneficial by 71% of patients. They were most beneficial in patients whose chief complaint represented a bladder pain disorder but were also found to be beneficial in the miscellaneous group, which typically did not present with bladder pain. Also, included in Tables 1 and 2 is a group of 120 patients, which represents a subpopulation of the cohort for which despite the suspicion of BPS/IC the TAC was found not to be helpful. This lack of response was found even though 77% of these patients were noted to have a positive PST. The most common final diagnosis within this subpopulation was myofascial pain (51%).

After this extensive evaluation, 97% of this cohort was found to have more than one diagnosis to explain the symptoms for which they were seeking care. The most common diagnosis involved PBS/IC in 79%, myofascial pain in 50%, and pelvic floor hypertonic dysfunction in 26% with most patients having both BPS/IC and pelvic floor disorders. Tables 1 and 2 summarize the cohort of patients both in its entirety and divided into the four subgroups as noted above.

The presence of bladder-based tenderness, pelvic floor tenderness, and hypertonic pelvic floor findings were all significantly associated with higher PUF scores (p < 0.0001in each case). The degree of inflammation found on office cystoscopy was not associated with PUF score (p=0.264). Increasing urethral pressure was associated with higher PUF scores (p=0.0134). A PST showing a change in pain and urgency scores  $\geq 2$  were associated with higher response rate to TAC (p=0.003 and p=0.002, respectively). The model built using logistic regression to predict response to TAC only retained a single explanatory factor, change in urge score (p=0.002). The entire cohort demonstrated a very high mean peak urethral pressure of  $131\pm$ 49 cm of water; normal for this age group would be considered between 60 and 80 [10]. However, this measure was not associated with the patient's response to TAC (p=0.122). Though it did not remain in the final logistic

# Table 1 Demographics

Average age <sup>a</sup> Most frequent chief complaint	Entire cohort N=408	PSB/IC N=157 50.1 (±16.9) Bladder symptoms	CPP N=98 44.2 (±15.3) CPP	Vulvodynia/ dyspareunia N=40	Miscellaneous N=113 52.9 (±13.8) SUI/UI/POP N=28, 24, 21	TAC not helpful N = 120 47.4 (±17.2) CPP myofascial pain
	48.3 (±16.1) Bladder symptoms			38.0 (±14.6) Vulvodynia/ dyspareunia		
History of dyspareunia	53.9%	43.3%	79.6%	92.5%	32.7%	56.7%
Hx of voiding dysfunction	69.6%	65.6%	69.4%	55.0%	80.5%	63.3%
Hx of recurrent yeast infections	36.5%	33.1%	37.8%	75.0%	26.6%	37.5%
History of recurrent UTI	45.3%	55.4%	43.9%	27.5%	38.9%	41.7%
History of endometriosis	13.2%	8.9%	30.6%	5.0%	7.1%	14.2%
History of fibromyalgia	7.8%	5.7%	10.2%	0.0%	11.5%	6.7%
Recurrent diarrhea	20.1%	18.5%	27.6%	20.0%	15.9%	18.3%
Recurrent constipation	55.6%	54.1%	66.3%	47.5%	51.3%	45.8%
Prior hysterectomy	41.4%	35.7%	50.0%	22.5%	48.7%	38.3%
Prior LAPS evaluation <sup>b</sup>	21.7% (374)	14.8% (142)	48.9% (94)	11.1% (36)	9.8% (102)	25.0% (100)
Childhood bladder dysfunction	16.2%	12.7%	15.3%	22.5%	19.5%	15.0%

<sup>a</sup> Standard deviation

<sup>b</sup>N

regression model, subjects with an abnormal uroflow were more likely to have found TAC helpful (p<0.001 from bivariate analysis). A patient's response to TAC was not associated with PUF score (p=0.458) as patients with high PUF scores had a similar response to TAC as those with low PUF scores.

# Discussion

As clinicians and researchers, we continue to struggle with how to define BPS/IC. It has been a topic of many international meetings over the last 10 years. This report represents a large cohort of patients felt to meet the

## Table 2 Office evaluation/testing results

	Entire cohort N=408	IC/PBS N=157	CPP <i>N</i> =98	Vulvodynia/ dyspareunia N=40	Miscellaneous N=113	TAC not helpful N=120
Average PUF score <sup>a</sup>	15.9 (±6.4; 369)	16.5 (±6.2; 141)	18.3 (±6.2; 89)	16.3 (±6.1; 39)	12.9 (±6.1; 100)	15.3 (±6.7; 100)
Bladder base tenderness <sup>b</sup>	78.6% (388)	82.2% (146)	94.8% (97)	84.6% (39)	56.6% (106)	76.6% (107)
Pelvic floor tenderness <sup>b</sup>	82.4% (391)	86.3% (146)	93.9% (97)	89.7%	63.9% (108)	83.2% (107)
Pelvic floor hypertonus <sup>b</sup>	70.4% (392)	67.6% (148)	82.5% (97)	82.1% (39)	59.3% (108)	72.2% (108)
PST-difference noted <sup>b</sup>	82.8% (402)	81.2% (154)	85.7%	85.0%	81.8% (110)	76.7% (116)
PST—urge increased $\geq 2^{b}$	60.1% (403)	57.1% (154)	70.4%	57.5%	55.8% (111)	48.3% (116)
PST—pain increased ≥2 <sup>b</sup>	58.8% (403)	55.8% (154)	65.3%	62.5%	55.9% (111)	47.4% (116)
First sensation <sup>a</sup>	135 cm <sup>3</sup> (±75; 346)	139 cm <sup>3</sup> (±70; 130)	136 cm <sup>3</sup> (±88; 87)	125 cm <sup>3</sup> (±67; 31)	133 cm <sup>3</sup> (±73; 98)	142 cm <sup>3</sup> (±71; 88)
Cystometric capacity <sup>a</sup>	352 cm <sup>3</sup> (±140; 348)	338 cm <sup>3</sup> (±29; 131)	372 cm <sup>3</sup> (±163; 87)	332 cm <sup>3</sup> (±151; 32)	360 cm <sup>3</sup> (±129; 98)	363 cm <sup>3</sup> (±140; 88)
Maximum urethral pressure <sup>a</sup>	131.0 (±49; 343)	125.1 (±47; 129)	136.7 (±47.9; 85)	141.0 (±57; 32)	131.0 (±49; 97)	128.0 (±52; 88)
Abnormal uroflow	79.7%	76.4%	84.7%	72.5%	82.3%	69.2%
Abnormal cystoscopic vascularity <sup>b</sup>	57.3% (321)	53.9% (115)	51.3% (78)	46.7% (30)	69.4% (98)	50.0% (78)
TAC helpful	70.6%	73.7%	67.3%	50.0%	77.0%	0.0%
Greater than 1 diagnosis <sup>b</sup>	97.0% (396)	97.3% (148)	98.9%	87.5%	98.2% (110)	85.8%

<sup>a</sup> (±Standard deviation; *n*)

b n = the number with documentation of assessment when < total in group

diagnosis of PBS/IC as described by the International Continence Society and who were thoroughly evaluated. It documents the characteristics (clinical, urodynamics, cystoscopic, and urothelial) of the group in the hope that it will elucidate their heterogeneity and potentially help clinicians recognize subpopulations. This should lead to a targeted therapeutic approach that includes the identification and management of each pain generator and its associated dysfunction.

This cohort of patients was made up of 408 patients from 1,958 new patients seen in this practice during this 3-year period for various urogynecologic problems. A very important finding was that 113 patients who were felt to have symptoms compatible with BPS/IC presented with chief complaints that were not associated with any pain disorders, including stress incontinence, urge incontinence, and pelvic organ prolapse. During this same study period. this center saw 441 new patients with a chief complaint of stress incontinence, 259 new patients with a chief complaint of urge incontinence, and 423 patients with chief complaints of pelvic organ prolapse. This establishes the prevalence of BPS/IC in this population of patients that makes up a traditional urogynecologic practice to be 6.1%, 9.3%, and 5.0% in each group, respectively. This center typically identifies these patients and treats their bladder pain disorders prior to treating any non-pain disorder especially if that treatment required surgery. It is well known to all clinicians that surgery can induce and/or flare pre-existing pain disorders. This group of patients with chief complaints that were not related to pain disorders but whose review of systems was positive for these complaints responded equally well to interventions such as TAC. It is also well known that approximately 15% of patients with IC can also have associated detrusor overactivity [11], and it has been the experience of this center that management of both the BPS/IC and the overactive bladder is key to symptom improvement.

The PST is used by many centers to assist in the identification of patients that might have BPS/IC. Its use demonstrates for both the patient and the clinician that the bladder may represent a symptom generator because the introduction of potassium may increase the patient's symptoms such as pain or urgency. This response is generally thought to represent identification of an urothelial dysfunction that allows urinary solutes and cations to penetrate the mucosa depolarizing the sensory nervesespecially c-fibers-that therefore recreating the patient's symptoms. Many authors also feel that a bladder that has c-fiber up-regulation even without a significant urothelial defect may also produce a positive response [12]. There are many clinical circumstances in which c-fiber up-regulation could be present without the patient having interstitial cystitis (based on the more restrictive diagnostic criteria). This is an

example of what some authors would describe as a falsepositive PST [13]. However, we must remember that c-fiber up-regulation is a classic finding in patients with IC, and urothelial-directed treatments still result in favorable responses.

Many centers use the anesthetic bladder challenge that anesthetizes the bladder urothelium to determine if this provides pain relief. This is consistent with the practice commonly used by physicians who specialize in pain management of using a diagnostic anesthetic block. A variety of intravesical therapeutic anesthetic cocktails are commonly used to treat patients with BPS/IC [14], and this approach was used in this cohort of patients even if the PST was found to be negative. This is because many would consider the PST to have a 20% to 30% false-negative rate. The vast majority of patients in this cohort (71%) responded favorably to TAC. This would support that the bladder is a symptom generator and that therapy needs to be directed toward the bladder urothelium and c-fiber up-regulation. The most common urothelial therapy that was offered for this entire cohort of patients was pentosan polysulfate/Elmiron® with 78% of patients being treated with this oral agent as part of a multi-modal approach to their pain.

Pelvic floor hypertonic dysfunction is seen in many patients with various pelvic pain and pelvic floor disorders, including IC, vulvodynia, urgency frequency syndromes, urinary retention, dyspareunia, and obstructed defecation syndromes [15]. Its identification is easily accomplished by a careful history and physical examination. Objective verification can be achieved by urodynamic findings associated with urethral instability and/or hypertonus, surface EMGs, or voiding cystourethrograms. This problem has been reported in the literature for years but is often overlooked in the evaluation of patients with many of these pelvic floor pain disorders. The prevalence of hypertonic pelvic floor dysfunction was demonstrated in this cohort with BPS/IC to be well over 70%. Voiding dysfunction was reported by 70% of the cohort, and urodynamics demonstrated voiding dysfunction in 80%. This is a very important finding, and this symptom resulted in many patients in the past being treated by urethral dilation. It is felt that this voiding dysfunction is a manifestation of the patient's poor relaxation of her pelvic floor during attempts at voiding. This of course represents an intermittent functional bladder neck obstruction in some of our patients. Bladder neck obstruction can easily result in symptoms of urgency and frequency as well as irritated voiding symptoms. Animal research shows that partial urethral obstruction quickly results in c-fiber up-regulation as well as physical changes within the bladder itself and behavioral changes that would be associated with pain and urinary frequency [16]. C-fiber up-regulation is considered by most to represent a key step in the cascade of events that results in urothelial allodynia and bladder up-regulation seen in patients with IC [17].

This cohort of patients demonstrated a history of childhood bladder disorders as suggested by a history of nocturnal enuresis past the age of 6, recurrent bladder infections, and urethral dilations in childhood in 16%. The prevalence of these disorders is typically thought to be in the range of 7% in the normal population [18], and therefore, this study demonstrates at least twice the normal prevalence. While there are many etiologies to childhood urinary dysfunction and many are associated with overactive bladder symptomatology as well as pain disorders. every study has demonstrated a relatively high prevalence of voiding dysfunction in this population. This voiding dysfunction is thought to be the cause of many of the children's urologic problems, including recurrent UTIs, chronic constipation, and vesicoureteral reflux. Therapy directed toward this dysfunctional voiding has been associated with successful management of symptoms. including vesicoureteral reflux in over 50% of patients [19].

Pelvic floor dysfunction is certainly part of the BPS/IC syndrome [20]. The causes of this hypertonic dysfunction can be primary pelvic floor dysfunction as a result of persistence of childhood elimination disorders or can be secondary to one of many potential "insults" to the pelvic floor. Potential insults include direct trauma to the pelvic floor musculature [21] such as obstetrical injury or surgical trauma (such as mesh or permanent suture placement in the muscles). Secondary pelvic floor hypertonic disorders can also occur as part of local or diffuse myofascial pain disorders (such as chronic myofascial back pain disorders, e.g., fibromyalgia) or as the result of "behavioral" triggers like anxiety or insomnia. The most common cause of secondary pelvic floor hypertonic pain and dysfunction involves a viscero-muscular reflex that is often seen in patients with any visceral/chronic pain disorder, including BPS/IC, endometriosis, irritable bowel syndrome, and vulvodynia. The hallmark of any visceral pain syndrome is central sensitization with its neuropathic up-regulation and the development of abnormal sensory processing and pathologic reflexes such as pelvic floor hypertonus. The cascade of visceral pain and pelvic floor dysfunction with its associated voiding dysfunction is a major trigger to the self-perpetuation of visceral pain syndromes such as BPS/IC [22].

One of the most interesting findings in this cohort was the high prevalence of voiding dysfunction that is associated with the findings of high urethral pressure and pelvic floor hypertonic dysfunction. Voiding dysfunction was also associated with a favorable response to TAC. Prior authors have reported hypertonic urethral pressures in patients with IC [23] but not to the magnitude or prevalence demonstrated in this study. This high prevalence of voiding dysfunction and hypertonic urethral pressures points out one of the keys to the persistence of symptoms when the therapies chosen are directed only toward the urothelium and not toward the pelvic floor. This functional voiding disorder results in perpetuation of c-fiber up-regulation and secondarily results in urothelium dysfunction. When therapy is directed toward the pelvic floor dysfunction as well as the urothelium, many have seen a much improved response to therapy in patients with BPS/IC.

Any successful center that specializes in pelvic pain disorders recognizes the importance of early identification and treatment of all pain generators. Pain generators that have been targeted in this group include the urothelium, the pelvic floor, the gastrointestinal tract, and the vulva [24]. These patients were also offered management of their sleep disturbances, anxiety, and depression when reported by the patients. The treatment of the pelvic floor dysfunction was one of the main targets of therapy for this cohort of patients. Treatment modalities used include physical therapy referral for specialized pelvic floor rehabilitation (including biofeedback. myofascial release techniques, and trigger point therapy), pelvic floor trigger point injections using local anesthetics, Botox, as well as the aggressive use of systemic muscle relaxers such as Tizanidine/Zanaflex<sup>®</sup>, cyclobenzaprine/ Flexeril<sup>®</sup>, and compounded baclofen vaginal suppositories. This combined urothelium and pelvic floor directed therapeutic approach will be the subject of an outcome-based analysis in the future from this center.

There are many shortcomings to any retrospective chart review, including missing data, variable follow-up, and issues of selection biases. This center does have a high index of suspicion for BPS/IC but the accepted diagnostic criteria for BPS/IC is a clinical one and certainly that is how this cohort of patients was chosen. All diagnoses were made in a single urogynecologic center, which does encourage internal consistency in diagnosis, interpretation of findings, and management. The accuracy and reproducibility of urethral pressure profilometry has been found to be less than ideal but even with a test-retest variability of 15.4 cm H<sub>2</sub>O (two standard deviations) [25], this cohort would still have elevated urethral pressures. This population of patients may not be generalized to all patient populations since the center is considered a tertiary care center for IC and pelvic pain disorders.

# Conclusions

The purpose of this study was to characterize a large cohort of patients that were thought to have BPS/IC based upon the use of the presently accepted symptom-based diagnostic criteria. This cohort demonstrates a high incidence of childhood bladder disorders and pelvic muscle dysfunction with associated symptoms and findings of voiding dysfunction. The importance of identifying the pelvic floor component of chronic pain disorders was discussed. The cohort also demonstrates a high prevalence of urothelial dysfunction as measured not only by PST but also by response to therapeutic cocktails that involve an anesthetic agent as well as a GAG layer supplement. Predictors of a patient's response to TAC included PST positivity (especially urge score change  $\geq 2$ ) and (in bivariate analysis) abnormal uroflow. A favorable response rate to TAC of 71% points out the importance of the urothelium being one of the therapeutic targets for our management of patients with BPS/IC. The clinician must also be aware that between 5% and 10% of patients with more traditional urogynecologic disorders like urinary incontinence and prolapse may also have BPS/IC.

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