Research Article

Evaluation of outcomes of clinical phenotyping-based treatment for bladder pain syndrome/interstitial cystitis

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Abstract

Introduction: Bladder pain syndrome/Interstitial cystitis (BPS/IC) is clinically of diverse types because different causes contribute to the development of their symptoms. It is important to classify patients into various groups based on the possible etiopathogenesis of their condition. Treatment may be tailored to each specific group according to the possible cause. **Methodology:** Twenty-five patients diagnosed with BPS/IC were categorized into four different clinical phenotypes (CP) based on their history of symptoms, allergy, dysfunctional voiding, neuropathic pain, and the presence of Hunner's ulcer. Some patients could be classified into multiple groups. The patients were given oral pentosan polysulfate, and treatment specific to their CP. Patients in CP1, CP2, and CP3 groups received, respectively hydroxyzine, clonazepam, and amitriptyline. Patients with Hunner's lesions (HL) (CP4) underwent hydro distension and ablation of the lesion, followed by intravesical instillation of heparin and hydrocortisone. The patients were evaluated using the Apollo clinical scoring (ACS) system and their clinical scores were recorded at 1, 3, and 6 month(s). **Results:** Among the 25 patients, 5, 7, 4, and 9 patients were classified into CP 1 – CP4 groups respectively, and were all subjected to ACS assessment. In CP1 group (allergy group), 80% (4/5) of patients responded well to the treatment and 20% (1/5) had unsatisfactory responses. In CP2 group (dysfunctional voiding group), 71.42% (5/7) patients had good, and 28.57% (2/7) had excellent responses. In CP3 group (neuropathic pain group), 28.57% (3/4) patients had excellent, and 75% (1/4) patients had good responses. In CP4 group (HL group), 33.33% (3/9) patients had unsatisfactory, 44.44% (4/9) achieved good, and 22.22% (2/9) had excellent responses. Overall, 16% (4/25) patients had unsatisfactory, 56% (14/25) attained good, and 28% (7/25) had an excellent response at the completion of the study. **Conclusion:** Using clinical phenotyping-based features indicative of etiology could potentially improve treatment outcomes by targeting the specific pathological processes contributing to the patients' symptoms.

Keywords: Clinical phenotypes, Apollo clinical scoring, Interstitial cystitis, Bladder pain syndrome, Hunner's lesions

1. INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) represents a chronic bladder disease and is a combination of heterogeneous clinical entities, ranging from intense transmural inflammation with or without urothelial ulceration of the urinary bladder or a phenomenon occurring outside the bladder, that is, in pelvic floor muscles or nerves, and manifesting as bladder pain with frequency and urgency [1]. It is a syndromic presentation of patients suffering from urinary symptoms consequent to various pathophysiological pathways working in the bladder and non-bladder domains, characterized by a group of symptoms including pelvic pain, especially in urogenital areas, associated with urinary symptoms such as frequency and urgency [2].

Various risk factors and comorbidities might be solely associated or associated, as a causal relationship, with BPS/IC. Type A personality, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and Sjogren's syndrome are, to name a few, conditions that are associated with BPS/IC. Furthermore, it has been recently revealed that mental health was correlated with lower urinary tract symptoms [3].

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It is, therefore, expected that one single treatment cannot be suited for all patients as the etiology of individual patients varies. Etiopathogenesis of this heterogeneous entity is quite variable and if these patients could be classified based on clinical clues to the underlying etiopathogenesis, the therapies specifically addressing these pathogenic mechanisms may attain better results [4]. The objective of this prospective study was to categorize patients with BPS based on their clinical presentation and possible pathogenic processes, and then apply a group-specific treatment modality, depending on the clinical presentation. The outcomes of the group-specific treatment were evaluated periodically for up to 6 months.

A recently published review article found that out of seven randomized control trials, five mentioned a clear beneficial role of oral pentosan polysulfate (PPS) in BPS/IC. The only study that did not perform cystoscopy as a diagnostic means and as an inclusion criterion failed to show any benefit of oral PPS compared to placebo. Two out of three meta-analyses clearly concluded that oral PPS had a positive role in the treatment of BPS/IC. Most studies concluded that oral PPS remains a useful drug for the treatment of BPS/IC, even though it may be effective only in a subgroup of patients. The deficient glucosamine glycan (GAG) layer in the urothelium, which is damaged in BPS, appears to be the reason for the perpetuation of pathogenic mechanisms and pain in these patients. Oral PPS has been found to cover the deficient GAG layer and block the back diffusion of toxic solutes of urine into the interstitium of the bladder, thus causing the healing of tissues [5].

Hydroxyzine is seen, by many urologists, as a first-line treatment for BPS/IC, as mast cells play a major role in allergies. Hydroxyzine is a first-generation histamine receptor antagonist that blocks inflammation by stabilizing the mast cells in addition to blocking the histamine receptors. Since an inflammatory component is involved in the IC, which is triggered presumably through allergic mechanisms and mediated through degranulation of mast cells, hydroxyzine has been shown to mitigate the symptoms of IC [6]. The dose typically starts at 10 mg daily, given at bedtime, and should be slowly titrated to 50 – 75 mg. Prolonged administration (3 – 4 months) may be needed before any beneficial effect shows. In an open-label study, 40% of patients receiving hydroxyzine for more than 3 months reported improvement [7]. However, in a well-designed trial supported by the NIDDK, hydroxyzine did not yield consistent results [8].

Amitriptyline, an oral tricyclic antidepressant, is commonly used for the treatment of BPS/IC. It is a neuromodulator that inhibits the presynaptic reuptake of serotonin and noradrenaline. This lowers pain signals to the brain by modulating neuronal function [8]. The only available placebo-controlled randomized controlled trial proved that amitriptyline could effectively improve symptoms of patients with BPS/IC [9]. Long-term follow-up (19.0 – 12.5 months) of patients on amitriptyline showed a response rate of 64%. Other studies recommended that amitriptyline should be given at the lowest possible dose (10 mg daily) and then titrated to the effective dose [10,11]. Relaxation of an overactive pelvic floor can be achieved by the use of specific skeletal muscle relaxants such as cyclobenzaprine, oral clonazepam, or vaginal diazepam suppositories. In addition, pelvic floor relaxation exercises were found to be beneficial in this group of patients. A combination of intravesical hydrocortisone and heparin along with oral bladder selective and systemic steroids has been used with encouraging results in a small group of patients with bladder-centric IC [12]. Heparin is a glycosamine that resembles and takes over the function of the GAG layer of the bladder, while hydrocortisone is expected to ameliorate the inflammation.

Nickel *et al*. proposed using the UPOINT phenotyping system for the classification of BPS/IC based on relevant domains such as physiological, neurological ones, and tenderness. They hypothesized that the UPOINT system can help guide multimodal therapy and improve outcomes [13].

O'Leary MP, Sant *et al*., in their study published in 1997 entitled, "The IC Symptom Index and Problem Index," concluded that their indices would be useful in evaluating and managing patients with BPS/IC. They further added that these indices would be particularly helpful in clinical trials of new therapies for this condition, where reliable, validated, and reproducible outcome measures are critically important [8].

A recent retrospective study by Taneja *et al*. stratified BPS patients based on their clinical phenotypes (CP) and possible indicators of etiopathogenesis. They concluded that the treatment outcome improved if specific modalities of treatment were administered [14].

The present work was a prospective study designed to evaluate the outcomes of CP-based treatment for BPS/IC. The main objective was the classification of these patients into "clinical phenotypes" based on possible underlying predominant etiopathogenesis, application of group-specific modality of treatment, and evaluation of the outcome. As BPS/IC etiopathogenetically is a heterogeneous entity, it is logical to target the pathogenesis underlying it and not to subject all the patients to an umbrella treatment.

Furthermore, studies were the potential benefits of specific natural compounds, including D-mannose, chondroitin sulfate, *N*-acetylcysteine, and hyaluronic acid, in promoting urinary tract health and preventing UTIs through the action of the urothelial barrier [15].

2. METHODOLOGIES

2.1. Study subjects

This was a prospective, observational, single-center study that was cleared by the ethics committee of the hospital after going through due procedures. All patients with BPS/IC who reported to the urology outpatient department of a tertiary care center in north India, and met the European Society for Study of IC (ESSIC) criteria for diagnosis of BPS/IC were included in the study.

Inclusion criteria as described below:

- Patients who satisfied the ESSIC criteria of diagnosis of BPS/IC were included in the study.
- ESSIC definition: BPS was diagnosed based on chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one of other urinary symptoms such as persistent urge to void or frequency [1].

Exclusion criteria are listed in Table 1.

Informed consent was obtained from all patients before enrolment into the study. A standard workup, including a detailed history and physical examination, was conducted. The history included the characteristic presentation of BPS/IC, such as pain, frequency, nocturia, sexual dysfunction, present problems interfering with quality of life, and urgency. The physical examination included an abdominal and pelvic examination, with a particular focus on looking for masses, bladder distension, hernias, and tenderness. A musculoskeletal and focused neurological examination was also conducted. Suprapubic tenderness and bladder neck point tenderness were noted in both men and women. A digital rectal examination (DRE) was performed in men to assess prostate characteristics along with discrete point tenderness of the prostate and pelvic floor muscles. The female pelvic examination included screening for vulvodynia, vaginitis, atrophic changes, prolapse, cervical pathology, and adnexal masses or tenderness. Point tenderness, lump, and expression of pus on palpation of the urethra were checked to rule out the presence of urethral diverticulum. Investigations, including urine routine microscopy, culture, frequency volume chart, and ultrasound KUB with post-void residual, intravesical anesthetic challenge test (if the diagnosis was in doubt), cystoscopy along with assessment of maximum bladder capacity under anesthesia anesthetic bladder capacity, and bladder biopsy were done [16]. Routine biochemical and hematological investigations, including complete blood count, serum creatinine, and blood sugar, were performed. Additional investigations were done wherever necessary as per any coexisting medical conditions.

Patients were classified into CP1-CP4 groups according to signs and symptoms specific to a particular group, and some patients who had overlapping signs and symptoms were assigned to the CP group in terms of predominant etiopathological features.

Table 1. Confusable diseases for bladder pain syndrome

Confusable disease	Excluded or diagnosed by
Carcinoma and carcinoma *in situ*	Cystoscopy and biopsy
Infections	Urine routine showing pyuria
Herpes simplex and human papillomavirus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with iatrogenic acid	Medical history
Bladder-neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or hematuria: Upper urinary tract imaging such as CT or IVP (optional)
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Uroflowmetry
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis (optional)
Pelvic floor muscle-related pain	Medical history, physical examination

CT: Computed tomography.

2.2. CPs

The methodology of categorization in various CPs that was used is as follows.

All the patients underwent detailed focused evaluation toward understanding the most predominant etiologic pathway culminating in their symptoms. The patients who had Hunner's lesions (HL) on cystoscopy were distinct and easily classifiable into one category (CP), that is, HL.

The "presenting complaints" of patients who did not have HLs were the guiding principles for categorization

into various other phenotypes. Patients with pain and a predominant history of allergic reactions since childhood were categorized into the CP 1 (allergy group). As an example of overlap, a patient with HL had allergy was classified as HL with allergy.

Patients whose presenting complaint was hesitancy and difficulty in voiding were grouped as CP 2. In addition, if patients had tender points or myocardial bands on examination, they were classified as CP of dysfunctional voiding due to an overactive and dysfunctional pelvic floor.

Patients presenting with predominant neuropathic pain characterized by pricking sensations were classified as the CP 3. Some of these patients may also have had other secondary features. Nonetheless, since the main presentation was a neuropathic type of pain, they were grouped as CP 3.

Upon being grouped as aforementioned, if patients also happened to have some features of other categories, those were recorded and patients were also prescribed specific medication linked to those groups.

CP categories of patients with BPS/IC:

Clinical phenotype 1 (CP1): Allergy
Patients with a history of any kind of allergies were included in this group.
1. Seasonal rhinitis,
II. Vasomotor rhinitis
III. Asthma,
IV. Urticaria and Hives
V. Dermatological hypersensitivity
VI. Allergies to food items
VII. Allergies to drugs
VIII. Any other history suggestive of allergies

Clinical phenotype 2 (CP2): Dysfunctional voiding
Patients having 3 or more of the following features were included in this category.
2. Marked hesitancy especially difficulty in initiating stream in public
II. Nocturia <3
III. Constipation
IV. Aching pain in the anal canal
V. Clinical signs of overactive pelvic floor
VI. Presence of myofascial bands in perineal muscles

Clinical phenotype 3 (CP3): Neuropathic pain
Patients having any one of the following were included in this group
3. Pricking pain in the vulva, commonly the clitoris, forcing them to void
II. Burning pain in the perineum
III. Burning pain in anus somewhat relieved on passing urine.

Clinical phenotype 4 (CP4): Hunner's Lesions
Patients who had Hunner's lesions on cystoscopy were included in this group. Many patients qualified to be placed in more than one group were put in the group with predominant features.

All patients underwent cystoscopy according to the prevalent methodology described and published recently [14]. All patients received oral PPS, at 100 mg 3 times a day during the period of study. In addition, all patients were given group-specific treatment based on their CP. All 25 patients (100%) enrolled in the study received group-specific oral medications as follows: The allergy group (CP1) received tablet hydroxyzine at 25 mg once a day; patients in the dysfunctional voiding group (CP2) received cyclobenzaprine extended-release tablets at 15 mg once daily and/or clonazepam at 0.25 – 0.5 mg twice daily. Patients in the neuropathic pain group (CP3) received amitriptyline at 10 – 25 mg once a day. As many patients were eligible for being grouped in more than one CP group, treatment specific to the other group was also administered. Patients with a minimum follow-up of 6 months were included in the study and all the patients received these medicines throughout the study period. The patients' symptoms were scored using the Apollo clinical scoring system (ACS), which was prevalent in the institution at the time of induction, at 1, 3, and 6 month(s).

The ACS assesses clinical symptoms, such as urgency, frequency, nocturia, pain, sexual dysfunction, and psychological impact on quality of life, with a maximum score of 50. This is different from the existing O'Leary-Sant scale as the modified BPS Index used by the authors includes new additions to the scale in items 5 and 6, whereas items 3 and 4 are assigned more numerical weightage than in the original scale (Table 2) [16].

2.3. Patients' responses

Patients' responses were then stratified into three categories.

I. Unsatisfactory response: Little or no relief in symptoms (drop in score <10).
II. Good response: Significant relief of pain with manageable reduction/without significant reduction in frequency (drop in score between 11 and 29).
III. Excellent response: Relief of pain as well as a significant reduction in frequency (drop in score more than 30). For statistical analyses, the data were presented in descriptive statistics: Range (minimum, maximum), mean (± SD)/ median, and interquartile range for the quantitative variable at baseline at 1 month, 3 months, and at 6 months follow-up. The qualitative variables were expressed as frequency (%) under different categories at the time of baseline and follow-up. The data analyses were performed using Statistical Package for the Social Sciences (SPSS) statistical software, version 22.0.

3. OBSERVATIONS AND RESULTS

Etiopathologically-based CP groups (n = 25): Out of 25 patients enrolled in the study, 5 (20%) had a history of allergies and were placed in CP Group 1 (CP1- allergy

Table 2. Apollo clinical scoring system [16]

Sexual dysfunction			Psychological impact
Female	**Male**		**During the past month, how much have the symptoms bothered you mentally?***
No problem with sexual activity	No problem with sexual activity	0	No problem
Can engage in sexual activity with minimal discomfort	Post-ejaculatory discomfort	1	Very small problem
Non-penetrative genital contact can be tolerated	Moderate to severe pain post–ejaculation	2	Small problem
No genital contact can be tolerated	Pain at the time of erection	3	Medium problem
Vulvodynia	Complete loss of erection	4	Big problem
Aversion to sexual thoughts	Loss of libido with ED	5	Suicidal tendency
Domain total	**0 – 5**	**Domain total**	**0 – 5**
Existing scale (O'Leary – Sant)		**Proposed scale**	
Urgency	0 – 5	Urgency	0-5
Frequency	0 – 5	Frequency	0-5
Nocturia	0 – 5	Nocturia	0-10
Pain	0 – 5	Pain	0-20
Total	0 – 20	Sexual dysfunction	0-5
		Psychological impact	0-50
		Total	

group). Seven patients (28%) were included in CP Group 2 (CP2- dysfunctional voiding group). Four patients (16%) were diagnosed with neuropathic pain and were put in CP Group 3 (CP 3- neuropathic pain group). Nine patients (36%) were found to have HL in the bladder on cystoscopy and were thus in CP Group 4 (CP4- HL group). Patients could belong to more than one CP group (Table 3).

Treatment Given (n = 25): All 25 patients (100%) enrolled in the study underwent cystoscopy and hydrodistension under general anesthesia. Nine patients (36%) from the HL group (CP4) underwent ablation of HLs. 13 Eighteen patients (72%), who qualified to be included in more than 1 category were assigned to the group with predominant symptoms but received treatment for both categories.

Table 3. Clinical phenotype (CP) Groups (n=25)

Etiopathological group	Number	Percentage
Allergic (CP1)	5	20
Dysfunctional voiding (CP2)	7	28
Neuropathic pain (CP3)	4	16
Hunner's lesion (CP4)	9	36

Figure 1. Phenotype-wise response to treatment as assessed by Apollo clinical score over 6 months

3.1. Response to treatment in different groups (Figure 1)

3.1.1. CP1 (allergy group)

Out of 25 patients enrolled in the study, 5 (20%) patients had a history of allergies and were placed under CP1. In addition to these five patients, 6/9 in the HL group, 1/7 in the dysfunctional voiding group, and 1/4 in the neuropathic group also had some symptoms of allergy. Thus, 13/25 patients had a history suggestive of some form of allergy. 80% (4/5) of patients responded well to the treatment and 20% (1/5) had unsatisfactory responses as measured by ACS.

3.1.2. CP2 (dysfunctional voiding group)

Seven patients (28%) were assigned to CP2 based on diagnosis. However, 1, 2, and 4 patients in CP1, CP3, and CP4 also had elements of dysfunctional voiding, totaling 14 (56% [14/25]) patients. At the end of the study, 71.42% (5/7) patients had good and 28.57% (2/7) patients had an excellent response as rated on ACS.

3.1.3. CP3 (neuropathic pain group)

Four patients (16%) were diagnosed with neuropathic pain and were placed under CP Group 3 (CP3: Neuropathic pain group). Some elements suggestive of neuropathic pain were also found in 1, 2, and 3 patients in the CP1, CP2, and CP4, respectively. At the end of the study, 28.57% (3/4) patients

had excellent, and 75% (1/4) patients had good responses as assessed on ACS.

3.1.4. CP4 (HL group)

Nine patients (36%) were cystoscopically found to have HLs in the bladder and thus, placed in CP Group 4 (CP4- HL group). Of them, six had a history of allergies, four had elements of dysfunctional voiding and three had clinical features suggestive of neuropathic pain. At the end of the study, 3 (33.33%) patients had unsatisfactory, 4 (44.44%) had good, and 2 (22.22%) patients had excellent responses as evaluated by ACS.

With regard to the overall mean response, 16% (4/25) of the patients had unsatisfactory, 56% (14/25) had good and 28% (7/25) had excellent responses on ACS at the completion of the study.

The change in ACS on follow-up was analyzed using SPSS statistical software, version 22.0. Maximum change in ACS score from 0 to 1 month was 34, from 0 to 3 months was 38, and from 0 to 6 months was 38. The mean change in ACS score from 0 to 1 month was 17.08, from 0 to 3 months was 21, and from 0 to 6 months was 23 (n = 25) (Table 4).

4. DISCUSSION

With regard to clinical phenotyping based on symptoms (UPOINT phenotyping system), Nickel *et al*. hypothesized that classifying patients of IC based on clinically relevant domains can direct multimodal therapy and improve outcomes [13]. Others have also tried to classify the patients, but these efforts appeared to be based on biomarkers, clinical manifestation, urodynamics, radiological, cystoscopic, and histological features rather than based on possible etiopathogenesis [17].

It has been proposed that the patients with HL should be treated as a separate disease entity [18]. The present study aimed at classifying patients based on possible etiopathogenesis, administering group-specific treatment, and evaluating outcomes. In this study, patients were classified based on predominant clinical phenotyping-based features of a defined group (CP1-CP4), and 18 (72%) had overlying features. However, 7 (28%) did not have any overlapping features. Of 25 patients enrolled in the study, 5 (20%) had a history of allergies and were placed under CP1 (Allergic group). It is also interesting to note that, in addition to these 5 patients, 6/9 in HL group, 1/7 in the dysfunctional voiding group and 1/4 in the neuropathic group also had some symptoms of allergy. Thus, 13/25 patients had a history suggestive of some form of allergy. This may provide some insights into the etiopathogenesis of symptoms in this group. Seven patients (28%) were put in CP Group 2 (CP2-Dysfunctional voiding group) based on diagnosis. However, 1, 2, and 4 patients in CP1, CP3, and CP4 groups also had elements of dysfunctional voiding, adding up to a total of 14 (56%) patients in the overall group of study patients. This seemed to be similar to other prevalent studies [19]. Four patients (16%) were diagnosed with neuropathic pain and placed under CP Group 3 (CP3: Neuropathic pain group).

Some elements suggestive of neuropathic pain were also found in 1, 2, and 3 patients in the CP1, CP2, and CP4 groups, respectively. Thus, a total of 10 patients had some neuropathic elements in their symptomatology. Nine patients (36%) were found to have HLs in the bladder on cystoscopy and thus, placed in the CP4 group (HL group). Prevalence of HL has been variously reported in the literature and our study, it was less than reported by Whitmore *et al*. [20] It is also interesting to note that 6/9 had history of allergies, 4/9 had element of dysfunctional voiding and 3/9 had clinical features suggestive of neuropathic pain. Eighteen patients (72%), who qualified to fit in more than 1 category were assigned to the group with predominant symptoms but also received treatment for overlapping symptoms.

In CP1 group (allergy group), inflammation in the urinary bladder is proposed to be an indicator of mast cell activation, akin to the pathogenesis of allergy in other parts of the body. Hydroxyzine, which is expected to prevent mast cell degranulation, has been used to treat this subgroup of patients.

Theoharides and Sant recognized this fact and published an open-ended study in 1997, suggesting the role of hydroxyzine in the treatment of patients of IC with a history of allergies [7].

In the present study, 4/5 (80%) in CP1 group achieved a good response to the treatment, which justifies the use of hydroxyzine for CP1 group (allergic group). The patients in CP2 group (dysfunctional voiding group), had a history of marked hesitancy, especially difficulty in initiating stream in public, limited nocturia of up to 2 – 3 episodes per night, constipation, and aching pain in the anal canal. Examination of clinical signs of an overactive pelvic floor, presence of myofascial bands in perineal muscles, superficial dyspareunia,

Table 4. The change in ACS on follow-up (n=25)

Statistical parameters	Change in ACS		
	0 – 1 month	0 – 3 month	0 – 6 month
Number	25	25	25
Minimum	5	5	-2
Maximum	34	38	38
Range	34	33	40
Mean	17.08	21	23
Std. deviation	7.501	9.0185	11.34079
Median	16	20	26
Mode	16	12	18
Std. Error of mean	1.466	1.8036	2.2278158

ACS: Apollo clinical scoring.

and constipation also suggested pelvic floor dysfunction. These patients had painful urgency and frequency when awake but the symptoms were minimal after sleeping. Stressful situations could exacerbate these symptoms. Multiple studies showed that the presence of hyperactive pelvic floor in patients with BPS has been known to occur in up to 85% of the patients [19]. However, in our study, 56% (14/25) had symptoms pertaining to overactive pelvic floor. The hyperactive pelvic floor is postulated to result in turbulence during voiding and, in some cases, cause inflammation in and around the trigone region of the bladder. However, cystoscopic signs of inflammation are absent elsewhere in the bladder as this is not expected to cause any extensive mucosal inflammation of the bladder. Usually in these patients, bladder capacity is adequate, and they hardly benefit from hydro distension of the bladder. In the present study, all patients in the CP2 group (dysfunctional voiding group) received clonazepam (0.25 mg – 0.5 mg twice a day), cyclobenzaprine (extended-release form, 15 mg once a day) and were instructed to engage in pelvic floor relaxation exercises. Hence, pelvic floor muscle relaxation probably improves the symptoms of BPS/IC in patients of the CP2 group. At the end of the study, 71.42% (5/7) of patients responded well and 28.57% (2/7) excellently to the treatment as rated by ACS. While 50% of CP3 patients (neuropathic pain group) also had dysfunctional voiding, only 28.57% of CP2 (dysfunctional voiding) had neuropathic pain. These observations suggested that etiological pathways work outside the bladder and urinary symptoms and bladder pain results from some secondary extra-vesical pathology. In the present study, as mentioned above, patients classified under the CP3 group (neuropathic pain group) had pricking pain in the vulva (commonly at the clitoris) or at the tip of the glans penis, on filling of the bladder, forcing them to void frequently, with burning pain in the perineum and the anus being somewhat relieved on passing urine. Thus, it is mandatory, for these patients, to carry out the focused neurological examination, which can rule out identifiable sensory neuropathy or any other neurological diseases. Cystoscopic signs of bladder inflammation are usually absent in these patients. A burning or pricking sensation is typical of neurological pain and suggests neurogenic pathophysiology or inflammation. Patients with these symptoms are given amitriptyline, which is a tricyclic antidepressant and works by inhibiting the reuptake of serotonin and norepinephrine, thus playing a specific role in neuropathic pain and has also been studied in the past for its use in BPS/IC [20]. Unlike the present study, earlier studies, in which amitriptyline has been used in BPS/IC patients without stratification based on CPs, reported suboptimal results. Amitriptyline needs to be started at the dose of 10 mg *per os* at bedtime since sedation is its most common side effect. This agent is dose-dependent and most of the patients feel comfortable at this dose. The dose can be further increased to 25 mg once a day to achieve better results. With the prolonged use of the agent, its beneficial effects reportedly improved, possibly due to some kind of cumulative central effect [21]. At the end of 6 months, in the CP3 group, 28.57% (3/4) of the patients had excellent and 75% (1/4) patients had a good response as shown by ACS evaluation. Therefore, the judicial use of amitriptyline for clinically stratified neurological pain improves the overall outcomes in patients of BPS/IC. Patients who had HLs on cystoscopy were categorized into CP4 group (HL group). Notably, 66.67% of the patients in CP4 group had the presentation of allergies, 44.44% had symptoms of dysfunctional voiding and 33.33% had neuropathic pain. Patients with a high rate of overlapping symptoms were from the CP4 group since 66.67% of its patients also had a history of allergies. This may indicate that the bladder-centric inflammatory process is involved in the pathogenesis in these patients. These patients are usually present with suprapubic pain in the full bladder, which is relieved by passing urine, increased day- and night-time frequency, and forced sensory urgency because fear of pain in the full bladder compels them to void. Female patients had a history of deep dyspareunia. Functional bladder capacity is usually small in these patients. Most of the patients have suprapubic tenderness. In males, the absence of prostatic tenderness on DRE, in the presence of suprapubic tenderness, differentiates BPS/IC from prostatitis [22]. Cystoscopy is an important tool in the evaluation of these patients, as endeavors have been made in the past to predict the presence of HL based on symptoms, and clinical presentation has not been as good [23]. Cystoscopically, 9 (36%) patients in the present study had HLs. All of them underwent hydro distension and ablation of HL using electrocautery through a ball electrode, which is an effective treatment for symptomatic relief for a variable period in these patients [24]. The effect of treatment of CP4 patients (HL group) appeared to last for a few months and many of these patients had recurrence of symptoms, but none of them required repeat hydro distension and ablation within a 6-month study period. The recurrence of HLs and the requirement for re-treatment have been documented by other researchers [25]. At the end of 6 months, in the CP4 group (HL Group), 33.33% (3/9) of the patients had unsatisfactory, 44.44% (4/9) had good and 22.22% (2/9) had excellent responses as evaluated by ACS. Overall, 16% (4/25) of the patients had unsatisfactory, 56% (14/25) had good and 28% (7/25), had excellent responses as assessed by ACS after study. In November 2015, Ogawa *et al*. published a review on emerging drugs for IC/BPS and they also advocated the use of etiology-phenotype-based treatment for better outcomes [26]. The present study evidently showed that the clinico-phenotypically-based, group-specific, tailored approach was efficacious in BPS/IC patients, and outcomes appeared to be better than reported in the past. During the follow-up, the scores dropped, and

treatment continued. However, a few patients experienced a recurrence of symptoms. During the 6 months, clinical-phenotypically-based treatment was found to be effective, as patients had an overall good response.

This study has utilized the novel methodology of phenotyping the various groups of BPS/IC patients based on clinical clues to the etiopathogenesis underlying the disease process. Given the heterogeneity of the disease process, it is logical to target the individual etiological pathways to achieve clinically significant outcomes. This is a unique system of phenotyping since the treatment has been linked to possible etiological categories.

The most significant limitation of this study was the small sample size because this is an uncommon disease entity. Hence, it lacks any significant statistical value. Moreover, as a single-center study, it can only be labeled as a pilot study and more robust multi-centered trials are warranted to well establish this method as a routine.

5. FUTURE DIRECTIONS

It is now generally believed that BPS/IC is not a single disease entity but a heterogeneous group of conditions involving various etiopathological mechanisms. Categorizing patients into different categories based on phenotypes is expected to provide a direction for the development of novel treatment strategies. Phenotyping based on urinary biomarkers, the use of artificial intelligence, and serological tests may be the key to the management of these patients. "Card test," akin to the urine test for pregnancy, may be developed, and when applied to the test of urine of patients may serve as a specific biomarker that could guide the treatment. Urobiome analysis by next-generation sequencing, as has been studied in carcinoma of the urinary bladder, may be a useful tool in the future for the phenotyping of BPS/IC patients [27].

Multi-centered trials in diverse populations are essential to the verification of these concepts. The primary step would be to agree on definitions, translate these into local languages, and then collate the data thus generated. This would be of immense service to this group of patients.

6. CONCLUSION

Clinical phenotyping-based classification and treatment of BPS/IC patients, depending on possible indicators of etiopathogenetic mechanisms, appears to improve treatment outcomes. Although the sample size in this study was very small, it may serve as an indicator of the etiopathogenesis-based specific pathway in clinical and cystoscopic features. In the future, clinical phenotyping-based stratification of BPS/IC patients in this manner may also be used to predict outcomes. Small sample size may be a limitation of this study since BPS/IC is a rare disease and our study was carried out in a single center. Studies in a greater number of patients, with a longer period of follow-up, and in multiple centers with uniform methodology used should be done to draw a valuable conclusion. More research is needed to delve into more phenotypes and possible genotypes and the result may change the future course of treatment for BPS/IC.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the scientific research committee (SRC) of the Indraprastha Apollo Hospitals and the institution's ethics committee (IAH/DNB/PROTOCOL/URO/D3/2020/51).

CONSENT FOR PUBLICATION

All the participants gave consent to publish their data in this article.

AVAILABILITY OF DATA

Data used in this work are available from the corresponding author on reasonable request.

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