Invited Review

Cystoscopic evaluation and clinical phenotyping in interstitial cystitis / Bladder pain syndrome

Arcan and Tarcan. Classification of bladder pain syndrome

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Abstract

Herein, we aimed to review, report and discuss the role of cystoscopy and clinical phenotyping in interstitial cystitis/bladder pain syndrome (IC/BPS). For this purpose; a comprehensive nonsystematic review of the relevant literature was conducted. We reviewed articles published in English and indexed in the PubMed, Embase, and Google Scholar databases. Original manuscripts, review articles, case series, and case reports were taken into consideration. Data regarding the indications for, technique and possible findings of cystoscopy with hydrodistension (HD) and biopsy, as well as clinical implications of cystoscopic information and the concept and utility of clinical phenotyping within the context of IC/BPS were extracted and discussed. IC/BPS is diagnosed based on symptomatic assessment and exclusion of confusable diseases. There is not a universal agreement upon the evaluation and diagnostic algorithm of IC/BPS. The majority of the guidelines recommend cystoscopy with HD and biopsy as a diagnostic prerequisite. Various different techniques have been described for cystoscopy with HD. General or epidural anesthesia is more commonly preferred and advocated while assessing endoscopic alterations in patients suspected of having IC/BPS. Cystoscopy with HD and biopsy enables more objective exclusion of confusable diseases. It also provides the basis of European Society for the Study of Interstitial Cystitis classification. IC/BPS patients who demonstrate positive cystoscopic (glomerulations and/or Hunner lesion) and histologic findings have a more severe symptomatology and may benefit from lesion-targeted endoscopic treatments. Clinical phenotyping has been implemented for IC/BPS and may be used for individualized assessment and treatment.

Keywords: Bladder pain, cystoscopy, hydrodistension, biopsy, phenotyping

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disorder of unknown etiology and is one of the most debilitating conditions in urological practice. It is characterized by pain, pressure or discomfort perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence any identifiable cause such as infection (1, 2). IC/BPS can be recognized by the presence of consistent symptoms and signs. The disorders which may lead to a similar symptomatology should be excluded in order to confirm the diagnosis of IC/BPS (2).

There are significant variations regarding the evaluation and diagnosis of IC/BPS (3). The role of cystoscopy in the diagnosis and classification of IC/BPS has long been a matter of debate, with some authorities (such as European Society for the Study of Interstitial Cystitis-ESSIC) indicating cystoscopy as a diagnostic prerequisite while some others (such as American Urological Association-AUA) reserving it for complex cases (4).

Clinical phenotyping, which categorizes the disorder according to the presence or absence of clinically relevant domains, has been implemented in IC/BPS after its success for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in an effort to optimize diagnosis and treatment (5). Main purpose of phenotype mapping in IC/BPS was to better understand the multifactorial etiology of the disorder and enable multimodal and phenotype-directed targeted therapy (6).

Herein, we will review and discuss the contemporary English literature about cystoscopic evaluation and clinical phenotyping in IC/BPS.
Indications for Cystoscopy with Hydrodistension and Biopsy in IC/BPS:

Indications for cystoscopy within the context of IC/BPS evaluation and management exhibit considerable variation. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established cystoscopic discovery of glomerulations or Hunner lesions as an unchallenged diagnostic criterion for IC/BPS (7). However, NIDDK criteria were used mainly for the purpose of standardization in scientific studies and the strict application of these criteria would miss a significant proportion of patients who actually have IC/BPS (8). Many experts agreed that the absence of glomerulations or Hunner lesions does not rule out IC/BPS (9). ESSIC proposal highlighted the importance of excluding confusable diseases (such as carcinoma in situ) as the cause of symptoms and indicated cystoscopy under anesthesia with hydrodistension (HD) and eventual biopsy as a diagnostic prerequisite (2). Furthermore, cystoscopic and histopathological findings would enable further documentation and classification of IC/BPS (2). European Association of Urology (EAU) (10) and Japanese Urological Association guidelines (11), joint expert opinions from East Asia (12) and the Bladder Pain Syndrome Committee of the International Consultation on Incontinence (13) follow the recommendations of ESSIC. Conversely, AUA guidelines do not indicate cystoscopy as an integral part of the initial diagnostic work-up for IC/BPS (1).

Technique of Cystoscopy + Hydrodistension in IC/BPS:

Similar to its indications, technical protocol of cystoscopy and HD in IC/BPS is subject to considerable variation and lacks a consensus. NIDDK recommended cystoscopy and HD to be done under anesthesia, at a pressure of 80-100 cmH20, lasting 1-2 minutes and up to 2 cycles. The presence of Hunner lesions or glomerulations which are diffuse in at least three quadrants with ten glomerulations per quadrant were considered positive findings in favor of IC/BPS (14). ESSIC and EAU guidelines did not specify technical details about the cystoscopic evaluation for IC/BPS (2, 10). According to AUA guidelines, cystoscopy and HD should be done under anesthesia, at a pressure of 60-80 cmH20, and be no longer than 10 minutes when the aim is therapeutic (1). Japanese guidelines recommended lumbar anesthesia at the level of T6 during cystoscopy, with 80 cmH20 pressure and to stop the infusion when the volume is between 800-1000 ml despite low pressures (11). Apart from the guideline recommendations, some authors have proposed individual protocols. Turner and Stewart suggested a pressure of 100 cmH20 with a maximum infused volume of 1000 ml and the distention being maintained for 1 minute. According to their technique, bladder cycling should not be repeated more than 5 times and cystoscopic assessment should be done ideally at the initial and the last distensions (15). According to Nordling et al. the possible urethral urine leak around the cystoscope should be blocked digitally. They also suggested that the bladder should be filled with a pressure of 80 cmH20 until the infusion stops dripping, without any specification about the volume limit. Emptying should be started after waiting for 3 minutes with the bladder fully distended. During filling and emptying, which can be repeated one more time, endoscopic assessment is carried out. However, they recommend not to reach maximum capacity during the second cycle to better visualize lesions and optimize tissue sampling (16).

The majority of the published series about IC/BPS have stated general or spinal anesthesia as the preferred and recommended type of anesthesia to be applied during cystoscopy with HD. However, some investigators have suggested that glomerulations or Hunner lesions can be visualized under local/regional anesthesia (17). Yamada et al. supported the feasibility of epidural anesthesia in an effort to perform additional HDs on the next day following the initial cystoscopy + HD (18). Aihara et al. utilized local anesthesia via intravesical administration of lidocaine 10 minutes prior to the start of the infusion which was terminated when the patient reported intolerable pain or other local symptoms. They have reported favorable results in terms of the safety and efficacy of this approach (19).

Cystoscopic Findings in IC/BPS:

Hunner lesions and glomerulations represent the most characteristic findings which might be encountered during the cystoscopic evaluation for IC/BPS. Hunner lesion was initially named as an “ulcer”. However, it is actually an inflammatory lesion which ruptures through the mucosa and submucosa when the bladder is distended. Hence, the suffix “lesion” would more precisely define its characteristics. The Hunner lesion encompasses tiny vessels radiating towards a central scar which is covered by coagulum. When it ruptures upon bladder distension, petechial oozing of blood occurs in a waterfall manner (2) (Figure 1). Hunner lesion is not common, with only around 10-15% of the patients with IC/BPS showing consistent cystoscopic signs (19-21). Narrow band imaging, which helps to distinguish the vascularity of a given bladder mucosal abnormality, has been proposed as an aid to better identify Hunner lesion endoscopically (22). However, more studies are needed to advocate its routine use for this purpose.

Glomerulations are a separate entity and they are defined as small submucosal petechial lesions which become visible after bladder hydrodistension (23). They are classified into five grades according to the extent of submucosal bleeding and the presence/absence of mucosal disruption (16). The term “glomerulation” was introduced by Walsh who linked these mucosal changes to early stage disease and also highlighted that they
were not pathognomonic for IC as other bladder pathologies, such as dyskinesia, might lead to similar alterations in bladder mucosa (24). Being mainly related to IC/BPS, glomerulations are neither specific nor sensitive enough when used solely for diagnostic purposes. Patients with chronic inflammation of the urothelium, urinary tract stone disease, and benign prostate hyperplasia can exhibit endoscopic signs consistent with glomerulations (25, 26). Furthermore, Waxman et al. have shown that glomerulations can even be discovered in otherwise healthy women (27). On the contrary, the proportion of patients with a clinical diagnosis of IC/BPS but without any cystoscopic changes can be in the range of 24-34% (28, 29).

Classification of IC/BPS According to Findings at Cystoscopy with Hydrodistension and of Biopsies:
According to ESSIC; cystoscopy and hydrodistension with biopsy is an integral part of the diagnostic evaluation for IC/BPS. Cystoscopic positive signs in favor of IC/BPS are: glomerulations grade 2-3 or Hunner lesions or both. Infiltration of inflammatory cells and/or formation of granulation tissue and/or overexpression of mast cells and/or intrafascicular fibrotic changes represent the histopathological findings that are interpreted in favor of IC/BPS (2). IC/BPS subtypes are defined on the basis of cystoscopic and histopathological findings (Table 1). If cystoscopy or biopsy are not done, then the letter “X” is assigned. Biopsy findings are categorized as follows: normal (A), inconclusive (B), positive (C). Cystoscopic findings are interpreted as such: normal (1), glomerulations (2), Hunner lesion (3). This type of classification could not be possible if only clinical findings were utilized. Moreover, such a distinction would have implications regarding prognosis and treatment outcome.

Clinical Implications and Correlations Regarding Cystoscopy with Hydrodistension and Biopsy Findings in IC/BPS:
The clinical relevance of IC/BPS subtypes has long been questioned. However, the information gathered by the cystoscopic examination and histopathological assessment of bladder biopsy samples in IC/BPS offer several advantages regarding optimizing patient management and treatment outcomes. First of all, IC/BPS is essentially a diagnosis of exclusion. Cystoscopy with HD +/- biopsy offers the unique opportunity to exclude some of the confusable diseases (such as carcinoma in-situ, bladder stone, etc.) in a more reliable manner (2, 30).

Moreover, patients with Hunner lesion IC/BPS may benefit from targeted endoscopic interventions. Transurethral resection of Hunner lesions have been associated with symptomatic improvement rates in the range of 90% (31, 32). Hunner lesion-directed endoscopic treatment options were further enriched by studies investigating the potential utility of Nd:YAG laser, electrocoagulation, and instillation of triamcinolone (33-35) all of which reported impressive improvement rates ranging from 70-90%. This therapeutic benefit would not have been possible if these patients were not identified via cystoscopy +/- biopsy. It has been shown that a reliable distinction between Hunner lesion IC/BPS and nonHunner lesion IC/BPS is not possible via clinical assessment only (36, 37).

Furthermore, cystoscopy under local anesthesia can be utilized to monitor the effect of bladder distension and emptying on pelvic symptoms. Despite the limitation which might be induced by pain and/or discomfort, functional bladder capacity can also be assessed in the same setting (17).

Regarding the correlation between cystoscopy and clinical findings; recent studies have shown that the patients with Hunner lesion IC/BPS are more severely symptomatic than the patients without a Hunner lesion. In their study in which 393 patients with IC/BPS (55% with type 3C) were enrolled; Logadottir et al. have investigated the potential clinical similarities and dissimilarities between the main disease subtypes. They have found out that; patients with type 3C disease were older (62 vs. 42 years, p < 0.001) with a lower average maximal voided volume (206 vs. 289 ml, p < 0.001) and a lower average bladder capacity under anesthesia (459 vs. 743 ml, p < 0.001) (38). Boudry et al. assessed the utility of bladder diary in discriminating between Hunner lesion vs. nonHunner lesion IC/BPS. For this purpose, they have utilized the clinical data of 54 consecutive (39 women and 15 men) patients and discovered an association between the bladder diary parameters and cystoscopic alterations such that; those with positive cystoscopic findings having lower functional bladder capacities, increased rate of frequency and nocturia, and more marked relief of symptoms by voiding when compared with those who had normal cystoscopic findings (39). Ahn et al. studied the differences between Hunner lesion IC/BPS and nonHunner lesion IC/BPS with regard to bladder diary findings and urodynamic parameters in a cohort of 55 female patients. According to bladder diary data, the frequency of micturitions were higher in the Hunner lesion group (16.65 vs. 12.53, p = 0.045) together with a smaller amount of maximal voided volume (143.48 vs. 244.53 ml, p < 0.001). Regarding the urodynamic recordings; desires to void and maximum cystometric bladder capacity (MBC) (182.09 vs. 286.59 ml, p < 0.001) corresponded to significantly lower volumes in the Hunner lesion group. They have identified cut-off values for urodynamic parameters to predict the presence of Hunner lesion on cystoscopy and suggested that endoscopic evaluation of the bladder should be offered to the patients with an strong desire to void volume ≤ 210ml or an MBC ≤ 236ml (40).

Last but not the least, cystoscopy is not a morbid procedure with a fairly low incidence of complications. Relatively few publications have focused on the complications of cystoscopy and HD done primarily within the
context of IC/BPS management. Apart from the anecdotal reports of bladder rupture, bladder necrosis, and acute pyelonephritis, the procedure seems to be safe and well tolerated (41, 42).

Clinical Phenotyping in IC/BPS:
IC/BPS is a disorder without a universal agreement upon its etiology, diagnostic algorithm and management strategy. IC/BPS may be regarded as a component of a more generalized somatic problem reflections of which may affect urinary bladder and other pelvic organs via several proposed mechanisms. The release of mediators (such as leukotriene) from activated mast cells located close to the neural/perineural structures along the bladder wall is the most widely studied ethiopathogenetic explanation for IC/BPS (43). Diverse clinical phenotypes might be encountered within the context of IC/BPS (44, 45). The concurrent existence of IC/BPS with other chronic pain and symptom based syndromes have been documented (45, 46). The main aim of phenotype mapping for IC/BPS has been to provide more individualized and phenotype-directed clinical assessment and treatment. The UPOINT (urinary symptoms, psychosocial dysfunction, organ specific findings, infection, neurologic/systemic and tenderness of muscle) schema, which has provided better classification and treatment for CP/CPPS (45), has been extrapolated for IC/BPS. Nickel et al. categorized IC/BPS patients into 6 domains with the urinary domain including patients with bothersome lower urinary tract symptoms, the psychosocial domain being characterized by patients with clinical depression, or an identifiable maladaptive coping mechanism, the organ-specific domain being comprised mainly of patients suffering from the typical cyclic pain provoked by bladder filling and temporary relief with voiding and/or demonstrating positive cystoscopy + biopsy findings, the infection domain being consisted of patients with urine culture-documented urinary tract infections within the last 2 years which have provoked/exacerbated baseline symptoms, the neurological/systemic domain hallmark of which being prior diagnoses of disorders involving some degree of neuropathy or neural upregulation (such as of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, vulvodynia), and the tenderness domain patients of which demonstrate trigger point tenderness during physical examination. Patients with more UPOINT-positive domains experienced more severe symptoms of longer duration as determined by the interstitial cystitis symptom index (ICSI) (44). Treatment options which can be recommended based upon the UPOINT classification are summarized in table 2.

Doiron et al. investigated the utility of clinical phenotyping in distinguishing between Hunner lesion IC/BPS and nonHunner lesion IC/BPS in their cohort composing of 359 patients (12.3% of them with Hunner lesion) with documented cystoscopic findings. The Hunner lesion group reported higher ICSI scores together with higher rates of pain, frequency and nocturia when compared to the nonHunner group. However, the difference between the two groups was statistically insignificant in terms of the number and distribution of UPOINT phenotypes. Despite statistical insignificance, there was a trend towards more prevalent urinary domain in the Hunner lesion IC/BPS group (17). They have concluded that; patients with Hunner lesion IC/BPS can not be identified by clinical phenotyping only and cystoscopy is inevitable for such a discrimination.

Conclusions:
IC/BPS is diagnosed based on symptomatic assessment and exclusion of confusable diseases. There is a lack of consensus regarding the evaluation and diagnostic algorithm of IC/BPS. European and Asian guidelines recommend cystoscopy with HD and biopsy as a diagnostic prerequisite. On the other hand, cystoscopic examination is not a routine part of the diagnostic evaluation according to the AUA. Considerable variation exists about the technique of cystoscopy with HD. General or epidural anesthesia has been usually preferred while examining the bladder in patient with clinical signs of IC/BPS. However, certain authorities have supported the feasibility and highlighted the advantages of local anesthesia for the same purpose. Cystoscopy with HD and biopsy enables exclusion of the confusable diseases in a more reliable manner. It also forms the basis of ESSIC-proposed classification of IC/BPS. Identification of the patients who demonstrate positive cystoscopic signs and histopathologic alterations in favor of IC/BPS might have implications regarding treatment outcome since lesion-targeted endoscopic treatment has yielded promising results. Hunner lesion IC/BPS patients tend to be older with a more severe symptomatology in terms of pain and lower urinary tract symptoms when compared to nonHunner lesion IC/BPS patients. Clinical phenotyping has been implemented to IC/BPS. Categorizing patients according to UPOINT domains might enable individualized treatment.

References


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<tr>
<th>Table 1: Classification of types of IC/BPS according to findings at cystoscopy with hydrodistension and of biopsies.</th>
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<tbody>
<tr>
<td><strong>Biopsy</strong></td>
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<tr>
<td></td>
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<tr>
<td>Not done</td>
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<tr>
<td>Normal</td>
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<tr>
<td>Inconclusive</td>
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<td>Positive</td>
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Table 2: Treatment options which can be recommended based upon the predominant clinical phenotype of the patients with IC/BPS. CS: chondroitin sulphate, DMSO: dimethylsulfoxide, HA: hyaluronic acid, PPS: pentosan polysulphate.

<table>
<thead>
<tr>
<th>Clinical Phenotype</th>
<th>Treatment options</th>
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<tbody>
<tr>
<td>Urinary</td>
<td>Behavioural treatments, antimuscarinic drugs, intravesical treatment (Heparin, DMSO, HA, CS, PPS), hydrodistension, botulinum toxin A, sacral neuromodulation, radical surgery</td>
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<tr>
<td>Psychosocial</td>
<td>Stress management and psychosocial support</td>
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<tr>
<td>Organ-specific</td>
<td>Amitriptylin, cimetidine, hydroxyzine, cyclosporine A, PPS, quercetin, intravesical treatment (DMSO, heparin, HA, CS, alkalinized lidocaine, PPS), hydrodistension, botulinum toxin A, radical surgery</td>
</tr>
<tr>
<td>Hunner lesion (+)</td>
<td>Endoscopic treatment (fulguration, laser ablation, resection, steroid injection), hyperbaric oxygen, radical surgery</td>
</tr>
<tr>
<td>Hunner lesion (-)</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Infectious</td>
<td>Gabapentanoids, cimetidine, hydroxyzine, sacral neuromodulation</td>
</tr>
<tr>
<td>Neurological / systemic</td>
<td>Pelvic floor physiotherapy, massage therapy, acupuncture, trigger point injections</td>
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