



## Review Article

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# Update on the Pathology and Diagnosis of Interstitial Cystitis/Bladder Pain Syndrome: A Review

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by bladder discomfort, urinary frequency, urgency, and pelvic pain. The etiology and pathogenesis of this condition is still unknown and remains diagnosed by exclusion. The histologic findings are also neither specific for diagnosis nor correlated with symptoms. However, the definition and diagnostic criteria for the condition was established in the last decade. In this paper, we review the changes in the definition, terminology, and diagnostic scheme of IC/BPS, and summarize the histologic findings. We also briefly discuss some new pathologic suggestions and new urinary markers, focusing on the most promising ones.

**Keywords:** Interstitial Cystitis; Urinary Bladder; Pain Syndrome; Diagnosis; Pathology

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## INTRODUCTION

Interstitial cystitis (IC) or bladder pain syndrome (BPS) is a clinical condition that manifests as a sensory hypersensitivity of unknown cause, characterized by urinary frequency, bladder discomfort, and pelvic pain [1]. There is a 3:1 to 10:1 female preponderance in some studies [2]. Currently, the IC definition and diagnostic criteria are being redefined. The diagnosis of this condition was originally based on these symptoms—bladder pain, urinary urgency, and evidence of supportive bladder pathology on cystoscopy under anesthesia (inflammatory infiltrate, granulation tissue, detrusor mastocytosis, intrafascicular fibrosis, and Hunner's ulcers), and exclusion of other possible diagnoses. Numerous diagnostic markers have been also evaluated.

## DEFINITION

IC was primarily described by Hanash and Pool [3] as a condi-

tion characterized by urinary symptoms, markedly reduced bladder capacity, and cystoscopic findings of large irregular (so called Hunner's ulcers) [4], i.e., patches of reddened mucosa exhibiting small vessels radiating from a central pale scar [5]. This is "classic" or ulcerative IC. Messing and Stamey [6] described "nonulcer" IC, characterized by multiple strawberry-like petechial hemorrhages referred to as "glomerulations," and submucosal hemorrhages on cystoscopy and hydrodistension under anesthesia.

In 1987, the National Institute of Health-National Institutes of Diabetes, Digestive, and Kidney Disease (NIDDK) in the United States of America established clinical and cystoscopic diagnostic criteria that included symptoms of bladder pain, urinary urgency, and evidence of bladder pathology, with the exclusion of other possible diagnosis [7]. These strict criteria may exclude more than 60% of patients who actually have IC/BPS, because they do not meet the criteria [8]. In addition, there was neither any correlation between the histological severity of in-

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flammation and the symptoms, nor with the NIDDK definition [9].

In 2002, the International Incontinence Society revised the definition of BPS [10]. BPS was defined as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency without evidence of proven urinary infection or other obvious pathology.

More recently, the European Society for the study of IC/BPS (ESSIC) suggested a new nomenclature and classification system [11]. Since pain is the fundamental character of the condition, it was proposed that the name be changed to BPS. BPS is diagnosed based on the presence of chronic pelvic pain lasting more than 6 months, pressure/discomfort perceived to be related to the urinary bladder, and one or more urinary symptoms such as urinary urgency or frequency. The American Urological Association defined IC/BPS as follows [12]: “An unpleasant sensation (pain, pressure, or discomfort) perceived to be related to the urinary bladder, and associated with lower urinary tract symptoms of more than six weeks duration in the absence of infection or other identifiable cause.”

## DIAGNOSIS AND CLASSIFICATION

The ESSIC suggests an optimal modality for diagnosing IC/BPS using the 3-step-process described below [11].

The first step is the selection of patients. It was agreed that BPS would be diagnosed based on chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder.

The second step is exclusion of similar diseases through medical history, physical examination, urinalysis, urine cultures, prostate-specific antigen in males >40 years, uroflowmetry, postvoid residual urine volume by ultrasound scanning, cystoscopy, and biopsy. The diseases to be excluded include carcinoma, various infection, diverticulum, urogenic prolapse, endometriosis, vaginal candidiasis, gynecologic cancers, prostate cancer, benign prostatic obstruction, chronic bacterial/nonbacterial prostatitis, pudendal nerve entrapment, incomplete bladder emptying (retention), and pelvic floor muscle related pain. The sources of the urinary infection include common intestinal bacteria, chlamydia trachomatis, mycoplasma, corynebacteria, herpes simplex virus, and human papillomavirus.

The final step is the classification of BPS. The positive cystoscopic findings of BPS are grade 2–3 glomerulations, Hunner’s

lesions, or both. The positive histologic evidence of BPS includes inflammatory infiltrate and/or granulation tissue and/or detrusor mastocytosis and/or intrafascicular fibrosis. Each type is composed of 2 symbol-groups: symbols 1, 2, and 3 represent cystoscopic findings (X, not done; 1, normal; 2, glomerulation; and 3, Hunner’s lesion), while symbols A, B, and C indicate biopsy findings (X, not done; A, normal; B, inconclusive; and C, positive). For example, BPS type 1A means patients with normal finding at cystoscopy with hydrodistension and normal histology on biopsy.

## PATHOLOGIC FINDINGS

The diagnostic utility of bladder biopsy in patients with IC/BPS is contradictory. The most common indication is a search for urothelial carcinoma/carcinoma in situ of the bladder, which may be confused with IC [13]. One group of authors suggest that the histopathologic findings are nonspecific, and of limited value to rule out carcinoma in situ [14]. Others contend that the histopathologic findings are useful to confirm the diagnosis [15].

A significant number of patients with ulcerative IC show ulceration, severe inflammation, and granulation tissue [16]. The inflammatory infiltrates are usually superficial, and restricted to the lamina propria [17]. The pattern of ulceration is wedge-shaped and frequently filled with fibrin. The surrounding tissue of the ulcer may show many lympho-plasmacytic infiltrates, frequently forming germinal centers. Additionally, mast cells are significantly increased in the lamina propria and in the detrusor muscle. The overlying urothelium is frequently sloughed or floating above the surface. Mucosal sloughing is more common in ulcer type IC than in nonulcer IC, but is rare in patients without cystitis [15]. This phenomenon of denudation may result from instrumentation, but the urothelium in IC is particularly fragile, probably related to a type IV collagen defect in the urothelial basement membrane [18]. The lamina propria is edematous, with stromal hemorrhage and congested venules. About one-third of cases show abundant neutrophils in the venules with margination and involvement of the wall of the vein. Hemorrhage of the lamina propria is more common in patients with ulcers than those without ulcers. About 80% patients have perineural inflammation; however, this finding is frequently also seen in those with bladder cancer and is not specific for IC [19]. In these patients, the rupture of the bladder mucosa subsequently resulted in reparative granulation tissue. Significant

fibrosis of the detrusor muscle was present in only 10% of patients, and this is exclusively noted in patients with ulcer. One group of authors described intrafascicular fibrosis as a unique histopathologic finding of IC, but this finding has not been firmly supported by subsequent studies [20].

Faint histopathologic changes are seen in nonulcerative IC. Hemorrhage is present in 90% of cases with glomerulations [19], and while generally localized, the hemorrhage may extend into the urothelium. In 83% of cases, mucosal rupture is present and limited to the lamina propria without associated inflammation. Rupture may be related to suburothelial hemorrhage, likely secondary to a defect in the urothelial lining [19]. Most patients with nonulcerative IC have little or no inflammation, but edema and vascular congestion are frequently seen.

Some researchers consider that mast cells are strong histologic markers for IC [20,21], while others disagree [15,19]. The former group suggested a cutoff in the numbers of infiltrating mast cells. One study team suggested that up to 28 mast cells per square millimeter in the detrusor muscle was diagnostic of IC [19]. The latter group of authors who disagree found that control patients without IC had higher numbers of infiltrating mast cells [15,19,22]. Some investigators contend that isosmotic formaldehyde/acetic acid is a better fixative to identify all mast cells rather than the conventional toluidine blue stains and Giemsa stains [23]. This fixative might prevent initial aldehyde blocking, and subsequent staining with toluidine blue discloses well a second population of mast cells—so called mucosal mast cells [19]. In some cases of nonulcer IC, uroplakin immunohistochemical staining revealed discontinuously reactive superficial/umbrella cells of the urothelium, suggesting a diagnostic value that awaits confirmation. Uroplakin III- $\delta$ 4, a splicing variant of uroplakin III with significant upregulation has been reported in IC, suggesting a potential marker for identifying nonulcerative IC [24].

The deposition of Tamm-Horsfall protein in the epithelium and submucosa has been seen in patients with IC, indicating a barrier defect in this disease [25].

Recently, a group of pathologic investigators suggested that patients with IC had prominent plasma cell infiltration and fibrosis in the affected bladder tissue, raising the suspicion that IC could be part of a systemic IgG4-related disease [26]. Their cohort showed 60% IgG4 positivity in both serum IgG4 level and IgG4-to-IgG ratio. They proposed that a subset of IC may actually be an IgG4-related disease, potentially providing a better understanding of the pathogenesis of IC.

A new clinico-pathologic analysis for Hunner/classic IC (HIC) is suggested based on (1) light chain restriction of infiltrating B/plasma cells, and (2) fair correlation between the degree of lymphoplasmacytic infiltration and severity of urothelial denudation [27]. The researchers suggest that Non-HIC and HIC are distinct pathologic entities, and the latter is characterized by pancystitis, frequent clonal B-cell expansion, and epithelial denudation. An abnormality of the B-cell population (significantly increased lymphoplasma cells, and light chain restricted B cells) may be involved in the pathogenesis of HIC [28].

## URINARY MARKERS OF IC/BPS

One investigator performed an extensive search of the literature for urinary markers of IC/BPS, grouping findings according to their molecular structure and function [29]. The inflammatory mediators were mast cells, histamine, methylhistamine, IL-6, CRP, CXCL10, CXCR3, TNFSF14, Th chemokine, HIP, PAP, tyramine, 2-oxoglutarate, AIBG, and ORM1. These inflammatory markers are elevated in cystitis. Proteoglycans (GP-51, CD44, and Tamm-Horsfall protein) were shown to be a vital component of the bladder's defenses. Urinary hexosamines (uronate and glycosaminoglycan) were suggested as regulators of permeability. Various elevated proliferative factors (PD-ECGF, VEGF, NGF, EGF, HB-EGF, and antiproliferative factor [APF]) have been found in IC. Among them, APF was the most promising urinary biomarker. It was first discovered in 1996 as a "toxic factor" [30]. APF is a heat-stable sialoglycopeptide that is a homolog of the human frizzled 8 glycopeptide. Its role is mainly in the inhibition of urothelial proliferation, cooperated with other proliferative factors. It also moderates the cell cycle by G2 blockage. APF has been detected in the urine of 95% IC patients compared to 9% in a negative control group. Other studies also report high sensitivity and specificity in diagnosis. In many clinical studies, APF activity and heparin-binding EGF-like growth factor (HB-EGF) levels seemed to respond to hydrodistension. APF and HB-EGF levels were taken at baseline, was followed-up, and analyzed to assess for response assessment. Some investigators also attempted intravesical Bacillus Calmette-Guerin instillation in IC patients [31]. Nitric oxide gas production can be increased in tissue affected by inflammatory process and decreased during treatment with cyclosporine A.

Recently, gene analysis of urothelial proinflammatory markers has been actively tried—*CXCR3* cytokine, *TNFSF14*, *COX-2*, *MAPKSP1*, and *GSPT1*. As mentioned above, regulated by

APF, the proinflammatory genes promote inflammatory cellular responses within the bladder. These molecular entities constitute potential targets for therapeutic intervention.

## CONCLUSIONS

At this time, IC/BPS remains a diagnosis of exclusion. Independent of ESSIC recommendations, the first line of diagnosis is patient selection based on symptoms and an exclusion of other diseases with similar presentation. In addition, cystoscopy and biopsy can help with confirmation and classification. Finally, updated pathophysiologic knowledge including numerous urinary biomarkers has led to changes in the diagnostic criteria.

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