Etiology, Pathogenesis, and Diagnosis of Interstitial Cystitis

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Interstitial cystitis (IC) is a bladder syndrome of unknown etiology. The cause of IC is most likely multifactorial and includes genetic and environmental factors. Various pathophysiological changes in the bladder, pelvis, and peripheral and central nervous systems have been identified, and this has led to the emergence of biologically specific treatment modalities. Interstitial cystitis is being diagnosed with increasing frequency; however, current diagnostic criteria are non-uniform, and there is significant overlap between chronic pelvic pain syndromes in men and women, interstitial cystitis, recurrent “cystitis,” and the overactive bladder syndrome. The diagnosis of interstitial cystitis can be made clinically and by cystoscopy and hydrodistension. The sensitivity and specificity of urinary markers and the potassium sensitivity test have not been prospectively studied.


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Interstitial cystitis (IC) is a bladder syndrome characterized by pelvic pain and irritative voiding symptoms. As originally described, diagnosis was based on the presence of Hunner’s ulcers and reduced bladder capacity. This definition of “classic” or ulcerative IC remained the gold standard until the common type of “non-ulcer” IC characterized by glomerulations and submucosal hemorrhages was described. Over the last few years there has been an evolution in the diagnostic approach to IC toward clinical and minimally invasive diagnosis and less reliance on cystoscopic evaluation under anesthesia and bladder biopsy.
The pathogenesis and etiology of interstitial cystitis remain incompletely defined. However, there is an emerging consensus as to the central role of epithelial dysfunction, bladder sensory nerve up-regulation, and mast cell activation in the genesis of IC. The role of the spinal cord, central nervous system, and the pelvic floor in the pathogenesis and clinical manifestations of IC is now recognized. IC is not an exclusively urologic condition but can have gynecologic, neurogenic, pelvic floor, and gastrointestinal manifestations.

Etiology and Pathogenesis

**Epithelial dysfunction**

The urothelial surface is lined by an impermeable bladder surface mucin composed of sulfonated glycosaminoglycans (GAGs) and glycoproteins. Changes in this surface can cause permeability alterations that allow potassium ions to traverse the urothelium, depolarize sensory and motor nerves, and activate mast cells. This permeability dysfunction is manifested by increased urea absorption and positive potassium sensitivity tests in IC patients. The rationale for the use of “epithelial coating” drugs, such as pentosan polysulfate and intravesical heparin or hyaluronic acid, is their effect on surface epithelial function.

GAGs are not the sole repository of bladder wall impermeability. Other factors, such as intercellular adhesion molecules, extracellular matrix, and the cellular cytoskeleton may be important. A sizable number of IC patients relate the onset of their symptoms to episodes of bacterial cystitis. Bacteria can become sequestered within urothelial cells and cause permeability alterations.

Urinary antiproliferative factor (APF), recently described in IC, inhibits cell proliferation and impairs repair of damaged or denuded urothelium with resulting changes in the barrier function of the urothelium.

**Neuro–Urothelial Interactions**

In addition to its barrier function, the urothelium acts as a “mechanical sensor” of bladder distension and a “chemical sensor” of urine acidity, osmolality, and composition. C-fiber afferent nerves in the submucosa penetrate the urothelium and may mediate these functions. New information on the role of the urothelium as an extension of the sensory nerve system of the bladder is emerging relative to purinergic neurotransmission via the adenosine 5' triphosphate (ATP) pathway and the vanilloid and purinergic (P2X3) pathways. This information should lead to a better understanding of the pathophysiology of IC and the development of new therapies.

Substance P, a tachykinin released by activated C-fiber afferents, is involved in nociception in the central and peripheral nervous systems and also functions as an inflammatory mediator. Substance P release results in an inflammatory cascade with mast cell activation and up-regulation of adjacent nerves (sensory, autonomic, motor). Increased numbers of substance P-containing nerves and substance P receptor (neurokinin-1) mRNA occur in IC. Nerve growth factor (NGF) is also increased in IC, further confirming the role of neurogenic inflammation in IC.
Mast Cell Activation
Mast cells contain vasoactive and inflammatory mediators, (eg, histamine, leukotrienes, prostaglandins, and tryptases), and they play a central role in the pathogenesis of neuroinflammatory conditions, including IC. Release of the granules into the interstitium (degranulation) occurs as part of an immunoglobulin E–mediated hypersensitivity reaction or in response to substance P, cytokines, bacterial toxins, allergens, toxins, and stress. Mastocytosis occurs in 30% to 65% of IC patients. Increased levels of histamine, histamine metabolites, and tryptase occur in IC patients. Therapeutic response to treatment with antihistamines (eg, hydroxyzine) and leukotriene inhibitors speaks to the role of mast cells in IC pathogenesis.

Autoimmunity and Infection
IC has many features of an autoimmune disease—chronicity, exacerbations and remissions, clinical response to steroids/immunosuppressives, the high prevalence of antinuclear antibodies, and association with other autoimmune syndromes. Current evidence suggests that autoimmune phenomena (bladder antibodies, etc) are epi-phenomena that occur as a result of local bladder cellular damage. Cultures in IC patients are routinely negative, and polymerase chain reaction (PCR) studies have not consistently identified bacterial genetic material in IC. However, an episode of cystitis can cause bladder dysfunction that results in alterations in bladder permeability, neurogenic up-regulation (purinergic, afferent, etc), and mast cell recruitment and activation.

IC Pathogenesis:
An Integrated Hypothesis
No single pathological process is universally present in IC. IC may well have multiple etiologies that result in the symptoms of irritative voiding and pain. Changes in urothelial permeability, sensory nerve stimulation, and mast cell activation are interrelated with multiple positive and negative feedback loops occurring simultaneously. This vicious cycle contributes to the chronicity of IC and explains the sometimes disappointing response to single-drug treatment (Figure 1).

Individual patients may have a preponderance of neurogenic inflammation, bladder epithelial dysfunction, or mast cell activation. Once the sensory nerves in the bladder are up-regulated, neurons in the dorsal post-ganglia and spinal cord also release tachykinins (including substance P), leading to a state of neurologic “wind-up” manifested by visceral allodynia and hyperalgesia in the bladder and adjacent pelvic organs (gastrointestinal, gynecologic). This explains why many IC patients have pelvic floor dysfunction, gynecologic symptoms such as dyspareunia and vulvodynia, and gastrointestinal symptoms such as irritable bowel syndrome.

Diagnostic Considerations
Diagnostic approaches for IC are listed in Table 1. In the mid-1980s, the National Institutes of Health–National Institute of Diabetes & Digestive & Kidney Diseases (NIH-NIDDK) promulgated clinical and cystoscopic diagnostic criteria for research studies of IC. These criteria, including exclusions and cystoscopic findings of ulcers and glomerulations, were then widely adopted for both clinical and research purposes and inadvertently became the de facto criteria for clinical diagnosis!

IC patients frequently have overlapping symptoms related to the pelvic organs—urologic, gastrointestinal, gynecologic, and pelvic floor, including the prostate. Patients with the frequency–urgency syndrome,
painful bladder syndrome, and chronic pelvic pain syndrome most likely have IC (Table 2). Some IC sufferers have a preponderance of pain with minor or absent symptoms of frequency and urgency, others have bladder symptoms and no pain, and yet others have both pain and bladder irritability.

**NIH-NIDDK Criteria**

The Interstitial Cystitis Database Study (ICDB) concluded that the NIH-NIDDK criteria were too restrictive for clinical use, because more than 60% of patients regarded by experienced clinicians as suffering from IC failed to meet the criteria. Conversely, 90% of patients who meet the NIH-NIDDK criteria for diagnosis (glomerulations and/or ulcers) were believed by clinicians to have IC. The NIH-NIDDK criteria, though excellent for research studies, are not suitable for routine clinical diagnosis.

Clinicians are increasingly comfortable diagnosing IC on the basis of symptoms (frequency, urgency, nocturia, and pain) in the absence of known infectious and/or neoplastic diseases. Patients with significant microscopic hematuria require cystoscopy to exclude neoplastic lesions. Physical examination frequently reveals anterior vaginal wall and bladder base tenderness in women. This clinical approach to diagnosis is appealing to patients who want to avoid the risks, morbidity, and discomfort of cystoscopy and hydrodistension under anesthesia.

Individual patients request and many urologists continue to recommend cystoscopic evaluation under anesthesia for diagnosis. The advantages of this approach include photodocumentation of bladder inflammation (glomerulations, submucosal hemorrhages, ulcers), bladder capacity determination, exclusion of other diseases, and delineation of the degree and sub-type inflammation, if biopsies are performed. Hydrodistension is therapeutic, with 20%–30% of patients experiencing symptom relief for 3–6 months.

With advances in understanding pathophysiology and pathogenesis, it is probable that the biopsy will identify IC subgroups with differing therapeutic potential (e.g., patients with mastocytosis for antihistamine treatment). Patients with markedly reduced bladder capacities, ulcers, and scar tissue on biopsy are less likely to respond to pharmacological treatment and are more likely to need surgery.

Glomerulations are not pathognomonic of IC. A recent study reported glomerulations in 40% of “normal” women undergoing tubal ligation. Unfortunately, the women were not specifically questioned about urinary or gynecologic symptoms, such as chronic pelvic pain, or asked to complete voiding logs or pain scores. Some of these women may therefore have had “cryptic” IC characterized by pelvic pain and/or irritative voiding symptoms.

Some of the NIH-NIDDK exclusion criteria are problematic: The age exclusion criterion (less than 18 years) is untenable, as IC occurs in children and adolescents. Although involuntary bladder contractions are an NIH-NIDDK exclusion criterion, the ICDB study reported involuntary bladder contractions in 14.6% of IC patients. As previously noted, the major symptom in some IC patients is chronic pelvic pain (bladder, pelvic) with minimal or absent irritative voiding symptoms (frequency, nocturia). This subset of patients clearly does not satisfy the NIH-NIDDK criteria.

**Intravesical Potassium Sensitivity Test (Parson’s Test)**

Parsons introduced the potassium sensitivity test (KCI test) in 1994. Seventy-five percent (75%) of patients with IC (equal numbers of patients satisfying the NIH-NIDDK research criteria and clinical criteria without cystoscopy) have a positive KCI test.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Overlapping Syndromes</th>
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<tr>
<td>▪ Interstitial cystitis</td>
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<td>▪ Painful bladder syndrome</td>
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<td>▪ Frequency-urgency syndrome</td>
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<td>▪ Chronic pelvic pain syndromes</td>
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<td>▪ Overactive bladder syndrome</td>
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At least one quarter (25%) of patients with IC will remain undiagnosed if the KCI test is the sole diagnostic modality.
treatment. In a single-institution study of the utility of the KCl test for IC diagnosis, the sensitivity was 69.5% and the specificity 59%. This led to the conclusion that the test is not a valid diagnostic tool compared to the NIH-NIDDK clinical and cystoscopic criteria.

The rationale for the KCl test is the diffusion of potassium into the bladder wall resulting in nerve depolarization, chronic inflammation, and injury. An alternative explanation may be a primary neurogenic inflammation. The fact that 25% of patients with detrusor instability have a positive KCl test favors a neurogenic mechanism. Thus, the KCl test may be a marker of sensory nerve up-regulation in the bladder and pelvis rather than a marker of increased bladder permeability. The KCl test may identify a subgroup of IC patients with epithelial permeability dysfunction, and this may allow targeted therapeutic intervention with drugs, such as sodium pentosan polysulfate, that reverse epithelial dysfunction.

Further studies are needed to clarify the role of the KCl test in IC diagnosis.

**Urodynamics**

There is significant overlap between the symptoms of the overactive bladder syndrome and IC (ie, frequency, urgency, and urge incontinence). On simple urodynamic evaluation, many IC patients have sensory urgency and instability, reduced bladder capacities, and pain with bladder filling at low volumes.

The current consensus is that urodynamic evaluation is not required for diagnosis of IC but may provide useful information regarding the differential diagnosis of painful voiding disorders and the symptoms of the overactive bladder. Complex video urodynamic evaluation is not needed in the routine examination of patients with suspected IC.

**Bladder Biopsy**

Bladder biopsy is not required for the diagnosis of IC, as there are no pathognomonic histological features of the disease. Bladder biopsy is, however, useful to stratify patients with specific pathogenetic pathways and to exclude specific bladder diseases (eg, carcinoma-in-situ). It is also helpful in counseling patients regarding prognosis—degree and sub-type of inflammation, bladder capacity, presence of ulcers, degree of fibrosis, etc.

Interestingly, bladder biopsy is regarded as essential for diagnosis in Europe and elsewhere. This reliance on biopsy for diagnosis explains the significantly lower reported incidence of interstitial cystitis in Europe and Japan compared to North America.

**Urinary Markers**

The search for noninvasive techniques for diagnosis of IC has led to the study of urinary markers. IC patients with significant mast cell involvement have increased levels of urinary histamine, the histamine metabolite methylhistamine, and tryptase.

A urinary antiproliferative factor (APF) has been described, and levels of this marker are increased in IC patients. The urinary glycoprotein-51 (GP-51) may also be a clinical marker of IC. However, neither of these markers has been assessed prospectively for diagnosis of IC. Ongoing studies are attempting to correlate urinary levels of GP-51 and APF with cystoscopic and biopsy findings, and treatment outcomes.

**Underdiagnosed and Missdiagnosed IC**

The undue reliance on the NIH-NIDDK criteria for diagnosis has led to significant underdiagnosis of IC as shown by the ICDH Study (see Table 3). IC is underdiagnosed in women with symptoms of the overactive bladder syndrome (frequency, urgency and/or urge incontinence). IC needs to be considered in patients with symptoms of the overactive bladder (with and without pain) who do not respond to anticholinergics.

Many patients with IC are treated with repeated courses of antibiotics before they are definitively diagnosed. Urine cultures are usually negative, although urinalysis frequently reveals pyuria. IC should be considered in the differential diagnosis of patients with symptoms of cystitis that are unresponsive to antibiotics and/or culture-negative. Pyuria on dipstick urinalysis in IC patients is confusing, as it leads to the mistaken office diagnosis of bacterial cystitis and treatment with antibiotics.

Up to 70% of men with symptoms of nonbacterial prostatitis and prostatodynia have the cystoscopic appearance (NIH-NIDDK criteria) of IC when cystoscoped under anesthesia. IC in men frequently masquerades as nonbacterial prostatitis/prostatodynia. The recent classification of the Type 3 prostatitis syndrome as chronic pelvic pain syndrome (inflammatory

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**Table 3**

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<th>Underdiagnosed Interstitial Cystitis</th>
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<td><strong>Chronic pelvic pain syndromes</strong></td>
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<tr>
<td>- Women</td>
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<tr>
<td>- Men</td>
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<tr>
<td>- Nonbacterial prostatitis</td>
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<tr>
<td>- Prostatodynia</td>
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<tr>
<td>- Chronic pelvic pain syndrome (NIH Category 3)</td>
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<tr>
<td><strong>“Overactive” bladder syndrome</strong></td>
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<tr>
<td>- Frequency</td>
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<tr>
<td>- Urgency</td>
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<tr>
<td>- Unresponsive to anticholinergics</td>
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<tr>
<td><strong>Recurrent “cystitis” in women</strong></td>
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<tr>
<td>- Pyuria positive</td>
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<tr>
<td>- Culture negative</td>
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<tr>
<td>- Unresponsive to antibiotics</td>
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and noninflammatory) suggests that IC and chronic bacterial prostatitis/prostatodynia may be the same syndrome. The symptoms in both are similar: irritative voiding symptoms, pain (pelvic, bladder, prostate, genital), sexual dysfunction, depression, and anxiety.21

Chronic pelvic pain is frequently the primary symptom of IC. Patients with bladder pain, dyspareunia, and perimenstrual symptom exacerbation are usually referred for gynecological evaluation, whereas patients with bladder irritability present to urologists and gynecologists with symptoms of the overactive bladder and are treated with oral anticholinergics. IC is a common cause of chronic pelvic pain in women, and laparoscopic evaluation in this group of patients is negative or reveals microscopic endometriosis.22 A recent study in women with chronic pelvic pain attending a gynecologist’s office found that up to 80% had a positive KCl test.23 This raises the intriguing possibility that IC is perhaps the most common cause of chronic pelvic pain in women.

**IC Diagnosis: A Synthesis**

The previously rigid, monolithic approach to diagnosis employing the NIH-NIDDK criteria is no longer tenable, as clinicians increasingly rely on clinical diagnosis. This evolution in the diagnostic algorithm has clear parallels to the diagnosis of prostatism and benign prostatic hyperplasia (BPH). Like BPH, there are different approaches to diagnosis.

For routine clinical practice, the use of a validated symptom score instrument, such as the O’Leary-Sant Symptom and Problem Indices,24 and a voiding log may be sufficient for diagnosis, if urine culture and cytology are negative. A broader symptom definition is clearly needed too, so as not to exclude patients (men and women) with pelvic pain, gynecologic symptoms, and lower gastrointestinal symptoms.

Currently, there is no diagnostic tool for IC that has universal applicability. Each approach to diagnosis has inherent limitations. The lack of prognostic information relative to bladder capacity, degree of glomerulations, and ulcers hampers the purely clinical algorithm for diagnosis. The NIH-NIDDK “research” criteria result in the underdiagnosis of over half of patients with IC. Likewise the intravesical KCl test fails to diagnose IC in 25% of patients with cystoscopically confirmed (NIH-NIDDK criteria) or clinically suspected IC. Urinary markers, although attractive as noninvasive diagnostic tools, remain untested.

**Conclusion**

The multifactorial etiology of IC and its complex, interrelated pathogenesis involving the bladder urothelium, sensory nerves, and mast cells are being increasingly defined. The involvement of the pelvic floor, nonurologic pelvic organs, the spinal cord, and central nervous system explain the protean manifestations of IC.

A combination of clinical symptoms, exclusion of infection and cancer, and elevated urinary levels of AFP and GP-51 may prove to be a valid noninvasive diagnostic approach in the future. The NIH-NIDDK criteria remain the “gold standard” for research studies and is diagnostic, prognostic, and therapeutic. Bladder biopsy is best regarded as a research and potentially prognostic tool that stratifies patients with specific pathogeneses and therapeutic potential. The role of urinary markers remains to be elucidated in prospective, multi-institutional studies.

**References**