Interstitial Cystitis: Modern Tools for an Accurate Diagnosis

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Introduction
Interstitial cystitis (IC) is described best as a syndrome of urgency, frequency, and pelvic pain in the absence of positive urine culture or obvious bladder pathology. Patients complain of significant suprapubic pain that often is relieved with urination only. They often void more than 15 times daily, which interferes with work and personal life. These patients typically are women between the ages 30 and 40 years who were initially diagnosed with “recurrent urinary tract infections.” However, this epidemiology likely is caused by misdiagnosis in other population groups: men are diagnosed with benign prostatic hyperplasia or prostatitis and placed on α-blockers or antibiotics and children are told they are dysfunctional voiders and placed on timed voiding regimens.

Theories on Etiology
There are multiple theories regarding the cause of IC; however, no one cause has been proven conclusively. In the meantime, physicians are trying to accurately diagnose a disease that has no identified definitive cause. There have been multiple tests designed to aid in the diagnosis of IC and there are new tests on the horizon that appear promising. However, the diagnosis of IC still is one of exclusion and based primarily on clinical findings. The most useful tests are described in this article, which may make diagnosis a more accurate, less arduous process.

Diagnosis
If a clear etiology were defined, tests could be designed to make a diagnosis. In the meantime, we are left with a handful of tests, which try to make a proper diagnosis. The rest of this article is dedicated to the review of the most salient diagnostic tests, their benefits, and their shortcomings.

National Institute of Diabetes, Digestive, and Kidney Disorders criteria
By the late 1980s, enough people had been diagnosed with IC that the Interstitial Cystitis Association (ICA), a patient advocacy group, was formed. With encouragement from the ICA, the National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK) investigators met to set research criteria to help with the uniform selection of patient characteristics in studying this confusing disease [1•]. The committee decided on well-delineated research definitions composed of multiple inclusion and exclusion criteria to allow recruitment of a narrowly defined group of IC sufferers to be studied.

These NIDDK criteria soon were adopted by practicing physicians as a de facto diagnostic tool for IC, probably because there were no other systematic methods to diagnose IC. These criteria were not designed to be used in routine clinical practice; they likely are too narrow in their definitions. Hanno et al. [2] reviewed a large database of patients recruited for a natural history study of IC (the National IC Database Study). They found that the NIDDK criteria had a positive predictive value of 90% (90% of the patients diagnosed with IC by these criteria were deemed to have IC by treating clinicians). However, 60% of patients in this database were deemed to have IC, which did not meet the NIDDK criteria, by treating clinicians. A highly prevalent symptom of IC, pelvic pain, is not mentioned in the NIDDK criteria.

Although these criteria are helpful in making an IC study population uniform, they probably should not be used solely as a diagnostic instrument.

Questionnaire indices
Because clinical symptoms are such an integral part of the diagnosis of IC, several questionnaires have been designed to help clinicians make the diagnosis and follow the progression/treatment of the disease. These questionnaires have been validated for quantitating subjective symptoms of IC. The O’Leary-Sant IC Symptom and Problem Index [3] and the...
University of Wisconsin IC Symptom Scale [4] are such questionnaires that quantify the patient’s symptoms and determine how these symptoms impact quality of life. These questionnaires ask about patient’s urgency, frequency, pain, and nocturia and how these symptoms affect daily life.

The use of this questionnaire can help identify those patients suffering from IC if the score is sufficiently high. Including these questionnaires in a diagnostic work-up helps clinicians achieve a clearer picture of the magnitude of the problem and gives them a validated questionnaire to follow the patient’s IC symptoms.

**Cystoscopy with hydrodistension**

Cystoscopy with hydrodistension is the oldest and most commonly cited diagnostic tool used by surgeons to make an accurate diagnosis of IC. In 1915, Hunner [5] diagnosed IC by cystoscopic visualization of a “Hunner’s ulcer,” a small mucosal ulceration seen in the bladder on cystoscopy and a severely reduced bladder capacity. It is recognized that Hunner’s ulcers are present in no more than 10% of patients diagnosed with IC [6]. A nonulcerative IC label has been created to account for most patients without Hunner’s ulcers who clearly suffer from symptoms suggestive of IC, but do not have ulcers during cystoscopy. IC patients who do not have Hunner’s ulcer are described to have glomerulations or bladder petechiae after hydrodistention of the bladder only.

Patients frequently undergo this cystoscopy and hydrodistention because it is the current standard for diagnosis. The patient is placed on the operating table in the dorsal lithotomy position with general or spinal anesthesia. The bladder is examined cystoscopically to rule out any other causes of frequency and urgency such as foreign bodies or tumors and to look for Hunner’s ulcers. The bladder then is distended with irrigant that is placed at a height of 80 cm above the level of the bladder. When the irrigant flow stops, the bladder is maintained in this distended position for 2 to 5 minutes; then the bladder is drained. When another cystoscopy is performed after bladder drainage, the appearance of glomerulations or petechial hemorrhages in a concentration greater than 10 per field of vision in more than two quadrants of the bladder provides an objective criterion for the diagnosis of IC.

There are several issues with this test. First, it is an invasive diagnostic test involving anesthesia. Second, there is a subset of healthy patients who also may have glomerulations after this test. Waxman et al. [7] performed this test on 20 asymptomatic patients before tubal ligation and found 45% to have glomerulations. Third, a certain percentage of patients will have increased pain and worsened irritative voiding symptoms after this procedure, although it is typically self-limiting.

This test is used frequently by urologists to diagnose IC, despite its drawbacks. The test evaluates the anesthetic bladder capacity. A rare number of patients with IC will have severely diminished anesthetic bladder capacity, which suggests decreased bladder compliance. These patients may be candidates for more aggressive forms of therapy such as augmentation cystoplasty. Some patients with IC achieve temporary relief of symptoms after hydrodistension, which is another reason doctors are willing to perform this invasive test. Some urine markers that are being studied as potential diagnostic tests for IC normalize after bladder hydrodistension, perhaps suggesting that bladder stretch may be temporarily therapeutic [8].

**Bladder biopsy**

After hydrodistention, random bladder biopsies may be obtained. The bladder urothelium from IC patients has been studied for any abnormalities compared with control subjects. One observation is the presence of an abnormally high number of activated mast cells in the submucosa of IC patients. Some theorize that perhaps an abnormal, hyperactive immune response to urinary toxins is causing an allergic response in the bladder, leading to pain and irritation. Theorides et al. [9] studied the biopsies of 16 control subjects, 11 patients with bladder cancer, and 26 patients with IC. They found markedly more mast cells in the biopsies of IC patients than those of the control subjects, although bladder cancer biopsies also had many stable, inactive mast cells. However, 90% of the IC mast cells were activated, which was statistically higher than the control subjects. Bladder mastocytosis is not a diagnostic criterion for IC, but, with further study, may help define a clinical subset of IC patients that can be diagnosed histopathologically.

**Bladder permeability test**

Based on the theory that IC is caused by increased bladder epithelial permeability, several tests have been designed to detect this defect. If one can demonstrate increased bladder sensitivity to irritants or increased systemic absorption of substances, then a diagnosis of IC could be considered in a patient with appropriate symptoms.

Parsons et al. [10] developed the potassium sensitivity test to help diagnose IC. The patient is placed on a table in the supine position and 40 mL of water is instilled into the bladder as a negative control test. All of the patients, with or without IC, should not have any pain or urinary urgency elicited by water instillation. Next, 40 mL of a potassium chloride solution (40 mEq per 100 mL of water) is instilled into the bladder. The patients rate their level of irritation or pain from the instillation of potassium chloride. Control subjects should not respond, IC patients should describe significant irritation or pain and urgency with instillation of potassium into the bladder. Parsons et al. [10] report excellent sensitivity and specificity with this test, with more than 75% of IC patients and only 4% of control subjects testing positive.

Others have had difficulty reproducing these results with the potassium test. Chambers et al. [11] found the test to have a sensitivity of 70% and a specificity of 50%. Almost 50% of the subjects in their study with a negative potassium test were still thought to have IC. These data call into question whether the test truly provides an accurate diagnosis of IC. However, it is an inexpensive, less invasive way to test for IC (albeit, painful) and will continue to play a role in the diagnosis of IC.