

**INTERSTITIAL CYSTITIS AND CHRONIC PELVIC PAIN:
PRESENT VIEWS ON DEFINITION, CLINICAL PRESENTATION AND
MANAGEMENT**

Daniele Porru, Giovanni Luca Giliberto, Ramona Politanò, Matteo Gerardini, Antonio Cucchi,
Bruno Rovereto. Pavia, Italy

Published European Urology Today Volume 14, No. 4, December 2003

ABSTRACT

Interstitial cystitis (IC) is a clinical syndrome defined by chronic symptoms of urgency, frequency, and/or pain associated with the bladder and unexplained by any other reasonable causation.

The presence of IC is usually difficult to detect, both because of the intermittent and progressive nature of the symptoms and because the disease is easily mistaken for other urologic and gynaecologic disorders. The intravesical potassium sensitivity test helps to identify the presence of IC by detecting the abnormal bladder epithelial permeability that is present in most individuals with IC. Treatments for IC have ranged from pharmacological treatments that anaesthetize the bladder to antihistamines or drugs that reintegrate urothelial permeability, pain medications including tricyclic antidepressants. New options have been tried in cases refractory to more usual treatments, such as oral pentosanpolysulfate, and intravesical administration of different medications: dimethylsulfoxide (RIMSO), heparin, hyaluronic acid, BCG. More recently, detrusor infiltration with botulinum toxin by cystoscopy, and sacral neuromodulation have been tried. Some time and more extensive experience will be needed to evaluate the results of these new treatment modalities.

Definition and diagnosis of IC

The diagnosis and management of interstitial cystitis (IC) has a long and varied history. Leading theories for its pathogenesis include deficit of urothelial permeability, increased activity of mast cells, immuno-neural mechanisms and neuroplasticity, infectious etiologies.

The diagnosis of this syndrome was vague until 1987, when the US NIDDK developed criteria that were to be used in national research studies. Agarwal, O'Reilly & Dixon state "The criteria were intended to be for research purposes, to compare the patient population in various research studies, but because there were no other clinical guidelines, they were adopted by urologists worldwide for diagnosing patients"(1). The problem, though, was that not all IC patients in a typical urology practice met these strict guidelines. A patient with frequency, urgency or pain, with no evidence of petechial hemorrhages, may have been told that they had psychiatric problems. NIDDK criteria are therefore much too restrictive for clinical usage, and have resulted in many patients being left undiagnosed, and possibly untreated. A recent study (2), although confirming the research utility of the NIDDK criteria, shows that over 60 % of cases would not have been diagnosed if clinicians relied on the need to meet the NIDDK criteria to make the diagnosis; besides, IC has even been described in children (3), and should not be considered an unknown condition in men (4, 5). To the extent that treatment is delayed because of this, does patients a great disservice. The challenge to clinicians, when facing IC, is to diagnose the condition early and initiate therapy.

IC is still a diagnosis of exclusion, and since patients do not typically report a full constellation of symptoms at onset, it is useful to understand how the earliest symptoms appear. It is now

recognized that early cases of IC show no reduction in bladder capacity, performed under anaesthesia (6, 7, 8). Therefore it appears that advanced cases that would show a reduction in bladder capacity would also show petechial haemorrhages, thus excluding all the early cases.

There is no standard, accepted clinical definition of IC at this time. The closest thing we have is that IC is a clinical syndrome defined by chronic symptoms of urgency, frequency, and/or pain associated with the bladder and unexplained by any other reasonable causation.

Many cases of pelvic pain may be related to IC, according to the results of a study using the intravesical potassium sensitivity test (PST) (9). In this study, it is suggested that the frequency of IC in the United States may be 20 times greater than previously reported.

The presence of IC traditionally has been difficult to detect, both because of the intermittent and progressive nature of the symptoms and because the disease is easily mistaken for other urologic and gynaecologic disorders. The intravesical potassium sensitivity helps to identify the presence of IC by detecting the abnormal bladder epithelial permeability that is present in most individuals with IC.

Gynaecologists at different medical centres (9) administered the PST to 244 consecutive unselected patients with pelvic pain and to 47 control subjects. Although 84% of patients reported urologic symptoms, initial clinical diagnosis on the basis of the chief symptomatic complaint(s) was IC in only 1.6% of the patients. Other clinical diagnoses included endometriosis, vulvodynia (vulvar vestibulitis), and pelvic pain.

PST was positive in 197 patients (81%) and in none of the control patients ($P < .0001$). Frequency of positive PST was comparable across all four sites and all clinical diagnoses.

Interstitial cystitis may be a common unrecognised cause of pelvic pain in gynaecologic patients and deserves greater, if not primary, consideration in the differential diagnosis of pelvic pain. If IC goes unrecognised, the pain may become intractable because of altered pain pathways, or IC may reach advanced stages, when substantial damage to the bladder has occurred.

The delay between the onset of urinary symptoms and the diagnosis of IC is on average 5 years (10, 11), the course of the disease is chronic and aggravating, and therefore we tried to examine how disease progresses from the initial phase to late IC.

We reviewed and evaluated all patients diagnosed with IC between 2000 and 2003 in our Department. Patient records and case sheets were examined retrospectively and telephone interviews were conducted. The exact onset of urethral and/or bladder pain was recorded, as well as the time of presentation of frequency, urgency, nocturia and pain. The date of IC diagnosis and the interval from onset of clinical symptoms to diagnosis were determined. Diagnosis of IC was made when NIDDK criteria were met by patients with a clinical suspicion of IC. The interval between the onset of any urinary symptom and the onset of urgency/frequency, pain and nocturia was established and defined as symptom progression time. Different alternative diagnoses and surgical treatment received were also determined.

The study group included 25 female patients 27 to 69 years old when diagnosis was made. Mean age was 46.7. When first symptomatic, patients had a mean age of 41.9 years (range 18 to 66). Patients were symptomatic for a median of 4.9 years before a diagnosis of IC was made. No patient reported simultaneous onset of urgency/frequency, nocturia and pain as initial symptoms. Seventy per cent of patients had only one symptom at onset. Eleven months was the mean time from the onset of first symptom to the appearance of all symptoms. The most frequent initial diagnosis was urinary tract infection (UTI) in 16 patients (64 %), who had positive cultures; actually, during the first 6 months of the disease, the documentation of positive urine culture or pyuria on urinalysis was possible; subsequently, negative urine cultures were constantly detected. All 16 patients whose initial diagnosis was UTI (between 1 and 3 episodes of UTI with positive culture), had temporary resolution of symptoms with culture-specific antibiotics, and subsequent reappearance of "UTI" symptoms with repeated negative urine cultures; the final diagnosis was IC in 12-24 months time. Initial diagnoses were urgency-frequency in 26 % of cases and pain in 10 % (Fig. 1). Other previous diagnoses were endometriosis (6 cases), trigonal leucoplakia (5 cases), chronic cystitis (5 cases),

and bladder neck obstruction (3 cases). Three women received laparoscopy to assess pelvic endometriosis, and in 2 cases three laparoscopic operations were performed. Hysterectomy had been performed in 2 cases of a gynaecologic diagnosis.

Therefore, a condition of bacterial recurrent UTIs, with subsequent persistence of symptoms and negative cultures, could be detected as a harbinger of IC in 64 % of our patient group. Besides, IC may initiate with a single symptom before progressing to its full clinical manifestation. We can then argue that the diagnosis of IC does not require all its clinical features simultaneously to be suspected. Patients with the disease in its early phase should be carefully evaluated to make a correct diagnosis and start an appropriate treatment in the initial clinical course of the disease.

Various and different treatment regimens originated from different presumed etiologies, none of which emerged as suitable to eradicate the symptoms of this distressing condition. Treatments for IC have ranged from pharmacological treatments that anaesthetize the bladder to antihistamines or drugs that reintegrate urothelial permeability; pain medications including tricyclic antidepressants.

Chronic pelvic pain

On the basic science front there appears to be a surprising convergence of data suggesting common neural mechanisms associated with chronic pain, nocturia and urgency-frequency (10, 11, 12). Similar mechanisms may be involved leading to a limited spectrum of behaviours that the bladder can express, regardless of the etiology (neural, infection, inflammation). Chronic pain can follow two distinct pathways for its initiation and maintenance: one involves sensitisation of nociceptive pathways due to nerve growth factor (NGF) with activation of neurons in the CNS and silent-C fibers in the periphery; this pathway leads to “neuropathic pain”. Another pathway is associated with activation of silent C-fibers, and leads to chronic inflammatory pain.

Treatment of the two conditions is different. Prostaglandin inhibitors or opiates fail in the treatment of neuropathic pain; neurontin and anticonvulsive drugs are of limited value. On the other hand, COX2 inhibitors and opiates relieve inflammatory pain. It may be that one or both mechanisms play a role in the origin of discomfort and also urgency and frequency of IC.

Urologists are now investigating the potential uses for BTX-A for various urological problems including detrusor external sphincter dyssynergia (DESD), detrusor hyperreflexia, conditions of pelvic floor spasticity, and overactive bladder. By studying the nerve pathways that are affected by BTX-A, researchers hope to provide new targets and treatments for IC. This treatment is not currently approved for use in IC in the U.S. However, clinical studies are being planned.

A recent study (13) tested sacral nerve stimulation in 25 patients with severe IC. Of the 25, 17 showed significant benefit, and thus had the device permanently implanted. Before treatment, these patients had to void an average of 17.1 times a day and 4.5 times a night. After 14 months of treatment, those figures dropped to 8.7 and 1.1, respectively. Voided volume increased significantly, too. Patients reported an average decrease in pain of 4.2 points on a 10-point scale (dropping from an average of 5.2 to 1.6). Their scores on the Interstitial Cystitis Symptoms and Problem Index also dropped significantly—from 16.5 to 6.8 for symptoms and from 14.5 to 5.4 for problems.

In the near future, the explanation for why certain patients are predisposed to conditions such as IC, prostatodynia, fibromyalgia, and irritable bowel syndrome may be revealed by genomics; pharmacogenomics may provide us with new agents or approaches relying on turning off activated pain pathways and targeting specific neurotransmitter receptors or second messenger.

Efforts to make possible a more precise diagnosis of IC should be encouraged, given the uncertainty of the diagnostic process of this syndrome. As to the name of IC, Agarwal (1) offers compelling reasons for changing the name of this syndrome. "The term IC is fraught with problems: first, including the term cystitis makes the patient think that they have acquired some kind of infection and thus hope to benefit from anti-infective agents; second, the term IC gives no indication of the severity (or pain level) of the disease, the inflammation of the bladder walls seen in IC can be found

in many other bladder disorders... and therefore the term is incorrect even from a pathological perspective." It has been suggested that the term "painful bladder syndrome" is more appropriate. Still others have suggested the terms pelvic pain syndrome or lower urinary tract syndrome. In either case, it is clear that much work remains to be done. Above all else, we must be reassured that patients will not be told that it is "all in their heads" just because they fail to meet the strict NIDDK guidelines.

Presently, there is a tremendous push to reclassify several disorders and lump them together as chronic pelvic pain. These include what has been referred to in the past as "prostatitis" in men, pelvic pain and dyspareunia (painful intercourse) in women, and interstitial cystitis. We have to be careful and not eliminate distinctions between these disorders until we are sure that they have enough in common to justify inclusion under the same definition, and that doing so is in the best interest of enhancing research into etiology and cure, and ultimately helping the patients who suffer from them. Otherwise, although it might benefit the pharmaceutical companies by providing them with a larger market for sales, the benefits might prove to be illusory. Thus, I think we need to wait for the right questions to be developed and the answers to be critically examined before we speculate on what might prove to be a new definition of IC.

Fig. 1 Order of clinical presentation in IC

