Interstitial Cystitis: Current Issues and Controversies

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INTRODUCTION

Interstitial cystitis (IC) is a chronic, debilitating disease affecting mainly women, but also men and children. Characteristic clinical presentation includes urinary urgency, frequency and chronic pain without evidence of bacterial infection. Many patients have a very poor quality of life for many years as IC interferes with employment, social relationships and sexual activity. The course of the disease is usually marked by flare-ups and remissions. Other conditions that should be ruled out include bacterial cystitis, tuberculosis, carcinoma in situ, vaginitis and endometriosis. IC is diagnosed by cystoscopy and hydrodistention of the bladder. Glomerulations or Hunner's ulcers are typical findings. Oral treatments for interstitial cystitis include pentosan polysulfate, tricyclic antidepressants and antihistamines. Intravesical therapies include hydrodistention, dimethyl sulfoxide (DMSO), heparin, or a combination of agents.

That said, IC is an enigmatic disorder surrounded by controversy (Table 1). Its etiology is unknown [1], its pathophysiology remains uncertain [2], and the efficacy of treatment regimens is questionable [3]. Furthermore, knowledge of the epidemiology of IC is fragmentary, especially ascertaining the burden of disease in the population and the identification of possible risk factors [4]. This article reviews current issues and controversies relating to the definition, epidemiology, etiology, diagnosis and therapeutic aspects of the disease.

DEFINITION AND TERMINOLOGY OF IC

During the twentieth century several names were coined for the disease including cystitis parenchymatosa, Hunner's ulcer, painful bladder syndrome and detrusor mastocytosis, before it acquired its current name of IC [1,5]. The term IC is not without drawbacks: First, the word cystitis leads patients to believe that they have some kind of bladder infection; second, the problem of IC often involves not just the bladder structures but extends beyond.

Diagnostic critiera are an important current issue in the debate concerning IC. In the early twentieth century, it was considered mandatory that a clinician see the typical Hunner's ulcers and mast-cell infiltration through histology to diagnose IC. While urologists no longer seek Hunner's ulcers, petechial haemorrhages or glomerulations in the bladder after hydrodistension have become the hallmarks of current diagnosis. However, some evidence casts doubts on the specificity of glomerulations for the diagnosis of IC. Waxman et al [6] assessed 20 asymptomatic women undergoing tubal ligation to test for the presence of glomerulations on hydrodistension; the number of haemorrhages was scored on a scale of 1-5. The authors found that the increasing scores after hydrodistension in normal women was in identical proportion to that seen in patients with IC. Furthermore, glomerulations reportedly do not correlate with the degree of inflammation observed histologically [7] or with any symptoms [8].

The National Institute of Digestive, Diabetes and Kidney Diseases (NIDDK) criteria for IC were first laid down in a workshop of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases in 1987 [9] and were then revised in another workshop a year later [10, 11]. The NIDDK criteria were meant to provide a uniform population of patients for research studies. Since there were no other clinical guidelines, the criteria were adopted clinically by urologists worldwide for diagnosing patients. Although this provided a reference point, many patients were omitted as they failed to meet the criteria [12]. Only 36% of patients now considered to have IC meet all the criteria laid down by the NIDDK [13,14]. Thus adherence to NIDDK criteria for clinical diagnosis of IC is too restrictive and would exclude the majority of IC patients. A more inclusive definition of this symptom complex has been provided in the IC Database (ICDB) Study [15]. Of patients entered into the ICDB study with less stringent criteria than the original NIDDK criteria, 90% were considered by experienced clinicians to have IC.

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Table 1. Current Issues & Controversies about IC

Definition & Terminology	
	The term IC is not ideal.
	Should the term "painful bladder syndrome" replace "IC"?
	NIDDK criteria are too stringent.
	Should the ICDB definition be adopted universally?
	What is the distinction between IC and CPPS/CP in men?
Epidemiology	
	What is the true prevalence of IC?
	Is the increase in IC prevalence a reality, or simply due to changes in diagnostic criteria?
	What is the prevalence of IC in children?
Etiology	
	The exact etiology for IC remains unknown.
	Multiple etiological factors can act in combination.
	Neuropathological changes are important in perpetuating IC pain.
Diagnosis	
	Early diagnosis is crucial to improve treatment outcomes.
	IC is often associated with other diseases.
	The diagnostic value of cystoscopy is questioned.
	The diagnosis of IC can only be reached by exclusion.
	The value of PST is uncertain.
	Standard questionnaires should be developed.
	Urine markers hold promise.
Treatment	
	Effective treatment is lacking.
	Treatment goals must be realistic.
	Combination treatment is usually required.
	Psychological support is important.

On the other hand, if the NIDDK criteria were strictly applied to this cohort, >60% of patients regarded by the investigators as definitely or very likely to have IC would have been misdiagnosed and not classified as IC.

In a meeting of British Association of Urological Surgeons (BAUS), it was proposed that the term 'painful bladder syndrome' might be more appropriate for IC [16]. By calling the disease 'painful bladder syndrome' and diagnosing it on the basis of clinical symptoms of frequency, urgency, and chronic suprapubic/pelvic pain after exclusion of other known causes, would most likley significantly increase the number of IC patients. On the other hand, such an approach would cause confusion in distinguishing IC from other clinical entities which are also characterized by chronic pain in the pelvic region. Bogart et al [17] performed a systematic literature review to determine how best to distinguish IC from related conditions in women. The most commonly reported IC symptoms were bladder/pelvic pain, urgency, frequency and nocturia. IC and painful bladder syndrome share the same cluster of symptoms. Effective antibiotic use can distinguish recurrent urinary tract infections from IC in some cases. Pain distinguishes IC from overactive bladder. Dysmenorrhea may distinguish endometriosis from IC, however some women may have endometriosis plus IC.

Attention has also been given to the classification and description of the constellation of signs and symptoms presenting in men with chronic prostatitis, now called the chronic pelvic pain syndrome (CPPS) [18,19]. The hallmark symptoms of chronic prostatitis include pelvic pain, voiding dysfunction, painful ejaculation and sexual dysfunction [20-22]-symptoms that overlap considerably with those in men diagnosed with interstitial cystitis [23]. Preliminary studies suggest that the CPPS may indeed be a category of IC because only a small proportion of men with chronic prostatitis/CPPS have pathologically demonstrated prostate inflammation [24]. In addition, presence of bladder petechiae after hydrodistension has been demonstrated in men diagnosed with prostate pain [25]. Because of the considerable overlap of symptoms between chronic prostatitis and IC [26], misdiagnosis is likely to be common. Men presenting with a constellation of symptoms indicative of IC are more likely to receive a diagnosis of CPPS/chronic prostatitis than IC [23].

EPIDEMIOLOGY

According to Ratner et al IC affects as many as 700,000 women in the United States [27]. Data from the Nurses' Health Study (NHS) suggest that the prevalence of IC among women was about 67 per 100,000 in NHS-II and 52 per 100,000 in NHS-I [28]. The non-ulcera-tive type of IC occurs in about 90 percent of patients; the ulcerative form in about 10 percent. Women make up 90 percent of patients with interstitial cystitis while men comprise 10 percent [29]. Children can also have interstitial cystitis [28]. The onset of interstitial cystitis usually occurs between 30 and 70 years of age, with a median age of 43 [30].

The prevalence of the disease appears to be increasing among young and middle-aged women. However, as diagnostic criteria vary, so does the reported prevalence of IC. That said, prevalence data have changed significantly over the past 30 years. A population-based study reported a prevalence of 18.1/100,000 in 1975 [31]. The prevalence rate is much higher, at 510/100,000, in a self-report study done in 1997 [32]. Some people feel that the latter rate still represents a significant underestimate of the true prevalence. Given the new or expanded definitions of IC, Sant [33] estimated that about 10.8 million patients have IC in the United States. The NIH and NIDDK are sponsoring development of a consensus statement that hopefully will provide more appropriate diagnostic criteria for clinical use.

ETIOLOGY

Leading theories for IC pathogenesis include: (1) Changes in urothelial permeability; (2) increased mast cell activity; (3) neuro-immune abnormalities; (4) neuroplasticity of the nervous system; (5) infectious etiologies. While the exact cause of IC is not known, it is probably related to multiple factors in combination. One popular hypothesis suggests that a defect in the glycosaminoglycan component of the mucin layer that covers and protects the bladder urothelium leads to leakage of irritating substances in the urine into the underlying bladder wall. This mucosal failure or leakage causes inflammation, tissue injury, mast cell degranulation and sensory nerve depolarization, which result in the urinary urgency, frequency and pain patients experience [34].

On the other hand, it is generally accepted that the pathophysiology of IC involves neuroplastic changes that develop as a result of prolonged inflammatory or noxious stimuli, resulting in a self-perpetuating chronic pain syndrome [35]. Visceral pain syndromes involve chronic neurogenic inflammation, afferent overactivity, and central sensitization, which interact to perpetuate pain [36-38]. These patients may have multiple potential pain generators that lie outside of the bladder, which may cause a spectrum of clinical manifestations [39]. IC is not simply a disease of the bladder, but a clinical syndrome with features of urgency, frequency, and pain due to the development of neuropathology that results in a visceral pain syndrome.

DIAGNOSIS OF IC

Typically, IC is symptomatic for 4 to 7 years before being correctly diagnosed. The mean delay between occurrence of symptoms and diagnosis was 5.3 years in NHS-II and 7.1 years in NHS-I [28]. Early diagnosis and treatment in the course of the disease is crucial for successful therapeutic outcomes. In IC patients who were diagnosed within 2.5 years of the onset of symptoms, oral medication could achieve a better than 75% symptomatic improvement in more than 80% of patients [40]. However, the diagnosis of IC is complicated by the coexistence of other clinical entities. In comparison to the general population, individuals with IC are 100 times more likely to have inflammatory bowel disease and 30 times more likely to have systemic lupus erythematosus. Moreover, allergies, irritable bowel syndrome, sensitive skin, and fibromyalgia have an increased association with IC [41]. It is possible that in some IC patients, a certain underlying etiology may lead to several pathological processes occurring simultaneously in multiple organ systems. Until the etiology and pathophysiology of IC are elucidated, the clinical diagnosis of the disease will remain anything but straight forward.

Currently, there are no definitive positive diagnostic criteria for IC. Diagnosis works by exclusion and depends very much on symptoms. However, the symptomatic presentation in patients varies. In order of frequency, symptoms include urgency, urinary frequency, pelvic pain, pelvic pressure, bladder spasms, dyspareunia, burning, awakening at night with pain, and pain that persists for many days after intercourse.

The location of pain includes the vaginal area, the lower abdomen, suprapubic area, groin or lower back. Symptoms in females are often related to menstruation and 75% of patients feel that sexual intercourse exacerbates their symptoms [42]. The symptoms of IC typically worsen in the week before menstruation in contrast to the symptoms of endometriosis, which are worse during menses. Sometimes the symptoms of IC are exacerbated after patients consume certain foods, especially coffee, alcohol, carbonated drinks, citrus fruits, tomatoes and chocolate.

Conditions that must be excluded in the differential diagnosis include bacteriuria, urinary tract tuberculosis, Chlamydia trachomatis infection, prostatitis, carcinoma in situ, neuropathic bladder dysfunction and gynecologic diseases such as pelvic inflammatory disease, vaginitis, vulvar vestibulitis and endometriosis. Patients with pyuria, but a negative bacterial culture should be tested for tuberculosis and Chlamydia. A careful pelvic examination is needed to rule out vaginitis, vulvar lesions and urethral diverticula. Urinalysis for IC patients may be entirely normal or may show microscopic hematuria or pyuria. Urine culture results are usually sterile. However, patients with IC may also have a concurrent bladder infection. Urine cytology may be helpful in ruling out transitional cell carcinoma of the bladder. Urodynamic studies are not specifically diagnostic of IC. Radiographic studies, such as intravenous pyelography or voiding cystourethrography, are seldom indicated for the evaluation of IC patients.

Cystoscopy has continued to be the "gold standard" for the diagnosis of IC in clinical practice, even though evidence shows that the presence of glomerulations is non-specific [6]. One of the NIDDK criteria is cystoscopy under anesthesia that demonstrates either Hunner's ulcers or more than 10 glomerulations in three quadrants of the bladder, using a double-fill hydrodistention technique [43]. Cystoscopy should be used to exclude bladder carcinoma in selected cases with hematuria or elderly patients with recent-onset symptoms. Biopsies are indicated in patients with suspected pathology such as carcinoma, dysplasia or tuberculosis.

The intravesical potassium sensitivity test (PST) is based on the theory that patients with IC have a urothelial defect that allows cations to penetrate the mucosa, thus depolarizing the sensory nerves (C-fibers) and subsequently creating lower urinary tract symptoms [44]. PST is found to be positive in 78% of patients who meet all NIDDK criteria for IC and rarely so in controls. On the other hand, the test is also positive in patients with detrusor overactivity, radiation cystitis and bacterial cystitis. Moreover, false negative tests can occur with severe disease and after treatment [45]. Another problem is the pain experienced by the patient subjected to PST can be quite severe and may last for days or weeks. Thus although the test may identify a subset of IC patients with epithelial permeability dysfunction, less invasive and painful tests are preferable.

Since IC is a clinical syndrome with urinary urgency/frequency and/or pelvic pain, urinary diaries and questionnaires are useful tools to access symptom severity, as well as quality of life issues. O'Leary et al [46] has validated two tools for the quantification of symptoms of IC; the IC symptom index and the IC problem index. Parsons et al [47] recently developed and validated a self-administered questionnaire (pelvic pain and urgency/frequency symptom scale: PUF) that not only identifies bladder symptoms, but also identifies symptoms of pelvic pain and intercourse-related symptoms. This questionnaire has been validated using test/retest evaluation in patients with NIDDK IC as well as controls. Additionally, this eight-item scored questionnaire has been compared with outcomes when performing potassium sensitivity testing.

The search for noninvasive diagnostic methods for IC has led to the efforts to develop urinary markers. The more promising candidates are antiproliferative factor (APF), epidermal growth factor, heparin-binding epidermal growth factor-like growth factor, glycosaminoglycans, and bladder nitric oxide. The potential applications of these markers are: (1) as diagnostic markers; (2) distinguishing relevant subsets of IC patients; and (3) measuring disease activity and objectively following treatment responses [48].

The diagnosis of IC in children remains controversial. There is some likelihood that IC in children is under-detected, but childhood IC is a rare diagnosis made by urologists. Many cases of voiding dysfunction in children are self-limiting. How many of these cases are early IC? How many cases will re-emerge in adulthood? Would early treatment in children increase the chance of permanent remission? Approximately 25% of IC patients report they were plagued with chronic urinary tract problems as children [32]. It is hopeful that development of useful urinary markers as non-invasive diagnostic tools for IC will help increase our knowledge on IC in children.

TREATMENTS FOR IC

On account of the lack of a single, effective treatment for IC, multiple treatment modalities are available and combination therapy is usually required to obtain the best therapeutic outcomes. The patient must understand that IC is chronic in nature and the primary goals of therapy are symptom reduction and improvement of quality of life; cure or complete remission may not be attained. Current treatments for IC include dietary control, bladder retraining, oral medication, intravesical therapy, hydrodistension, neuromodulation, surgical intervention and psychological support.

Dietary control is a first-line approach to self-care for IC patients. Unknown metabolites from certain kinds of food are postulated to penetrate the bladder surface irritating hypersensitive nerves. Acidic foods, caffeine, alcohol, artificial sweeteners and chocolate are common offending elements which should be avoided. However, not every patient is sensitive to the same sorts of food. Patients must keep a record of their personal list of offending foods.

Most IC patients suffer the symptoms of urinary urgency and frequency. Constant urination at low volumes results in further loss of bladder functional capacity. A protocol of progressive small increments in voiding time intervals may be helpful to maintain bladder capacity. It has been demonstrated that this method has produced a 50% improvement in symptoms of frequency, urgency and nocturia [49].

Oral medications include tricyclic antidepressants (TCA), antihistamines and pentosan polysulfate (Elmiron). TCA block pain arousal and are often used in pain clinics. Commonly used TCA are amitriptyline (Elavil), doxepin (Sinequan) and imipramine (Tofranil). No placebo-controlled studies with tricyclic antidepressants have been performed, but these medications have been found to be beneficial in several open-label studies [50]. Use of hydroxyzine (Atarax), an antihistamine, is based on the hypothesis that histamine released by mast cell degranulation may be responsible for symptoms of interstitial cystitis. Hydroxyzine (in a dosage of 25 to 75 mg at bedtime) and the H2-receptor antagonist cimetidine (Tagamet), in a dosage of 300 mg twice daily, were both effective in open-label studies [51,52]. Pen-

tosan polysulfate is the only oral therapy for the treatment of interstitial cystitis symptoms that has been studied in placebo-controlled trials. Pentosan polysulfate is a highly sulfated polysaccharide with chemical and structural similarities to heparin sulfate, one of the constituents in glucosaminoglycans. In a placebo-controlled study, bladder pain was relieved by at least 50 percent in 38 percent of patients taking pentosan polysulfate, compared with 18 percent improvement in patients treated with placebo [53]. It usually takes three to six months for patients to respond to pentosan polysulfate. The standard dosage is 100 mg orally three times per day. Adverse reactions to pentosan polysulfate include diarrhea, dyspepsia, reversible alopecia, headache, rash, dizziness, abdominal pain and occasional liver function abnormalities.

Other medications that may reduce IC symptoms include sedatives and analgesics. Combination treatment with multiple drugs is often attempted in clinical practice. Some patients feel better after taking aspirin or a nonsteroidal anti-inflammatory drug, probably because mast cell degranulation releases prostaglandins and leukotrienes [33]. Other drugs that may be useful are anticholinergics, bladder analgesics such as phenazopyridine (Pyridium) or oxybutynin chloride (Ditropan), calcium channel blockers such as nifedipine (Procardia), or gabapentin (Neurontin). Supportive evidence for these treatments is lacking [54].

A commonly used agent for intravesical treatment of IC is DMSO. Intravesical drug administration provides high local drug concentrations in the bladder, avoids systemic side effects and eliminates the problem of low levels of urinary excretion with oral medications. A controlled study showed that 53% of patients in the DMSA treatment group had significant improvement of symptoms [55]. DMSO Instillations are usually given every one to two weeks for a total of four to eight treatments. Following the initial course of treatment, some patients achieve long-term remission, but most eventually relapse. Additional treatments may be needed for patients who relapse. Heparin sulfate is a glycosaminoglycan constituent. In an open-label study, 56% of IC patients obtained relief from symptoms using heparin intravesically, in a dosage of 10,000 U three times a week [56]. Instillation of hyaluronic acid, in a weekly dose of 40 mg, provided complete symptom relief in 25% of patients and partial relief in 46 percent [57]. In a controlled study using six weekly instillations of bacillus Calmette-Guerin, 60% of patients with IC had symptom reduction compared with 27 percent of patients receiving placebo [58]. The use of capsaicin, resiniferatoxin and anesthetic cocktail with a combination of DMSO, heparin, steroids, bicarbonate and a local anesthetic for intravesical administration has also been reported [59]. For patients who are suitably motivated and trained, the technique of intermittent self-catheterization and drug instillation can reduce the number of clinical visits. However, more controlled studies are required before recommendations can be made for various kinds of intravesical pharmacotherapy.

IC patients often have spasms of the pelvic floor muscles that contribute to symptoms of pelvic pain, urgency and frequency. Physical therapy with biofeedback for pelvic floor relaxation may be helpful. Neuromodulation is another alternative. Transcutaneous electrical nerve stimulation resulted in improvement or remission in 54 percent of patients with classic interstitial cystitis (i.e., Hunner's ulcers) and in 26 percent of patients with non-ulcerative interstitial cystitis [60]. More recently, clinical devices such as electromagnetic stimulation (Neotonus, Marietta, Ga) or sacral nerve root stimulation (Interstim, Medtronic Corporation, Minneapolis, Minn) have become available. However, few of these devices have been subjected to placebo-controlled randomized trials.

Surgical treatments for IC have demonstrated limited success. Sacral rhizotomies, augmentation cystoplasties, and cystectomies have failed to achieve long-term symptom remission in the majority of patients [61].

The psychological impact of relentless symptoms and disappointing treatment results on IC patients can be enormous. These patients are often unable to work, unable to perform routine daily activities, and unable to leave their own homes. Dyspareunia can be so severe that many patients abstain from sexual relations altogether. The stress of living day to day with these factors has led to despair and suicide of some patients. Patient mutual support groups are especially helpful. Physician support and attention to associated psychosocial problems can greatly improve the patient's response to treatment. In the United States, the founding of the Interstitial Cystitis Association (ICA) in 1984 has increased substantially the awareness of the disease within both the medical and patient communities [62]. In Taiwan, it is our hope that construction of the Taiwanese Continence Society (TCS) Clinical Practice Guideline for Interstitial Cystitis can be an important step for improving our care and support for IC patients.

CONCLUSION

Interstitial cystitis, a chronic pelvic pain syndrome that occurs primarily in women, is much more common than originally believed. Its etiology is unknown, its evaluation and diagnosis remain controversial, and its treatment is largely empiric. Continual basic and clinical research is necessary to unlock the mystery surrounding this disease. Before the etiologic, diagnostic and therapeutic puzzles can be solved, diagnostic awareness, realistic treatment expectations and psychological support for the patients are the keys to effective management at this point in time [63].

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