

CURRENT CONTROVERSIES THAT ADVERSELY AFFECT INTERSTITIAL CYSTITIS PATIENTS

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ABSTRACT

Interstitial cystitis (IC) remains a diagnosis of exclusion, based on the symptoms of urinary urgency, frequency, and pelvic pain in the absence of other definable causes. Certain areas of controversy in the field of IC research have a significant adverse affect on patients. Many physicians still do not believe that IC exists, or else believe that it is a rare postmenopausal condition. This can cause significant delays in diagnosis and treatment. It is particularly problematic in children, whose symptoms are often diagnosed as “voiding dysfunction” and are thought to be self-limiting. It can also be problematic for men, who are often unsuccessfully treated for prostatitis over the course of many years, and for whom the diagnosis of IC is never entertained. In some cases, when no diagnosis is made, patients are left to live with severe, debilitating symptoms and have nowhere to turn for help. Resistance to treating severe nonmalignant pain with opioid medication further compounds this problem and has led to suicide in this patient population. The “gold standard” of cystoscopy with hydrodistention is now being questioned, and an overreliance on the potassium test, which has a high false-negative rate, may lead to significant underdiagnosis of IC. New urinary markers hold promise for both diagnostic as well as therapeutic potential, but are not yet commercially available. IC may be an organ-specific disease in some patients and a systemic condition in others. Many patients have multiple disorders and have no physician to manage their overall health. The Interstitial Cystitis Association believes that the best way to address these unresolved areas of knowledge is to: (1) educate patients on all available diagnostic and therapeutic options so that patients, with the help of their physicians, can make the best informed decisions possible, and (2) aggressively pursue all avenues of research, particularly epidemiology. *UROLOGY* 57 (Suppl 6A): 89–94, 2001. © 2001, Elsevier Science Inc.

When a thing was new, people said, “It is not true.” Later, when the truth became obvious, people said, “Anyway, it is not important.” And when its importance could not be denied, people said, “Anyway, it is not new.”

—William James (1842–1910)

Interstitial cystitis (IC) is coming of age after years of misdiagnosis, misunderstanding, and outright denial. Characterized by varying degrees of pelvic pain, urinary urgency, and frequency, IC can dramatically impact the quality of life of those who have this disease. Although great strides have been made in IC research over the past decade, many fundamental questions remain unanswered. Since the founding of the patient-driven Interstitial

Cystitis Association (ICA) in 1984, awareness of the disease within both the medical and patient communities has increased substantially, and research has increased dramatically. The ICA’s work with the National Institutes of Health (NIH) and Congress has enabled the development of a dedicated international IC research community. Early diagnosis has increased significantly, and an array of treatment options is now available.

Despite this progress, there are many areas in the field of IC research that remain poorly understood, and as a consequence, have a major negative impact on patients with IC. These patients are faced with a myriad of confusing choices due to unresolved controversies, while trying to cope with a severely debilitating chronic illness.

THE IMPACT OF INTERSTITIAL CYSTITIS

Although the medical community may find this disease particularly frustrating to treat, and in fact may even deny the existence of the condition, the

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impact of IC on patients can hardly be overstated. The physical, emotional, psychological, and socio-economic impact of IC can be devastating. Worse yet, many in the medical community insist on adhering to the once commonplace myth that IC is a psychosomatic condition. A recent e-mail to the ICA web site exemplifies this problem. "I am a psychotherapist who has yet to be diagnosed with this disease, but I have every symptom listed on the Internet. My treatment by doctors has been abominable. I have been dismissed, ignored, and chastised for not emptying my bladder. I have been told it must be a problem in my marriage, and the doctor said he had no patience for psychosomatic disorders. I am grateful to find support on the Internet. It is a godsend to me to be validated. . . ." ¹ The ICA receives many similar letters and e-mails every week.

The quality of life of IC patients has been shown to be worse than that of patients undergoing dialysis for end-stage renal disease. ² In severe cases, the pain can be unremitting. Frequency of up to 60 times a day is not uncommon. Nocturia as often as every 20 minutes leads to severe sleep deprivation with resultant depression. 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 in some cases. The economic impact of the disease in 1987 was estimated at \$1.7 billion per year. ² These figures would be even higher today, nearly 15 years later.

Many of the controversies that exist in the medical community with regard to IC have a negative impact on IC patients. Conflicting opinions on epidemiology, diagnostic tests, etiology, and treatments have left IC patients trying to "second guess" much of the medical advice that they have received.

EPIDEMIOLOGY: THE MYTH OF "POSTMENOPAUSAL AND RARE"

Once thought of as postmenopausal and rare, IC is neither rare nor limited to the postmenopausal population. Approximately 25% of IC patients are under age 30. ² IC affects children and may affect many more men than formerly believed. ^{3,4} As with thyroid disease, if a physician does not specifically look for IC, he or she will not find it. Many physicians still dismiss the condition, leaving thousands of patients undiagnosed, untreated, and without anywhere to turn for help.

IC affects at least 700,000 people. A newer estimate of the incidence of IC is 50% higher than previously thought. ^{2,5} Others estimate that as

many as 1.8 million people in the United States live with this condition. ⁶ Despite this significant number, it remains a relatively little known disease compared with other well-known conditions such as inflammatory bowel disease (IBD) and multiple sclerosis, both of which affect a significantly smaller patient population. There is an urgent need for large-scale epidemiologic studies in the United States and abroad. Recently, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) issued a Request for Applications that will focus on the epidemiology of IC. Studies of this magnitude have been long awaited and will provide a much greater understanding of the condition.

CHILDREN AND INTERSTITIAL CYSTITIS

A 5-year-old IC patient's mother testified before the United States House Subcommittee on Labor, Health and Human Services, 1999: "The best way that I can convey to you what IC means, is to explain what I see my 5-year-old son endure on a daily basis. . . . He can have headaches, burning when he urinates, abdominal pain, urinary frequency — up to 40 times a day when he is symptomatic—or he may feel fatigued after only minimal activity. Many nights he sleeps with a hot water bottle to ease bladder pain. It is hard for J.T.'s brother and his friends to understand J.T.'s problem, because if you look at J.T. there are no visible signs of IC, as there are with many other diseases," she stated.

The diagnosis of IC in children remains controversial. Children with this disorder may go undiagnosed for decades. Many urologists think that IC does not exist in the pediatric patient population, or that it is exceedingly rare. Many cases of voiding dysfunction in children are self-limiting. How many of these cases are actually early IC and how many cases re-emerge as IC in adulthood? The percentage of these cases is unknown. Should we be aggressively treating these children who exhibit signs of voiding dysfunction or IC in early childhood to avoid the re-emergence of the disease later in life? Or are the risks of general anesthesia and a major urologic workup too great in children whose symptoms may spontaneously resolve, never to reappear? Would early treatment of children with symptoms of IC increase the chances of permanent remission? Approximately 25% of IC patients report that they were plagued with chronic urinary tract problems as children. ² Perhaps testing for urinary markers, such as antiproliferative factor (APF) and heparin-binding epidermal growth factor (HP-EGF) should be studied in children. This would obviate the need for more invasive procedures and would be very cost-effective. There is a

high likelihood that IC in children is underdiagnosed, as it has been in other patient populations for decades. Given the severity of the symptoms, the dramatic impact on quality of life, as well as the economic impact of this condition, the ICA strongly believes that children should be more aggressively evaluated and treated.

TREATMENTS: ADDRESSING THE PAIN

Treatment of IC pain has been inadequately addressed by many physicians. Although there are no uniformly effective treatments, many options are available, that, in combination, may provide significant relief. IC symptoms can vary from mild to severe. Patients with mild cases of IC may be helped by changes in diet, stress reduction, and bladder retraining. For more symptomatic patients, oral medications may be added, such as Elmiron (pentosan polysulfate sodium; Alza Pharmaceuticals, Palo Alto, CA) the first oral medication approved specifically for IC. Other oral medications that may help include tricyclic antidepressants (used for their analgesic properties), antihistamines, nonsteroidal anti-inflammatory drugs, and muscle relaxants. Bladder instillations of dimethyl sulfoxide or other agents are also common treatments for IC.

For some patients, the pain is severe and intractable, and should be aggressively treated when standard therapies have failed. Unfortunately, many physicians do not believe that that IC pain is severe enough to warrant opioids or that opioids should not be used in the treatment of nonmalignant conditions. There is also fear of reprimand by the Drug Enforcement Administration (DEA). As a result, patients are often told that they should simply learn to live with their pain. Depression, despair, and suicide may result. Treatment with opioids may include long-acting morphine (morphine sulfate), long-acting oxycodone, levorphanol, methadone, or fentanyl. Patients receiving these agents must also be supplied with a fast-acting rescue drug for breakthrough pain. Urologists are not typically trained in the management of chronic pain and may be uncomfortable treating this group of patients. It is imperative that these patients be referred to a pain specialist who is knowledgeable about IC and willing to aggressively treat the pain.

Newer experimental treatments for IC include TICE-BCG (bacillus Calmette-Guérin; N.V. Organon, Molenstraat, the Netherlands), and neuromodulation devices such as Medtronic's Interstim or Advanced Neuromodulation Systems' Renew (Medtronic Inc., Minneapolis, MN) hold promise for patients who do not respond to more conservative treatment measures. Surgery to augment or remove the bladder is used only as a last resort because of potentially serious complications and

its potential failure to relieve IC pain. Older therapies for IC, such as urethral dilatation, have largely been abandoned due to lack of efficacy.

The goal of pain management is to enable the patient to reclaim his or her life. The recent enactment of pain as the "fifth vital sign" by The Joint Commission on Accreditation of Healthcare Organizations and The American Pain Society is a step toward addressing the pain of IC and treating it adequately. Physicians confronted with a patient with the severe pain of IC often ask themselves whether the patient should receive treatment for pain. Perhaps the question should be, "Why should this person be left in pain?"⁷

DIAGNOSTIC TESTS AND MARKERS

Cystoscopy with hydrodistention under general or regional anesthesia remains the "gold standard" for diagnosis of IC. Drawbacks of this procedure include operative and anesthesia risks. However, it remains the best diagnostic test currently available, although 10% of IC patients show no signs of glomerulations or ulcers upon hydrodistention, despite their symptoms.⁸ Cystoscopy with hydrodistention has also helped to standardize diagnosis in the United States, which has greatly benefited patients. Yet this procedure has prompted recent controversy on the specificity of glomerulations.

In 1978, Messing and Stamey⁹ first reported that glomerulations seen during cystoscopy and hydrodistention were unique to the IC patient population. However, a study published in 1998 found that healthy women undergoing tubal ligation and cystoscopy exhibited the same mucosal lesions as IC patients.¹⁰ This study has provoked debate. The study sample was small. No assessment of urinary symptoms using either a voiding log or a validated questionnaire to assess pain symptoms was administered to "normal" study participants, and the severity of glomerulations was not documented. It is possible that some of the normal patients undergoing tubal ligation may have had symptoms of IC.

Presently, there is no more accurate diagnostic test or marker that could be used as a replacement for cystoscopy with hydrodistention. Although the potassium chloride sensitivity test has gained in popularity, this test cannot be considered a reliable, definitive diagnostic test for IC. The test consists of instilling a solution of potassium chloride into the bladder via urinary catheter, and uses pain as an outcome measure. It has been suggested for use as a diagnostic tool, a bladder permeability test, and a predictive test for response to IC-specific medications (heparinoids). A study in 1999 found the test to be only 60% accurate in the diagnosis of IC, leaving a 40% false-negative rate.¹¹ Another

study concluded that the potassium sensitivity test is not a reliable tool for the diagnosis of IC.¹² These researchers suggest that clinical findings (urinary urgency, frequency, and/or pain in the absence of other urologic conditions), along with cystoscopy/hydrodistention, are still the most consistently accurate and reliable means of diagnosing IC.

Other problems with the potassium test include: (1) the assumption that the bladders of all IC patients have permeable glycosaminoglycans linings; (2) the pain incurred by the patient subjected to the potassium test can be quite severe and may last for days to weeks; (3) a negative potassium test does not rule out IC. This can often lead to failure to diagnose IC; (4) the test is not specific to IC; and (5) for an IC patient already experiencing pain, the pain caused by the potassium test may be difficult to distinguish, making the test very subjective.

There are less painful, less invasive, and more accurate diagnostic tests under investigation. Researchers have identified 2 factors that may explain changes in the bladder of IC patients. The first factor, HB-EGF, is important for epithelial cell proliferation and wound healing. This factor is significantly decreased in both urine and serum specimens from IC patients when compared with specimens from asymptomatic patients or patients with other urologic conditions, such as urinary tract infections. The second factor is an APF isolated in IC patient urine specimens. This peptide may prevent the growth of new, healthy bladder epithelium. These research findings could lead to a diagnostic test as well as the identification of agents that will suppress production of the anti-proliferative protein or enhance production of the epithelial growth factor. Either mechanism could result in the formation of a healthy bladder lining.¹³⁻¹⁶ Decreased urine levels of the glycoprotein-51 have also been under investigation and may prove to be unique to IC patients.¹⁷

An instillation of lidocaine has also been proposed as a less painful test for IC; if the patient's pain is decreased with the instillation of lidocaine, then IC is suspected.¹⁸ A lactulose/rhamnose test, similar to the test used to diagnose gastrointestinal permeability, is being investigated.¹⁹ This test for bladder permeability involves instilling a sugar solution into the bladder and subsequently checking for levels of this sugar molecule in the serum. This new permeability test may distinguish intact versus permeable bladders, and is far less traumatic to the patient when compared with the potassium test. These new tests and markers currently under investigation will undoubtedly help to make the diagnosis and treatment of IC more accurate and less painful for patients in the future.

Until then, patients are faced with many confusing choices when trying to confirm a diagnosis of

IC. Add to this the already complex maze of medical visits to various specialists often needed to find a physician who is familiar with IC and the confusion and frustration increases significantly.

Until an equally accurate, less invasive, and less painful test becomes available, the ICA advocates that the diagnosis of IC be based on clinical findings in the absence of other identifiable causes, and cystoscopy with hydrodistention under regional or general anesthesia, as deemed necessary by the treating physician.

RELATED DISEASES: BLADDER DISEASE VERSUS SYSTEMIC DISEASE

According to Dr. Susan Keay, "the exact relationship between IC and other associated disorders will only be known once the cause and/or pathophysiology of each has been determined. However, it is important to establish whether an association exists between IC and any other disorder clinically, since research into one may help us to understand more about the etiology of the other."²⁰

Some IC patients have a greater risk of developing certain related disorders. These include irritable bowel syndrome (IBS), vulvodynia, fibromyalgia, endometriosis, chronic fatigue immune dysfunction syndrome (CFIDS), asthma, IBD, sensitive skin, and migraines. These disorders may have an underlying common etiology. This leads us to the following question: Is IC a systemic disease in some, and an organ-specific (bladder) disease in others? In 1997, Alagiri *et al.*²¹ evaluated other medical conditions occurring in the IC patient population and found that many of these conditions occurred at an appreciably higher rate than the normal population.

It may be that several different contributing factors or processes are occurring simultaneously in some IC patients. Or, there may be a single underlying problem that affects multiple organ systems. Researchers have begun to study the involvement of neural, immune, and endocrine systems. Of particular importance is new research on neuroinflammation, the autonomic nervous system, visceral pain syndromes, and pain pathways from the bladder to the central nervous system. Further research into these areas is urgently needed.

Presently, there are few treatment facilities throughout the United States that specialize in diagnosing and treating IC and its related conditions. IC patients with related conditions find themselves seeking help from specialists in many different fields of medicine, who provide conflicting treatment advice. These specialists often have little training or knowledge in any of the other related conditions. Finding a physician who is familiar with IC can be difficult. For patients with more

than 1 of these conditions, finding a physician who understands, or is at least aware of these connections, can be even more challenging. Until research is focused specifically on these related conditions, patients will continue to have great difficulty in obtaining adequate treatment.

WHAT CAN BE DONE?

THE INTERSTITIAL CYSTITIS ASSOCIATION: HELPING PATIENTS THROUGH THE CONTROVERSIES

Since its inception, the ICA has been helping patients to sort through controversies and make informed decisions. Our staff is responsible for research, compilation, organization, and dissemination of the most current information on IC, including the most effective treatments available, as well as those currently undergoing clinical trials. Brochures and fact sheets on numerous topics, including specific information sheets on each of the standard IC treatments, are available. A key resource is the ICA Treatment Guidelines, which provide physicians and patients with a 2-page summary of IC, including symptoms, diagnosis, epidemiology, and current as well as experimental treatments. A newsletter for patients, the *ICA Update*, as well as one for physicians, *ICA Physician Perspectives*, are produced on a quarterly basis.

The ICA has worked with Congress over many years to ensure that NIDDK receives funding for IC research. This funding has led to the establishment of an IC Database, an IC Clinical Trials Group, and numerous grants on basic science and clinical research. We have worked closely with NIDDK to develop an international community of IC researchers. The ICA funds its own Pilot Research Program and administers the Fishbein Family Interstitial Cystitis Research Foundation grant program. Many of the recipients of both programs have gone on to receive NIH funding.

The ICA and the NIDDK cosponsor a biennial international scientific symposium and a national patient conference. The most recent of these symposia was held in October 2000. This supplement is based in large part on that conference.

To assist patients further, the ICA is working with the US Social Security Administration (SSA) to seek faster and better-informed decisions on IC disability claims. This may include the addition of IC to the "Listing of Impairments," which is currently being revised, or the issuing of a "Ruling" on IC, which would instruct and advise SSA examiners how better to evaluate IC claims made on the basis of proven functional limitations. An increasing number of urologists are helping IC patients win their disability cases based on an IC diagnosis. To simplify the medical report writing process, the ICA has developed a variety of quick-read resource

materials that enable physicians to efficiently produce a medical report that will withstand the skeptical scrutiny of private and public-sector insurers. The most important of these resources for the physician is "Disability Evaluation in a Nutshell: a Three Minute Guide to Effective Medical Reports," by Doug Smith, Esq., which provides the treating physician with an invaluable "crash course" on the kind of report most insurers require to decide favorably on a disability claim. This guide contains a sample letter for physicians to use when writing disability reports. The "Nutshell" is available through the ICA.

CONCLUSION

Controversies in the areas of epidemiology, etiology, diagnostic testing, and the treatment of IC have compounded the burden already placed on IC patients. These patients live with a painful chronic condition that is poorly understood, and where uniformly effective treatments are not available. They are dependent on receiving proper diagnosis and treatment options from a medical community that is often reluctant to acknowledge the existence of the condition. Addressing areas of knowledge that are poorly understood will enable physicians to have a greater understanding of the difficulties that IC patients face. This will hopefully help them work as a team with their patients to provide the most current diagnostic and therapeutic options, so that patients can make the best informed decisions.

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