



Review Article

Interstitial Cystitis

Satpathy Hemant K, Taylor Richert

Department of Obstetrics and Gynecology, CUMC, Omaha, NE, USA, Assistant Professor, Department of Family Medicine, CUMC, Omaha, NE, USA.

In recent years, Interstitial Cystitis (IC) has undergone a major conceptual evolution. Previously considered a rare disorder, it is now known to be a chronic, severely debilitating disease of the urinary bladder. This is an important diagnosis, which should be kept in mind for all patients presenting with pelvic pain or urinary symptoms. Overly restrictive diagnostic criteria of the past have identified only patients with severe and advanced disease, and led to misdiagnosis and underreporting of this debilitating condition. The International Continence Society defines interstitial cystitis as a clinical syndrome consisting of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased day time and night time urinary frequency, in the absence of proven infection or other obvious pathology. It is a symptom-based diagnosis, not one based on cystoscopic findings or on the restrictive criteria promulgated by National Institutes of Health in 1988. Some people also describe this condition as Painful Bladder Syndrome or Tic Douloureux of Bladder. In fact, in 2002 the International Continence Society became the first organization to recommend that the term painful bladder syndrome/interstitial cystitis replace interstitial cystitis as both concept and a defining term.

Women make up 90 percent of patients with interstitial cystitis (IC), while men comprise the remaining 10%¹. It is most prevalent in the fourth and fifth decades of life. It has a predilection for Caucasian females although a similar prevalence has been reported in Hispanic females. The exact prevalence of IC in India is unknown.

It is classified into two different types. The first, early non-ulcerative IC occurs in 90 percent of affected patients. The more severe form of disease, the classical ulcerative type, is seen in the remaining 10 percent and is associated with Hunner's ulcers (a focal and often multiple lesion involving all layers of the bladder wall in chronic interstitial cystitis; the surface epithelium is destroyed by inflammation and the initially pale lesion cracks and bleeds with distention of the bladder).

This is a disease of unknown etiology. Instead of being considered as an end organ disease, i.e. a bladder disease, IC is now considered to be a visceral pain syndrome. Visceral pain syndromes involve chronic neurogenic inflammation, primary afferent nerve hyperactivity, and central sensitization, which interact to perpetuate pain. Another common theory behind this disease is a defect in the glycosaminoglycan component of the mucin layer that covers and protects the bladder's urothelium. Glycosaminoglycans are highly hydrophilic protein-polysaccharide complexes, which maintain a stable layer of water between the urothelium and bladder lumen, preventing adhesion of microcrystals, ions such as potassium, and proteins in the urine. This

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Correspondence :
Dr. Satpathy Hemant K
Chief Resident, Department of Obstetric and Gynecology,
CUMU, Omaha, NE, USA.

layer also interferes with bacterial attachment and invasion in the bladder, and is therefore highly protective. In the absence of this layer irritative substances in the urine may leak through the urothelium, causing inflammation, tissue irritation and injury, mast cell degranulation and sensory nerve depolarization, which result in the urinary urgency, frequency, and pain of IC. Other factors such as allergy, autoimmunity and infections have also been hypothesized to play a role in the disease process.

The underlying pathology is characterised by fibrosis of vesical wall, with consequent loss of bladder capacity. The mucosa is thinned, especially where the mobility is greatest

It is not only the etiology of IC, but also its difficult diagnosis that has troubled physicians. These patients, with irritative voiding symptoms and negative urine culture, frequently present a diagnostic challenge for primary care physicians. In fact, most of these patients consult at least five physicians over a period of five years before the diagnosis is made ². Misdiagnosis is also a large problem, as it is believed that the majority of patients diagnosed with the more common labels of chronic pelvic pain or overactive bladder, yet failing to respond to anticholinergic therapy, actually suffer from IC. Once the disease has reached the advanced ulcerative stage, it is easier to recognize and diagnose. However, the key is obviously to identify the disease in the same patient years earlier, when symptoms are insidiously progressing and intermittent. Therefore, IC should be a primary concern in patients with chronic pelvic pain. Although the tendency is to attribute chronic pelvic pain to a gynecologic origin as it is experienced in the pelvis, in reality the majority of pelvic pain is non-gynecologic. Approximately 38-85% of females suffering from chronic pelvic pain are found to have IC once they are evaluated for that possibility ³.

These patients usually present with urinary urgency, frequency, nocturia, and suprapubic pain (Table-1). The most common sequence of symptom progression is first the occurrence of urinary urgency/frequency, followed by development of nocturia second, and finally pain as the third symptom. The pain is often relieved by voiding small amounts of urine from the bladder, but soon recurs as the bladder refills. A constant urge to void which does not remit, even after the patient has voided, is also characteristic of

IC. With regard to frequency, typically patients void roughly 8 - 16 times a day, and 2 or more times at night. This collage of symptoms is almost always present for at least six months. The symptoms often wax and wane in the early stage of the disease and become more constant and severe as the disease progresses. Thusly, the disease tends to exist a continuum that spans decades of the patient's life. Flares of IC may be misdiagnosed during early stages as urinary tract infections. Other symptoms that may be associated include deep dyspareunia (approximately 60 percent of patients) and dysphoric mood. It should be noted, however, that the symptoms of incontinence and dysuria are not typical of IC. Several factors may exacerbate symptoms, including exercise, stress, sexual activity, prolonged sitting, sleep deprivation, and allergy activation. Certain foods, especially those with high potassium and acid content including beer, spices, banana, tomatoes, chocolate, strawberries, artificial sweeteners, oranges, cranberries and caffeine may also contribute. Roughly 60% of patients report a perimenstrual flare in symptomatology as well, typically the week prior to menses. Interestingly, symptoms are often improved by pregnancy.

Table 1. Symptoms of IC

Symptoms
● Generalized pelvic pain
● Voiding symptoms (frequency, urgency, nocturia)
● Dysparunia
● Premenstrual and menstrual exacerbation
● Exacerbation with sexual intercourse
● Worsening pain with bladder filling and relieved with voiding
● Waxing and waning of symptoms
● Duration more than 3-6 months

Physical findings are limited to suprapubic tenderness, dysphoric mood, levator ani tenderness and tenderness of the bladder base and anterior vaginal wall upon palpation. Vaginal examination is therefore very important to test for tenderness at these sites, and to rule out other pelvic pathology such as sexually transmitted disease, urethral diverticuli, and pelvic masses. In addition to palpating the bladder base for tenderness, the examining clinician should turn his or her fingers over and feel the levator muscles on both sides to diagnose

pelvic floor tension myalgia, which may be associated with IC.

There are several conditions that are often comorbid with IC, including irritable bowel syndrome, migraine or chronic headache, endometriosis, skin sensitivities, multiple drug allergies, constipation, vulvodynia, fibromyalgia, chronic fatigue syndrome, systemic lupus, and mood disorders, among others. IC should be considered in patients who have failed therapy following diagnosis of vulvodynia, endometriosis, and overactive bladder, especially overactive bladder without urge incontinence. Overactive bladder is differentiated from IC by asking the patient if she worried about loss of urine when her bladder gets full, or if bladder fullness causes discomfort. If the patient does experience discomfort, she should be further questioned if the discomfort is relieved by emptying the bladder. The latter symptoms may be suggestive of IC.

As mentioned above, it must be kept in mind that IC is often underdiagnosed or improperly diagnosed. In fact, gynecologists correctly diagnose only 2 percent of patients, with the remaining 98 percent are misdiagnosed³. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established diagnostic criteria for research subjects to make the picture of IC diagnosis more clear. However, the criteria are overly stringent, and roughly 60 percent of women with symptoms typical of IC do not qualify for the diagnosis by these standards⁴. Obviously, this majority of symptomatic women should not necessarily be excluded from diagnosis and treatment. Essentially, the diagnosis is usually based on clinical criteria and there are no definite diagnostic tests to confirm it (table 2). Validated questionnaires such as the Pelvic pain and Urgency/Frequency scale (PUF) (Table 3), the O’Leary-Saint symptoms and problem index, or the Wisconsin IC scale that quantifies patient symptoms, are often useful for identifying IC. The PUF is the most commonly used, with higher scores indicating a greater likelihood of IC, particularly at scores of 8 – 10 and above. Patients should be asked to keep a 24-hour log of voiding activity for frequency of urination and voiding patterns. IC sufferers typically show a high frequency of urination, averaging 16 times but sometimes as many as forty times per day, with low volume (less than 100 cc), with no demonstration of incontinence. Urodynamics are unnecessary for making the diagnosis, however, if done to rule out

overactive bladder, these tend to show a small bladder capacity of less than 350 cc (usually 174-220 cc), and volume at first sensation is 66-67 ml with sensory urgency.

Table 2. Suggested tools and procedures for initial screening and diagnosis of IC

• Recommended
History and physical
Validated symptoms questionnaires
-PUF
-O’Leary-Saint
-University of Wisconsin IC Scale
PST
ABC
Urine analysis and culture
Urine cytology
Voiding log or diary (for 24 hour)
Cystoscopy
• Optional
Cystoscopy with or without hydrodistension and bladder biopsy
Urodynamics
Pelvic ultrasound

Other in office tests such as the Anesthetic Bladder Challenge (ABC), and Parson’s Potassium Sensitivity Test (PST) may also be utilized in diagnosis. The ABC consists of a mixture of 8 ml of 2 percent alkalinized lidocaine solution, 2 ml of 20,000 units heparin and 4 ml of 8.4 percent bicarbonate, which is instilled into bladder for 60 minutes. The test result is negative (positive?) if the patient reports a 50 percent reduction in baseline pain on a visual analogue scale. A limitation of this test is that patients must be in pain at the time of the testing. The PST (Table 4) is another optional method that can be used to help confirm the suspicion of IC. It is designed to detect dysfunction of the bladder epithelium using potassium as an irritant. A solution of potassium is instilled into the bladder to determine if it provokes pain or urgency. A positive test, indicates epithelial dysfunction, which is seen in patients with radiation cystitis, chemical cystitis, an acute urinary tract infection as well as in IC. However, patients with chronic urinary tract infections, bladder outlet obstruction, or overactive bladder have a low rate of response to intravesical potassium. PST helps to confirm IC, and is positive in 75 percent of patients with IC, and only 5 percent of controls. The level of pain experienced by the patient is similar to that

Table 3. Pelvic Pain and Urgency/Frequency

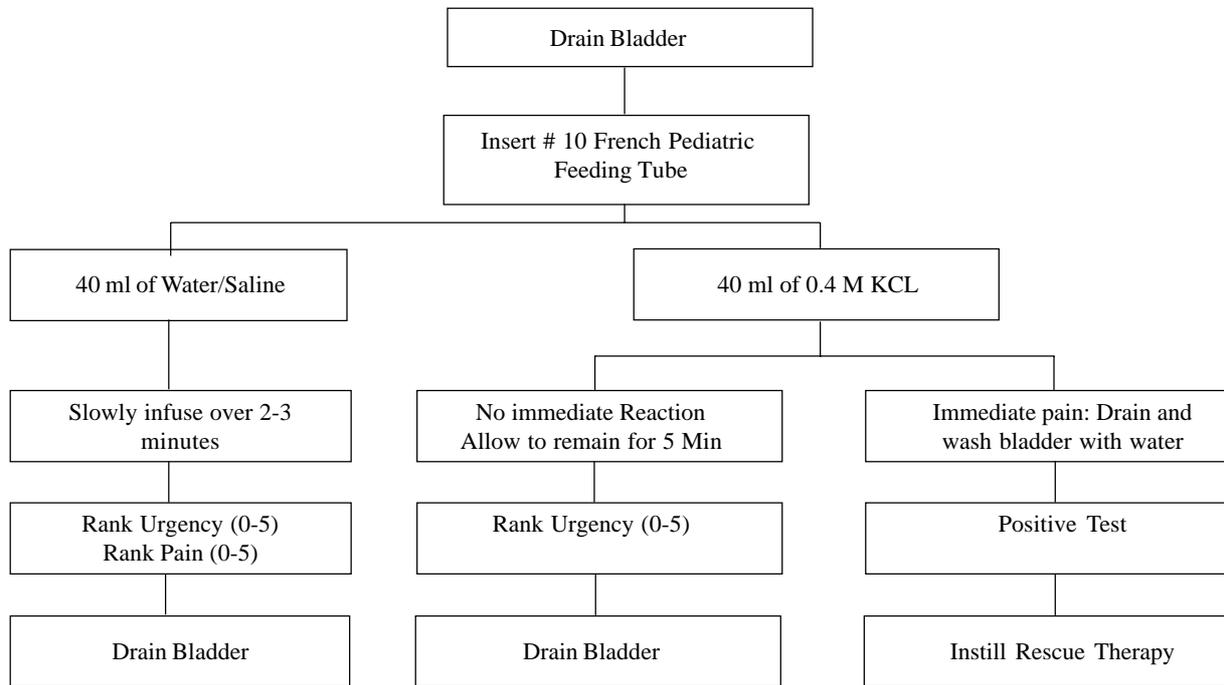
Patient Symptoms Scale					
Patient's Name _____		Today's Date: _____			
Please circle the answer that best describes how you feel for each questions					
	0	1	2	3	4
1. How many times do you go to the bath room during the day?	3-6	7-10	11-14	15-19	20+
2. a. How many times do you go to the bathroom at night?	0	1	2	3	4+
b. If you get up at night to go to the bathroom, does it bothers you?	Never bothers	Occasionally	Usually	Always	
3. Are you currently sexually active? Yes— No—					
4. a. If you are sexually active, do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always	
b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always	
5. Do you have pain associated with your bladder or in your pelvis?	Never	Occasionally	Usually	Always	
6. a. If you have pain is it usually		Mild	Moderate	Severe	
b. Does your pain bother you?	Never	Occasionally	Usually	Always	
7. Do you still have urgency after you go to bathroom?	Never	Occasionally	Usually	Always	
8. a. If you have urgency, is it usually		Mild	Moderate	Severe	
b. Does your urgency bother you?	Never	Occasionally	Usually	Always	
Symptom score (1, 2a, 4a, 5, 6a, 7, 8a)					
Bother score(2b, 4b, 6b, 8b)					
Total score (symptom score+ bother score)					

Total score ranges from 1 to 35.

experienced during pap smear; however, to avoid inflicting pain needlessly, the decision to perform the test should be thoughtfully considered for each patient. When the test is properly administered, an anesthetic solution is given quickly to minimize any discomfort.

Traditionally, cystoscopy with hydrodistension has been considered essential for diagnosis, but no reports in peer reviewed literature have demonstrated sensitivity nor specificity of this method in the diagnosis of IC. It adds little diagnostic value and correlates poorly with symptoms. If done, it may show

Table 4. Potassium Sensitivity Test



terminal hematuria (seen in 90 percent of patients), glomerulation on bladder mucosa (pinpoint hemorrhages or fissures with bleeding) following hydrodistension, Hunner’s ulcerations (small reddish brown spots on the bladder mucosa seen in 10 percent of patients with IC), bladder scarring, and small bladder capacity of less than 350 cc. Negative cystoscopy should not exclude IC. Similarly, the presence of the above findings, such as glomerulations, do not necessarily establish the diagnosis, because they could be found in asymptomatic women. Bladder biopsy is also not indicated for making the diagnosis. Common laboratory tests such as urine analysis and culture are essential for any patient with urinary urgency, frequency, or pelvic pain. Some encourage catheterized urine specimens to avoid contamination. In patients with IC, urine analysis may be completely normal, or may show hematuria, which mandates evaluation for genitourinary cancer. When risk factors for bladder cancer are present, such as age above 40 years, smoking history, or the presence of hematuria, urine cytology should be ordered to rule out malignancy. Roughly one to two percent of patients labeled as IC actually have bladder cancer.

Other testing, such as evaluation for sexually transmitted diseases, pelvic ultrasonography, or computed tomography, may be necessary, depending on the clinical circumstances. If indicated tuberculosis should be ruled out with urine testing for Acid Fast Bacilli or bladder biopsy. Urine biomarkers, such as antiproliferative factors (APF), have been heralded as a new diagnostic marker, but are not yet ready for clinical use.

Common differential diagnosis includes chronic pelvic pain, overactive bladder, irritable bladder syndrome, recurrent UTI, endometriosis, vulvodynia, urethral pain syndrome, pelvic adhesions, vaginitis, urethral diverticulum, pelvic inflammatory diseases, genital herpes, etc. As mentioned above, these may be common misdiagnoses for patients actually suffering from IC.

There is currently no cure for IC, a chronic disease with relapses and remissions. Although it does not progress once it develops fully, improvement is slow, usually occurring after 3 months or more of treatment. Not surprisingly, no single treatment works for all patients, so empiric trials with various agents may

be needed (Table 5). Treatment is often multimodal, and the rationale for each therapy should be explained. Maintaining a voiding diary before and after treatment, as well as during flare-ups, often helps to provide evidence of improvement and to identify triggers. The basic concept in addressing IC is to treat the triggers, the epithelium, any allergies, and their resultant neural upregulation. Although treatment is usually nonspecific and empiric, and there is no consensus for optimal management, relief of symptoms should be the goal. Treatment, especially in young patients with nonulcer IC should involve the least invasive therapy that provides reasonable symptomatic improvement. Caregivers and family should provide support, understanding and reassurance to the patient throughout treatment, and management of comorbid conditions should not be forgotten.

Table 5. Conservative treatment of IC

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- **Pentosan Polysulfate Sodium (PPS)** 100 mg three times a day
 - **Amitriptyline** (if needed) 25 mg at bedtime, increase to 50 mg/day after 1-2 months
 - **Hydroxyzine** (if needed) 25 mg at bedtime, increase to 50-100 mg/day during allergy season
 - **Intravesical therapy solution** 3-7 times a week for at least 2-3 weeks for immediate, temporary symptomatic relief at start of treatment or for symptom flares or for failed oral treatment.
 Mix together the following and instill into empty bladder, and retain for 30 minutes
PPS one or two 100 mg oral capsules, (each dissolved in 10 cc of buffered normal saline)
 or **Heparin** 10,000 to 40,000 units
Lidocaine 1% 10 ml or 2% 16 ml
Sodium bicarbonate 8.4 % 3 ml (to increase absorption of lidocaine)
 - Evaluate at 3-6 months after the start of treatment
 If responding continue treatment
 If not responding, refer for further urologic workup
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Nonpharmacological treatments are varied, and success is patient dependent. Quitting smoking should be encouraged, though its impact is equivocal. Dietary restriction, physical therapy, exercise, ice packs, sitz baths, or heating pads may

be helpful. Bladder training and behavioral therapy should also be undertaken to improve the interval between voids. Thiele massage, consisting of transrectal and transvaginal manual therapy of the pelvic floor muscles in the presence of pelvic floor muscle tenderness and spasm, may also play a role. Cystoscopy with hydrodistension may offer temporary symptomatic relief, but is not proven in the treatment of IC. It provides therapeutic benefits in 56 percent of patients, with responders reporting a mean relief of 2 months. Only 2 percent of patients get lengthy symptomatic relief lasting 24 months. Possibly the most important strategy is avoidance of triggers, or activities associated with flares, which is fairly simple once these are well defined. Patients should be instructed to pay attention to any foods or activities that exacerbate symptoms. Calcium glycerophosphate, available in health food stores, seems helpful for about 82-95 percent of patients with food triggers.

Pharmacological treatment should include a course of empiric antibiotics, if not already tried. Oral medications are utilized first. These include tricyclics (e.g. Amitriptylin, doxepine, imipramine), antihistamines (e.g. Hydroxyzine, cetirizine), and pentosan polysulfate sodium (e.g. Elmiron). The latter is the most effective oral therapy and is the current cornerstone IC treatment, owing to its ability to restore the integrity of the mucous layer. It takes 3-6 months to be most effective, and patients should be committed to the drug for at least 6 months to determine if they are responders. Elmiron is more beneficial longer it is used, and patients who understand this are more likely to comply with the treatment regimen. Elmiron relieves pain in 40-60 percent of patients after 3 months of treatment, a response which is typically maintained over the long term⁵. Oral Elmiron and intravesical heparin are the only compounds that have been found to have long term effectiveness to treat IC. This therapy can be used indefinitely, and side effects are generally mild and mostly gastrointestinal. Hair loss, which occurs in 4 percent of users, is almost always confined to single area on the scalp and is reversible. It should be kept in mind that Elmiron is a weak anticoagulant, which may increase bleeding. The approved dose is 100 mg orally three times a day, however some patients takes 200 mg twice a day, which improves compliance.

Other oral medications that can be tried include

neuroleptics (e.g. Topiramate, pregabain, gabapentine), nifedipine, oral L-arginine, nonsteroidals and narcotic analgesics. Narcotic therapy may be used for symptom flare ups, but is usually not encouraged due to resultant urine acidification, which may worsen bladder pain. Oral medications can be used in combination if needed. If the patient has allergy history, or allergic or mast cells were confirmed on bladder biopsy, an antihistaminic such as hydroxyzine should be given either alone, or in combination with Elmiron. When used as part of a multimodal treatment in addition to Elmiron, amitryptiline may be tapered off once remission is attained. Antimuscarinic agents may be used to treat urinary urgency, but can also be counterproductive as they can impair bladder emptying and exacerbates pain.

Intravesical therapy offers high local drug concentration, avoids systemic side effects and eliminates the problem of low levels of urinary excretion of oral agents. As mentioned above, it should be used when oral medications have failed or for acute flares before oral medications take effect. It may also be used as an adjunct to oral therapy. Dimethyl sulfoxide (DMSO) used to be most commonly used intravesical agent. DMSO is less favored currently because of side effects, specifically the garlic odor or taste that last for 72 hours after each treatment. When treatment with DMSO is given on a frequent basis, patients are encouraged to have their eyes examined due to the possibility of cataract formation. It induces remission in 50-70 percent of patients for up to 24 months⁶. It works by directly reducing bladder wall inflammation, blocking pain, and preventing bladder muscle contractions. It is often used mixed with other drugs and is held in bladder for 15-30 minutes and then urinated. The treatment is repeated every 1-2 weeks for about 6-8 weeks. Most notice improvement in 3-4 weeks after the first treatment. 50 ml of 50 percent DMSO is used commonly. Some patients have long term remission. But most have relapses. Additional treatment schedule for relapses vary, but usually at 4-6 week intervals. Currently, the most often used intravesical treatment is a cocktail of heparin or Elmiron with lidocaine and sodium bicarbonate. This cocktail relieves symptoms in 75 percent of patients with IC, and at home instillation can be easily taught. Other agents used intravesically include heparin, lidocaine, hyaluronic acid, Bacille Calmette Guerin, capsaicin,

rsiniferatoxin, botulinum toxin A, chondroitin sulfate, steroids, and Elmiron.

Oral prednisone could be used in advanced disease in the presence of Hunner's ulcers. Other drugs rarely used for IC include cyclosporin A, IL-10, imatinib, methotrexate, suplatast, misoprostol, and quercetin. Growth factor inhibitors, gene therapy, RDP 58, and vitamin B3 analogue (BXL 628), are under investigation and could be of use in the future treatment of IC. Silver nitrate and chorpactin have fallen out of favor secondary to lack of efficacy and potential side effects

Transcutaneous electrical nerve stimulation (TENS), acupuncture, intravaginal electrical nerve stimulation, urinary chelating agents such as polycitra-K crystals and Urocit-K, Prelief (an over the counter food additive) and herbal remedies such as Algnot Plus, CystoProtek, Cysta-Q, and aloe vera may play a role in the management of IC.

Major surgical interventions are not the mainstay of treatment. Patients whose condition is extreme, and are miserable, may consider surgery if medications fail. Sacral neuromodulation (Interstim) is the current preferred surgical intervention. It is helpful in well-selected patients whose symptoms are refractory to other forms of therapy. From 60-80 percent of patients seem to improve relative to voiding frequency as well as pelvic pain⁷. However, anecdotal data suggest that the response rate tends to diminish with time. Laser ablation, fulguration or resection can be offered if Hunner's ulcers are seen on cystoscopy. These therapies have a relapse rate of more than 50 percent. Cystourethrectomy with urinary diversion is rarely done, and augmentation cystoplasty is not currently recommended. Similarly presacral or sacral neurectomy and perivesical procedures (cystolysis, cystoplasty, transvesical neurectomy) is to be condemned, as it is rarely of long lasting effect.

Once treatment is started, symptoms may take up to 2 years to resolve. Close follow up is essential. To ensure that treatment is as effective as possible, these patients are often followed monthly for the first three months and at three-month intervals thereafter. Frequent follow up ensures compliance, allows for titration of medications, and reinforces behavioral modifications such as dietary changes. Voiding

diaries and the PUF scale are helpful in monitoring treatment response.

Difficult cases should be dealt with in a multimodal fashion, in consultation with a urologist, pain specialist and physical therapist. Patient and family educational materials are best obtained from the IC support group, the IC association and the IC network.

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