The management of interstitial cystitis: an update

Sagar Phatak and Harris E Foster Jr*

SUMMARY

Treating interstitial cystitis (IC) is one of the greatest challenges facing physicians and other health care providers who manage patients with this condition. The symptoms of urinary frequency and urgency, dysuria, and chronic pelvic pain characterize IC, but it is the debilitating pelvic pain associated with IC that is most difficult to control. The pathophysiology of IC pain is poorly understood, but is thought to be a complex entity including nociceptive, visceral, and neuropathic components. There are currently no universally effective therapies available. Oral treatments, however, are frequently used, including nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, gabapentin, and pentosan polysulfate, all of which have shown varying degrees of efficacy. Recognition that IC pain is multifactorial, and probably has a neuropathic component, has led to the use of some of these agents, previously prescribed for other neurologic conditions associated with chronic pain. Intravesical and surgical options are also available, which expands the armamentarium for those who treat pain secondary to IC. Treating IC requires managing all of the symptoms of this disease. This review aims to cover standard and novel treatment options, while concentrating on the management of pain.

KEYWORDS chronic pelvic pain, interstitial cystitis, neuropathic pain

REVIEW CRITERIA

Information presented in this article was obtained by a review of the literature on pain management for interstitial cystitis using both the PubMed and Ovid medical databases for articles published between January 1980 and August 2005 using the keywords "interstitial cystitis", "chronic pelvic pain", "clinical trials", and "bladder physiology".

S Phatak is a Resident in Urology and HE Foster Jr is an Associate Professor of Surgery in the Section of Urology, Yale University School of Medicine, New Haven, CT, USA.

Correspondence
*Department of Surgery, Section of Urology, Yale University School of Medicine, PO Box 208041, New Haven, CT 06520-8041, USA
harris.foster@yale.edu

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INTRODUCTION

Interstitial cystitis (IC) treatment primarily involves managing patients' symptoms in order to improve their quality of life. This difficult-to-treat disease, with an etiology as yet undefined, is a benign disorder that, nonetheless, can have devastating effects on a patient's physical and mental health. Although urinary frequency and urgency (both symptoms of overactive bladder) are problematic for the patient, pain remains the hallmark of this disease and can be difficult to manage, which is frustrating to both the patient and the treating physician. This review covers the current pharmacologic and nonpharmacologic management options for IC, with an emphasis on pain management. The relative efficacy of different treatments for IC will be reviewed, including nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentin, pentosan polysulfate, antidepressants, intravesical agents, and surgery.

ETIOLOGY OF INTERSTITIAL CYSTITIS

IC is a chronic, noninfectious, probably inflammatory disorder of the urinary bladder that primarily affects women (approximately 90% of patients are female).[1] The disease can also affect men and possibly children; however, these groups of patients have been studied or characterized to a lesser extent than women. It is believed that IC prevalence ranges from 1 in 100,000 to 5.1 in 1,000 of the general population worldwide, and by definition the symptoms include some component of pain, usually CHRONIC PELVIC PAIN.[2,3] Some authors think that the diagnosis of NONBACTERIAL CHRONIC PROSTATITIS in men might actually represent IC.[4] Symptoms of IC include urinary frequency and urgency, dyspareunia, and, most commonly, debilitating pelvic pain. It is believed that symptoms might be progressive if left untreated, and can severely decrease patients' quality of life. The symptoms of IC can lead to depression, social isolation, and, in rare instances, suicidal thoughts.[5]

The pathophysiology of IC remains elusive; many theories have been formulated, and in part

GLOSSARY

CHRONIC PELVIC PAIN
Nonmenstrual pain of 3 months duration or longer that localizes to the anatomic pelvis and is severe enough to cause functional disability

NONBACTERIAL CHRONIC PROSTATITIS
A condition affecting patients who present with symptoms of prostatitis without a positive urine culture or expressed prostate secretion culture; symptoms often include pelvic pain, penile and perineal pain, dysuria

HUNNER'S ULCER
Characteristic mucosal ulcer seen in classic, ulcerative interstitial cystitis (in 10% of patients with interstitial cystitis)

GLOMERULATIONS
Objective finding in the diagnosis of interstitial cystitis characterized by petechial hemorrhages that occur after distension of the urinary bladder

have driven therapy. The bladder transitional-cell epithelium is normally covered by a mucin layer composed of glycosaminoglycans. This layer is thought to be almost impermeable, thereby preventing urine solutes from diffusing into the subepithelial components of the bladder. IC might affect this layer by increasing solute permeability, possibly leading to irritation, inflammation, and sensory-nerve sensitization of the bladder.[5] Potassium could be the main offending substance, and its diffusion across the permeable transitional epithelium the primary irritant; hence the development of the potassium sensitivity test for the diagnosis of IC.

DIAGNOSIS AND MANAGEMENT OF INTERSTITIAL CYSTITIS

Traditionally, diagnosis of IC includes obtaining a complete patient history and conducting a physical examination. Cystoscopy with hydrodistension under anesthesia is often performed, in an attempt to detect the characteristic features of a HUNNER'S ULCER and/or GLOMERULATIONS. The introduction of the potassium sensitivity test and questionnaires such as the O'Leary–Sant Interstitial Cystitis Symptom Index and the Pelvic Pain, Urgency and Frequency Questionnaire have provided further tools to assist in the diagnosis of IC.[6,7] It is critical, however, that a thorough evaluation first rules out any reversible causes of patient symptoms, including infection, cancer, urolithiasis, obstruction, neurologic disease, or gynecologic disorders such as endometriosis. Once other causes are excluded and a diagnosis of IC is confirmed, therapy should be aimed at controlling symptoms, particularly pelvic pain, which can often be debilitating.

Pain can be classified as nociceptive, visceral, or neuropathic. IC pain is rather complex and can often include all three types of pain, making management extremely difficult. The most successful approaches have been multimodal therapies that incorporate psychologic interventions, physical therapy, pharmacotherapy and in some cases procedural treatments, such as sacral neuromodulation. Attempting to address all aspects of pain management is beyond the scope of this review. This paper will specifically outline the current pharmacologic options available for managing IC pain, including some new developments.

It should be noted that there are few well-performed, placebo-controlled, randomized trials that have investigated the various IC treatments. Historically, for a variety of reasons (i.e. chronic pain syndrome, low incidence of disease), it has been difficult to enroll IC patients in randomized studies, particularly those that involve the use of a placebo. As there are no universally successful therapies, randomized clinical trials for IC should include a placebo arm whenever possible. It has been suggested that limiting the length of treatment and follow-up, allowing open-label treatment at completion, and/or providing appropriate, reasonable compensation can partly ameliorate the potential problems experienced by patients in the placebo arm.[8]

ORAL TREATMENTS FOR INTERSTITIAL CYSTITIS

Nonsteroidal anti-inflammatory drugs, narcotics, and antihistamines

The initial management of most chronic pain conditions including IC should involve NSAIDs, and, if needed, narcotics. Unfortunately, NSAIDs and narcotics have been ineffective in many patients with IC.[9,10] The anti-inflammatory effects of NSAIDs might help to reduce some bladder inflammation (assuming it exists), thereby reducing pain. Specifically, these agents might relieve symptoms in a minority of patients by the inhibition of prostaglandin formation.

It is believed that narcotics affect Type C post-ganglionic pain fibers that possess slow conduction. These pain fibers are characterized by a dull, aching, 'deep' pain.[11] Extended-release formulations of oxycodone and morphine are likely to provide better pain relief than short-acting agents such as meperidine. Narcotics should be introduced in gradually increasing doses, starting with small doses at set time intervals, allowing for 'rescue doses' if patients experience recurrence of pain. In addition to oral agents, some drugs (such as lidocaine) can be given intravesically as a 1–2% solution for acute flare episodes in IC.[12] Improvement in pain scores when lidocaine is combined with intravesical heparin occurs in 50% to 94% of patients.[13] There might also be some potential efficacy with lidocaine when delivered via a transdermal patch, although further study is needed.

Nalmefene is a long-acting opiate antagonist that has been used to treat IC pain with only limited success. The drug was originally developed as a long-acting version of naloxone, with the primary function of reversing the depression of the respiratory and central

Table 1 Summary of oral therapy for interstitial cystitis.

Therapy	Efficacy of treatment	Evidence of efficacy
Nonsteroidal anti-inflammatory drugs and narcotics	Variable	Open-label trials[9–13]
Nalmefene	50% of patients reported improvements in pain symptoms	Phase II trial[15]
Hydroxyzine	No benefit over placebo	Randomized, controlled trial[18]
Pentosan polysulfate	45–50% of patients responded by 32 weeks of treatment	Randomized, controlled trial[24]
Amitriptyline	63% of patients were satisfied with treatment	Randomized, controlled trial[26]
Gabapentin	50% of patients reported improvements in pain symptoms	Case series[31]
Prednisone	69% of patients reported improvements in pain symptoms	Case series and open-label trials[35]
Cyclosporine[a]	90% of patients reported no bladder pain	Open-label trial[37]

[a]Also known as ciclosporin.

GLOSSARY

SUBSTANCE P
11-aminoacid-neuropeptide that functions in the transmission of pain impulses from peripheral receptors to the central nervous system

nervous systems observed in opioid intoxication.[14] It was, however, observed to decrease mast-cell degranulation, and as such was tested in a phase II clinical trial to treat IC.[15] That study in 1994 did show a 50% decrease in suprapubic bladder pain; however, no other studies have been published on the efficacy of this drug in the treatment of IC pain.[15] As such, while nalmefene is available, its use in the treatment of IC requires further study.

Antihistamines have also been used to treat IC in open-label studies. The number of mast cells has been shown to be increased in bladder biopsies from some IC patients.[16] Decreasing mast-cell activity might, therefore, decrease bladder inflammation. As histamine, released in many instances by mast cells, has been implicated in the pathophysiology of IC, antihistamines have been used with varying efficacy for the treatment of this disease. The most commonly used antihistamine for IC has been hydroxyzine,[17–19] which acts by blocking both mast-cell secretion and the H_1 receptor. An additional neurogenic mechanism of mast-cell release involves SUBSTANCE P;[20] Studies in animal models have demonstrated that the release of substance P is inhibited by hydroxyzine.[21] Inhibition of histamine and substance P release are thought to lessen the ensuing hyperemia that is associated with both of these substances, and reduce the fibrosis associated with substance P.

In an open-label study, the use of hydroxyzine was shown to improve symptom scores by 40% from baseline.[17] Drowsiness, however, is a common adverse effect associated with antihistamines, but might abate after chronic use. A randomized trial comparing hydroxyzine to pentosan polysulfate either alone or in combination, however, failed to show a significant advantage over placebo.[18] Other promising areas of research have been aimed at regulating mast-cell activity. Degranulation of mast cells can occur when their opiate receptors are stimulated, and inhibition of these receptors by an opiate antagonist such as nalmefene has demonstrated some efficacy.[15,19]

In summary, while the classes of oral agents discussed above might help some patients, many will often require additional agents to ameliorate their IC symptoms, particularly the pain. The most effective treatment will include concomitant therapy with additional oral agents such as pentosan polysulfate, antidepressants, or gabapentin (Table 1).[22]

Pentosan polysulfate

An oral agent frequently used to treat the symptoms of IC is pentosan polysulfate sodium (PPS). PPS remains the only FDA-approved oral agent for the treatment of IC. An oral heparinoid, it is thought to augment the glycosaminoglycan layer of the bladder; repairing deficiencies in this layer might lead to improvement of IC symptoms. The use of PPS for IC was originally described in 1990 and continues to be investigated.[23]

A randomized, controlled trial investigating the use of PPS to treat IC that was published in 2005 is the most vigorous study to date.[24] Various

GLOSSARY

5-HYDROXYTRYPTAMINE
A neurotransmitter associated with the sleep cycle, which is believed to play a role in depression, bipolar disorder, and anxiety

doses have been tested (ranging from 300 mg to 900 mg once a day), but overall response rates approach 15–67% at the 300 mg dose, with no significant improvement seen with higher doses.[24] Ultimately, the duration of dosage appears to be more important than the level of dosage itself. The severity of symptoms does not appear to affect patients' responses to pentosan polysulfate. Modest improvements in symptoms have been described at 4 weeks into therapy, with continued steady improvements over time.[24]

It is often difficult to delineate symptoms within IC, and determining response to treatment is aimed at evaluating improvement of IC as an entity, rather than just the analgesic effects. On closer inspection of the 2005 study, however, this agent seems to improve urinary frequency symptoms more than pain.[24] Adverse effects associated with PPS have generally been modest and resolve without intervention or long-term sequelae. The most common treatment-related adverse effects of PPS include gastrointestinal disorders, headache, and alopecia.[24]

Tricyclic antidepressants

Many of the agents previously discussed are aimed at both the nociceptive and visceral pain associated with IC. The tricyclic antidepressant amitriptyline, however, is directed at treating the presumed neuropathic pain component of IC. In 1987, Hanno and Wein first described the use of amitriptyline in the treatment of IC.[25] Its anecdotal efficacy has led to it becoming one of the most frequently prescribed oral agents for IC.[9] It was not, however, until 2004 that amitriptyline was shown to be effective in a randomized, placebo-controlled, double-blind trial. In this report, 63% of patients reported satisfaction with therapy compared to 4% in the placebo group.[26] Specifically, mean pain intensity, as measured by a visual analog scale, revealed statistically significant improvements in the amitriptyline group, but not in those who received placebo. The mechanism of pain relief obtained with amitriptyline treatment is still not completely understood. Its effects on urinary frequency symptoms and bladder capacity are more readily explained by its concomitant anticholinergic properties.

Amitriptyline also has serotonergic effects by its inhibition of 5-HYDROXYTRYPTAMINE reuptake. This mechanism of action is thought to occur within the spinal and supraspinal neuronal pathways that coordinate bladder function.[27] Current data indicate that 5-hydroxytryptamine receptor activation, induced by amitriptyline, affects the neuromodulation of afferent and efferent nerve pathways that signal pain and urgency sensation within the bladder. In addition, amitriptyline might improve IC symptoms through its antihistamine properties. Amitriptyline is a potent tricyclic antidepressant in terms of blocking H_1-specific receptors, including those on mast cells. Adverse effects associated with amitriptyline's anticholinergic properties occur in over 90% of patients receiving the drug, and considerably limit its use.[9] Nonetheless, this tricyclic antidepressant represents a powerful, safe, and apparently effective tool in the treatment of IC pain. A beneficial side effect of this drug is its sedative properties, which can promote restorative sleep. This can vastly improve the quality of life of IC patients, although this sedative effect can also limit the tolerated dose.

Gabapentin

The use of the anticonvulsant agent gabapentin for IC pain relies on the drug's well-documented efficacy in chronic pain conditions. The mechanism of action of gabapentin is not fully understood, but the agent has been shown to be effective for neuropathic pain in conditions such as diabetic neuropathy, reflex sympathetic dystrophy, and postherpetic neuralgia.[28] It could be considered an ideal drug, as it does not require monitoring of blood levels, unlike other anticonvulsants such as carbemazapine. Additionally, gabapentin is not metabolized by the liver, but is excreted unchanged in the urine. Over the past decade, the use of gabapentin for IC pain has increased anecdotally, but no clinical trials have tested its efficacy in a randomized, prospective, double-blind setting. Most descriptions of its use in the literature are case reports and open-label studies.

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA); however, it is not known to bind to GABA receptors or have any effect on the activity or metabolism of GABA. Even less is known about its effect on analgesia, although it is believed to modulate calcium channels, specifically at the α-2-γ subunit.[29] These channels are thought to be specifically associated with neuropathic pain.

There is also evidence that gabapentin might exert some activity against the N-methyl-D-aspartate (NMDA) receptor. It is believed that gabapentin competes with other compounds

at the NMDA receptor, which indicates that it has activity against this receptor.[30] Gabapentin is thought to exhibit an indirect action on the NMDA receptor, thereby improving pain symptoms, in addition to reducing sympathetic tone in the bladder. Furthermore, it is known that gabapentin enhances endogenous opioid release in the limbic system, subsequently increasing pain control.[30] This mechanism might also enable patients to reduce their use of exogenous narcotics while achieving the same level of pain control.

A single-center, clinical trial by Sasaki in 2001 reported the efficacy of gabapentin on refractory genitourinary-tract pain.[31] Pain reduction was observed in nearly 50% of the 21 patients treated with gabapentin. This encouraging outcome was seen in a patient population with refractory pelvic pain that was very difficult to manage, and oral gabapentin might be more successful in the treatment of newly diagnosed IC pain. Additionally, Hansen reported significant improvements in IC pain in two patients in a case report.[32] Given its minimal adverse-effect profile and overall safety, gabapentin can be used effectively and safely by physicians treating IC pain. Dosing can begin at 100 mg daily and be titrated up to 3.6 g. Although gabapentin has shown promise as an adjunctive treatment in the management of various chronic pain syndromes, its efficacy in treating IC pain will have to be established in a multicenter, randomized, clinical trial.

Pregabalin is a drug similar to gabapentin, and it is actively being studied as a treatment for neuropathic pain in disease states such as diabetic neuropathy and postherpetic neuralgia. Pregabalin selectively binds to the α-2-γ subunit of calcium channels, thereby reducing calcium influx and modulating release of downstream excitatory neurotransmitters.[33] A randomized, controlled trial designed to treat pain associated with diabetic neuropathy showed a 50% decrease in pain symptoms.[34] Such promising results in treating neuropathic pain are encouraging and suggest that pregabalin might have a role in treating IC pain; however, no clinical trials have investigated its use in IC.

Immunosuppressive agents

Efforts to use immunosuppressive drugs such as prednisone or cyclosporine A (CA) (also known as ciclosporin) have shown some success in treating the pain, and some other symptoms, associated with IC. Immunosuppressive agents are thought to reduce the inflammatory response in the bladder and to treat empirically the autoimmune processes thought to be associated with IC. In a small, Canadian study 14 patients with the ulcerative form of IC were treated with 25 mg of prednisone daily.[35] A decrease in pain symptoms was reported by 69% of these patients. Although the results of this study are impressive, it was small, and only targeted patients with confirmed Hunner's ulcers. This limits the applicability of prednisone, as approximately 90% of patients with IC do not have the ulcerative form of the disease. Another factor that could limit the use of immunosuppressants for the treatment of IC is that diabetic control was compromised by the use of steroids in some of the patients in the study. Despite these limiting factors, the study does suggest a potentially new area of therapy for IC pain.

The use of low-dose CA for the treatment of IC has also been investigated by a group in Finland.[36,37] In their original report, 11 patients with IC were initially treated with 2.5–5.0 mg/kg of CA daily, which was then reduced to a 1.5–3.0 mg/kg/day maintenance dose for 3–6 months. Bladder pain either decreased or disappeared in 10 patients, in addition to significant increases in mean and maximum voided volumes and reduction in voiding frequency.

In a more recent study from the same authors, reporting the effects of long-term treatment (>1 year) with CA (initially 3 mg/kg/day, gradually decreasing to as low as 1 mg/kg/day) 20 out of 23 patients were completely relieved of their bladder pain.[37] Furthermore, mean 24-h urinary frequency decreased from 20.8 (standard deviation [SD] 6.3) to 10.2 (SD 3.8), mean maximal bladder capacity increased from 161.8 ml (SD 74.6) to 360.7 ml (SD 99.3), and mean voided volume increased from 101.4 ml (SD 42.7) to 246.4 ml (SD 97.9), all of which were statistically significant compared to baseline. It should be noted that symptoms recurred in all nine patients who stopped CA. No renal toxicity occurred; however, seven patients developed adverse effects such as hypertension, gingival hyperplasia, and increased hair growth. There is concern about the development of skin malignancies with long-term use of CA, and one patient developed a basalioma after 5 years of treatment.

While these immunosuppressive drugs, particularly prednisone and CA, have shown

GLOSSARY

T_H1 CELLS
Cells that participate in cell-mediated immunity and are essential for controlling intracellular pathogens as viruses and certain bacteria

T_H2 CELLS
Cells that provide help for B cells and are essential for antibody-mediated immunity

Table 2 Summary of invasive therapy for interstitial cystitis.

Therapy	Efficacy of treatment	Evidence of efficacy
Hydrodistension	12–70% of patients had symptom improvement	Nonrandomized open-label studies[39,40]
Bacillus Calmette–Guèrin	No benefit over placebo	Randomized, controlled trial[49]
Resiniferatoxin	No benefit over placebo	Randomized, controlled trial[50]
Dimethylsulfoxide	50–93% of patients had improved pain symptoms (high relapse rate)	Randomized, controlled trial[43]

some early promise, it is clear that larger, prospective, randomized trials are still needed to demonstrate therapeutic improvement in IC symptoms before their widespread use can be advocated.

INVASIVE TREATMENTS

Pain management for IC can also involve more invasive treatments such as intravesical instillations and surgical procedures. A detailed discussion involving the surgical management of IC pain is beyond the scope of this paper; however, a brief review of hydrodistension, intravesical agents, and sacral neuromodulation follows (Table 2).

Hydrodistension

Cystoscopy, combined with hydrodistension, under anesthesia, is often the first diagnostic and therapeutic choice for IC in many urologic practices. If it is considered necessary to conduct a bladder biopsy, it can be performed at the same time. The efficacy of hydrodistension has proven to be variable.[38] Hanno and Wein have described response rates ranging from 12% to 26%.[39] A more recent study from Japan reported a 70% improvement in symptoms in patients whose bladder capacity is greater than 100 ml following hydrodistension under anesthesia.[40] The mechanism of action behind this treatment is believed to be a mechanical stretch of the bladder mucosa and damage to the submucosal neuronal plexus, which thereby decreases pain transmission through the afferent fibers. Although treatment efficacy can range from 12–70%, the effects of therapy have been reported to be brief, lasting no longer than 3–6 months. Nonetheless, this therapy can be useful in managing the pain from IC in many circumstances.

Dimethylsulfoxide

With the exception of PPS, intravesical dimethylsulfoxide (DMSO) is the only other FDA-approved drug for the treatment of IC. The mechanism of action is not entirely clear, but DMSO is known to deplete substance P in the bladder and to stimulate mast-cell degranulation.[41] Originally popularized by Stewart *et al.* in 1967, who reported overall improvement in IC symptoms (not specifically pain) in up to 75% of patients,[42] more recent DMSO trial results have not been encouraging. In a 1998 study, Perez-Marrero *et al.* showed improvements in pain symptoms in 93% of patients versus 35% improvement in the saline-placebo group. Unfortunately, the same study revealed that 59% of the patients relapsed in the following 4 weeks.[43] The same authors later showed that the beneficial effects of DMSO instillation can be moderately prolonged with the use of heparin.[44] In a European study of 28 patients, a modest response to DMSO instillations was also noted.[45] More importantly, the study showed that the adverse effects associated with DMSO therapy could be well tolerated, so that a 6-week course of treatment could generally be completed. Urethral irritation was evident in nearly 50% of patients, but was reported as tolerable. Although certainly not a long-lasting treatment for pain and other symptoms associated with IC, DMSO instillation offers another tool in the treatment of IC pain.

Bacillus Calmette–Guèrin and resiniferatoxin

The use of intravesical bacillus Calmette–Guèrin (BCG) for the treatment of IC is based on the proposed role of immune dysregulation in the etiology of IC, specifically an imbalance of the T_H1 CELLS and T_H2 CELLS. First reported in an open-label study by Zeidman *et al.*, in which improvement was seen in all categories of IC symptoms, BCG treatment seemed promising.[46] Peters *et al.* performed a small, randomized, placebo-controlled study and reported that 67% of patients treated with BCG noticed an

improvement in IC symptoms, compared to 33% in the placebo group.[47] With respect to pelvic pain, 53% of BCG-treated and 33% of placebo-treated patients had a subjective improvement in symptoms. When followed for at least 2 years, 81% of initial BCG responders continued to experience reduced pelvic pain.[48] By contrast, a recently published large-scale study conducted by the Interstitial Cystitis Clinical Trials Group demonstrated little benefit for this therapy when compared to placebo; 21% versus 12%, respectively, reported moderate or marked improvement in their IC symptoms on global response assessment ($P = 0.06$).[49]

Similarly, resiniferatoxin had theoretical promise as an intravesical agent to help control pain in patients with IC. It is a vanilloid-receptor agonist that desensitizes C-fibers that transmit pain within the bladder. In a randomized, double-blind, placebo-controlled trial published in 2005, no statistically significant benefit was seen with the use of this agent.[50] On the basis of currently available evidence, both BCG and resiniferatoxin should still be considered investigational interventions for the management of IC symptoms.

Sacral neuromodulation

The use of sacral nerve-root stimulation for the treatment of bladder dysfunction has been well described since Schmidt, Bruschini, and Tanagho reported on this technique in 1979.[51] Most studies have evaluated the effects of sacral neuromodulation on urinary frequency, urgency, incontinence, and nonobstructive urinary retention.[52,53] An implantable, neuroprosthetic device that stimulates the transforaminal sacral nerve (InterStim®, Medtronic Inc., Minneapolis, MN) has been FDA-approved for these symptoms. There is a paucity of information available about the effects of sacral neuromodulation on chronic pain.

Studies have suggested that pelvic pain can be ameliorated in some instances by the use of this device.[54,55] In a study of just 10 patients, Siegel *et al.* demonstrated that 9 out of 10 patients received some level of pain relief with sacral-nerve stimulation.[54] Similarly, a more recent study revealed that nearly two-thirds of IC patients treated with sacral-nerve stimulation had reduced pain following implantation.[55] Peters *et al.* reported a 36% decrease in narcotic use, as defined by morphine dose equivalents, after implantation of the InterStim® device, with 4 out of 18 patients completely stopping narcotic treatment.[56] These data are preliminary and involve small numbers of patients, and it is clear that this mode of therapy needs further investigation. Sacral neuromodulation might, however, offer a promising option for the treatment of IC in the future, including managing the pain associated with this disorder.

CONCLUSION

IC remains a frustrating clinical problem for any physician treating this disorder, particularly with regard to the debilitating pain associated with IC. The pathophysiology of this disease remains poorly understood, but current knowledge has spurred the investigation of novel therapies. A multitude of pain-relieving oral agents are now available to patients with IC, including narcotics, antidepressants, gabapentin, and PPS. While intravesical therapy has not been shown to be particularly successful, some instillations might help to temporarily alleviate symptoms, particularly in the management of chronic pain and acute flares.

There are also a limited number of surgical options available that could potentially treat the pain caused by IC. A multimodal approach is probably necessary to obtain the most successful outcomes. IC remains a painful clinical entity that requires additional investigation to understand its pathophysiology, and further improvements in pain management.

Note added in proof While this article was in press, a prospective, open label, randomized trial has been published comparing the use of CA to PPS in the treatment of IC.[57] A group of 64 patients were randomized to receive either a low dose of CA (3 mg/kg) or PPS 100 mg three times a day. CA was superior to PPS in all clinical outcomes. CA treatment at 6-month follow-up showed a 34% decrease in urinary frequency, while no improvement was seen in the PPS group. Additionally, the clinical response rate as measured by the global response assessment improved in 75% of the patients in the CA group, compared to only 19% of those in the PPS group. These promising results continue to suggest that IC symptoms can be successfully managed with low-dose CA therapy. Long-term studies are clearly required, with particular attention paid to the potential adverse effects of CA.

KEY POINTS

- Interstitial cystitis (IC) is characterized by lower urinary tract symptoms of frequency, dysuria, urgency and chronic pelvic pain
- The pathophysiology of IC is poorly understood, and several mechanisms have been implicated in this chronic condition
- The majority of treatments for IC are aimed at treating the pain associated with the disorder, which is the most debilitating symptom
- Several oral agents have been shown to be effective in controlling the pain associated with IC in some patients, including narcotics, antidepressants, gabapentin and pentosan polysulfate
- Some invasive therapies such as hydrodistension, intravesIcal treatments and sacral neuromodulation are also being investigated for the treatment of IC

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HE Foster Jr declared competing interests; go to the article online for details. S Phatak declared he has no competing interests.