

Treatment Approaches for Interstitial Cystitis: Multimodality Therapy

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Interstitial cystitis is an increasingly common disease characterized by urgency, frequency, and pelvic pain. Its etiology is poorly understood but is likely to be multifactorial. A proposed pathophysiology describing a cascade of events, including epithelial dysfunction, mast cell activation, and neurogenic inflammation, is presented. Using this model, multimodality therapy regimens have been developed that treat all components of this cascade. Multimodality therapy appears more effective than single agents in the treatment of interstitial cystitis. [Rev Urol. 2002;4(suppl 1):S16–S20]

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Interstitial cystitis (IC) is a bladder condition that presents with a range of symptoms, including bladder pain, urinary urgency and frequency, and nocturia. Current estimates of disease prevalence suggest that at least 1 million people in the United States are affected.¹

The etiology remains uncertain, although a number of potential causal factors have been proposed.^{2–7} The variation seen in both the range of symptoms and in patients' responses to therapy suggest that multiple factors are involved in this disease process. There remains the possibility that subgroups of patients may exist with differing etiologies.

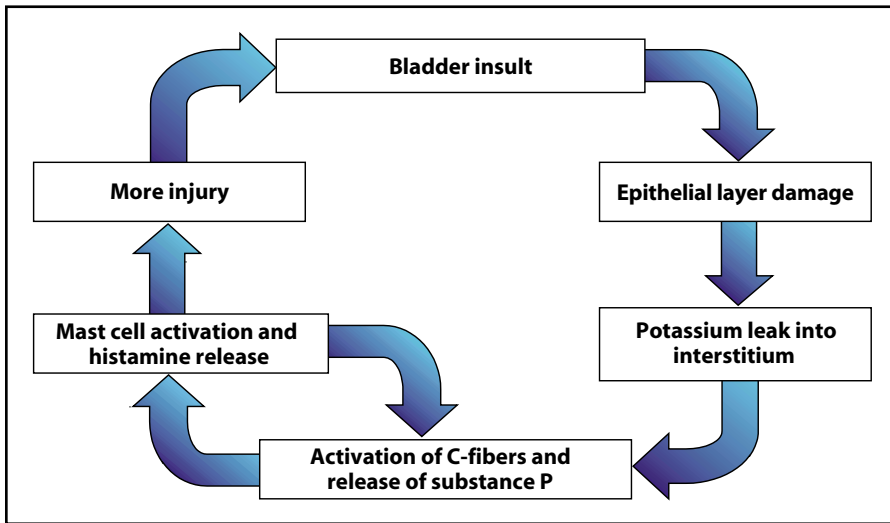


Figure 1. A proposed model for the pathogenesis of interstitial cystitis.

A large number of therapies are available to treat patients with IC. Because of variation in response to therapy, the clinical approach to treatment has been largely empirical. Increased understanding of the etiology of IC and identification of factors involved in the pathophysiology of the disease will allow treatment regimens to be better targeted toward each individual patient's conditions.

A Proposed Model for IC Pathogenesis

Many theories have been proposed to explain the pathogenesis of IC, but none have been conclusively proven to be true. Proposed causative factors include epithelial dysfunction,³ mast cell abnormalities,⁵ subclinical infection,⁴ neurogenic inflammation,⁶ vascular abnormalities,⁷ and autoimmune phenomena.² With so many possible factors influencing the development of IC, it is likely that there is not a single etiology for the disease. It is far more likely that the etiology is multifactorial. A model has been proposed for the development of IC that takes into account not only the experimental data currently available

concerning the possible mechanisms for the development of IC, but also the clinical histories commonly seen in this patient population (see Figure 1).⁸

In this proposed model, the cascade of events that lead to the development of clinical IC begins with the development of an injury to the bladder or epithelium. In many cases this may have occurred following an episode of bacterial cystitis, but in other patients, pelvic surgery, childbirth, or urologic instrumentation may be the initiating event. In normal patients, uroepithelium is expected to heal following appropriate therapy, but in this group of patients healing of the uroepithelium does not occur. Recent reports have suggested that patients with IC have urine that contains an anti-proliferative factor that retards or prevents normal epithelial healing.⁹ In addition, epithelial growth factor is decreased in urine of IC patients. This combination of elevated anti-proliferative factor and diminished epithelial growth factor seems to prevent normal uroepithelial repair.

Over time, these patients develop abnormalities of the glycosaminoglycan (GAG) layer. Parsons has

demonstrated that IC patients suffer from a defective GAG layer that allows urinary metabolites such as potassium to pass through the bladder wall and into the submucosal space.¹⁰ Potassium leaking through the uroepithelium causes depolarization of smooth muscles of the bladder and the pelvis, with activation of sensory nerves. The constant irritation of the submucosal space by leakage of urinary metabolites through the defective bladder lining causes an inflammatory reaction marked by the proliferation and activation of submucosal mast cells. When activated, mast cells release histamine and other mediators, stimulating sensory nerve fibers and eliciting local tissue damage and vascular constriction.

Mast cell degranulation activates capsaicin-sensitive nerve fibers, leading to the release of substance P as well as other neuropeptides, causing additional cell damage and further activation of mast cells. Over time, the ongoing effects of both the mast cell activation and the stimulation of the capsaicin fibers are more local tissue damage, ongoing injury to the GAG layer, further injury to the bladder smooth muscle, and development of fibrotic changes within the bladder. Over time, if this cascade of events is left untreated, the bladder will decrease in size and the functional bladder capacity will plummet.

The inflammation and activation of the capsaicin fibers can lead to neural up-regulation and the development of neural changes within the spinal cord. Once this occurs, patients will suffer from chronic pelvic pain, urgency, and frequency. The "up-regulation" that occurs in patients with long-standing IC explains why many patients continue to have vaginal and pelvic pain even after cystectomy.

Although it is not clear why this cascade of events occurs in this

Table 1
Principles of Multimodality Therapy for Interstitial Cystitis

- Repair endothelial dysfunction
- Modulate neural activity
- Stabilize mast cells

patient population, this theory of a multifactorial etiology for IC is extremely helpful in planning effective therapy. To prevent the development of end-stage IC, aggressive and early detection, combined with a multimodality therapy approach to address not only the deficiency of the GAG layer but also mast cell abnormalities and neurogenic inflammation, may help stop the progression of the disease and over time allow for the redevelopment of a more normally functioning bladder epithelium.

Implementing a Multimodality Treatment Strategy

Given the multifactorial nature of IC, it is unusual for patients, particularly those with more severe disease, to respond to a single agent. It is crucial to utilize a multimodality treatment strategy in selecting appropriate therapy for IC. In patients who are candidates for long-term oral therapy, select agents that will treat GAG layer dysfunction, mast cell abnormalities, and neurogenic inflammation (see Table 1). The side effects of the medications selected need to be considered so that if two medications have similar side effects, such as sedation, dose modifications may be made. Table 2 lists the components of oral therapy discussed below.

Pentosan Polysulfate

Pentosan polysulfate (PPS) remains the **cornerstone of drug therapy** for

most patients. Although the exact nature of PPS on the bladder is not completely clear, it is felt to function by coating the bladder lining, re-establishing normal GAG layer function and decreasing potassium leak into the interstitial space.¹¹ The recommended dose is 100 mg t.i.d., but higher doses such as 200 mg t.i.d. or 300 mg t.i.d. have been used. Alternative dosing schedules to improve patient compliance have been used at many IC centers, with 200 mg b.i.d. a common starting dose.

Patients starting therapy with PPS need to be told that the full effect may not be seen for 6–9 months, but they can be reassured that many patients see improvement in as little as 4 weeks. Patients taking PPS need to be encouraged to stick with therapy, because the most important factor in determining the benefit of therapy with PPS is the length of time under treatment. Patients on PPS need to be reassured that the side effects sometimes seen with this medication (including headache, gastrointestinal upset, and hair loss) are generally mild and usually will not necessitate withdrawal of the medication.

Antihistamines

The central role of the mast cell in IC is clear.¹² Any form of multimodality therapy should include therapy that blocks the effect of histamine. Hydroxyzine hydrochloride remains the most effective agent for the management of mast cell dysfunction.¹³ Because of its sedative properties, it is generally administered at night in doses ranging from 25 to 75 mg. In patients who are highly sensitive, doses as low as 10 mg can be used. In the spring and fall, when many IC patients suffer from seasonal allergies, an additional 10–25 mg every 6 hours can be beneficial. In patients who cannot tolerate a sedating antihistamine, cetirizine hydrochloride

may be a reasonable alternative. The addition of H2 blockers to more standard antihistamine therapy has been reported, but the results are somewhat inconclusive.¹⁴

Antidepressants

IC patients often benefit from an antidepressant therapy, particularly tricyclic antidepressants such as amitriptyline hydrochloride.¹⁵ These antidepressants are particularly effective, because in addition to the antidepressant effect they modify pain, have a mild antihistamine effect, can decrease urgency and frequency through a modest anticholinergic effect, and are also effective as sleep aids.¹⁶ Amitriptyline is generally administered at night in doses ranging from 25 to 100 mg q.h.s. with dose titration over time until adequate symptom control is achieved. If patients are also taking an antihistamine the dose may need to be decreased, with some patients responding to doses as low as 10 mg q.h.s.

If patients cannot tolerate amitriptyline they may respond to alternative tricyclics, including trazodone, doxepin, and nortriptyline. One antidepressant that should be avoided is imipramine, as the sympa-

Table 2
Components of Oral Therapy for Interstitial Cystitis

- Pentosan polysulfate
- Antihistamines
- Antidepressants
- Anticholinergics
- Urinary analgesics
- Narcotics/pain relievers
- Gabapentin
- Other

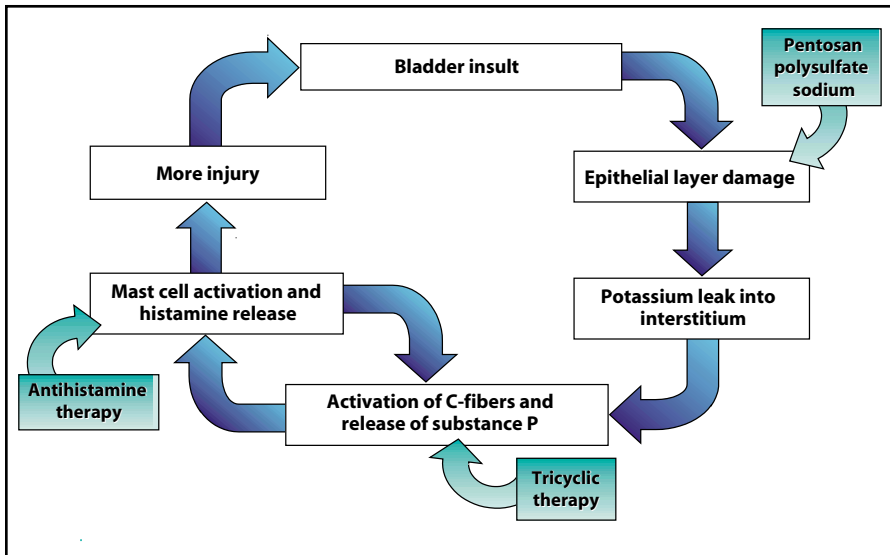


Figure 2. The role of multimodality therapy as related to the proposed multifactorial etiology of interstitial cystitis.

thomimetic effect of this agent often exacerbates dysfunctional voiding.

Patients who truly cannot tolerate tricyclic antidepressants may benefit from the administration of selective serotonin reuptake inhibitor (SSRI) antidepressants. This is particularly true for patients who also suffer from fibromyalgia. Commonly used SSRIs include paroxetine hydrochloride, fluoxetine hydrochloride, citalopram hydrobromide, venlafaxine hydrochloride, and sertraline hydrochloride. There have been no placebo-controlled trials for SSRI as treatment for IC.

Gabapentin

Pain and dysfunctional voiding may continue even after appropriate therapy with pentosan polysulfate and other agents. This may be due to “up-regulation” and the development of neurogenic inflammation within the spinal cord. Gabapentin can decrease neurogenic inflammation and is used in patients with severe and unrelenting chronic pain.¹⁷ It is usually given in divided doses ranging from 300 mg to 2400 mg daily. This drug requires very careful dose titration, balancing symptom control

with side effects such as sedation. If a urologist is uncomfortable using agents of this nature, referral to a pain clinic is appropriate. Phenytoin, carbamazepine, and valproic acid are alternatives to gabapentin.

Supplementary Oral Therapies

Urinary analgesics and antiseptics such as phenazopyridine hydrochloride, Uromax, and Urised are not effective as primary therapy, but can be helpful for the management of short-term symptom flares or after urologic instrumentation. Other agents that are occasionally helpful include urinary alkalizers, which can decrease

bladder discomfort by lowering urinary acidity.

Pelvic floor dysfunction is often present concomitantly with IC. Benzodiazepines or other skeletal muscle relaxants are appropriate therapy. Moldwin has demonstrated that doses as low as 2 mg t.i.d. of diazepam can relax the pelvic floor and ease dysfunctional voiding (personal communication, RM Moldwin). Anecdotal use of alpha blockers, including tamsulosin hydrochloride, for male and female patients with dysfunctional voiding may be beneficial, but no controlled studies have been completed.

Intravesical Agents

For patients who do not respond to oral therapy or for those patients who suffer from a flare and require additional treatment, several intravesical agents are available. Although dimethyl sulfoxide (DMSO) is the principle intravesical agent approved by the U.S. Food and Drug Administration (FDA), numerous other agents have been used.¹⁸ DMSO is generally administered once weekly for at least 6 weeks, and administration can be done either in the clinic or at home by patients capable of self-catheterization. Multidrug cocktails, including DMSO (50 cc), sodium bicarbonate (48 meq), heparin (20,000 units), and triamcinolone acetonide (1 amp) are

Figure 3. A summary of multimodality therapy for interstitial cystitis.

- Diet and Self Help

Pathogenic Factor	Therapy
Epithelial dysfunction	Pentosan polysulfate
Neuromodulation	Antidepressants
Mast cell activation	Antihistamines

- Don't withdraw therapy when adding new modalities

commonly used. For patients who are capable of self-catheterization, an anesthetic cocktail consisting of bupivacaine (30 cc), heparin (20,000 units), sodium bicarbonate (48 meq), and triamcinolone acetonide (1 amp) can be self-administered on a daily basis. Patients who are unable to take pentosan polysulfate because of side effects may respond to either intravesical pentosan polysulfate or intravesical heparin administered daily.¹⁹ Intravesical oxybutynin (5–10 mg crushed and suspended in 10 cc of water) has also been used to control bladder spasms.

Other intravesical agents not FDA approved include hyaluronidase²⁰ and bacillus Calmette-Guérin (BCG).²¹ A clinical trial of hyaluronidase is currently underway, and it is anticipated that a BCG trial will commence shortly.

Discussion

A majority of patients will respond to a multidisciplinary approach consisting of dietary modification, behavioral modification, pentosan polysulfate, and either hydroxyzine, a tricyclic antidepressant, or both (Figures 2 and 3). If patients respond to multimodality therapy, they can be slowly weaned from their medications. Narcotics, neuroleptics, and antidepressants are eliminated first. If patients tolerate this, continue to sleep well, and have good pain control,

their antihistamine dose can be decreased and possibly eliminated. The pentosan polysulfate dose can also be titrated downward. Although some patients can eliminate all medications and do well, most require a maintenance dose of pentosan polysulfate, often as little as one or two pills daily. Patients are encouraged to follow their IC diet carefully and continue with stress management techniques. If at any time symptoms flare, their medications can be temporarily increased and then once again decreased back to baseline once the symptom flare has been controlled.

Conclusion

The proposed multifactorial etiology of IC has led to the development of an appropriate multimodality therapy for the disease. Most patients will respond to this multimodal approach with significant improvement and in general can tolerate this treatment regimen in the long term. ■

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Main Points

- A multifactorial model has been proposed for the development of interstitial cystitis (IC).
- In this model, an injury to the bladder or epithelium of the IC patients does not heal normally; leakage of urinary metabolites through the defective bladder lining causes mast cell activation and neurogenic inflammation; over time, if this cascade of events is left untreated, the bladder will decrease in size and the functional bladder capacity will plummet.
- When treating patients with IC, it is crucial to utilize a multimodality treatment strategy, including agents that will treat glycosaminoglycan (GAG) layer dysfunction, mast cell abnormalities, and neurogenic inflammation.
- Pentosan polysulfate remains the cornerstone of drug therapy for most patients; it functions by coating the bladder lining, re-establishing normal GAG layer function and decreasing potassium leak into the interstitial space. Urinary analgesics and antiseptics, urinary alkalizers, and benzodiazepines can also be useful in some settings.
- For patients who do not respond to oral therapy or for those patients who suffer from a flare and require additional treatment, several intravesical agents are available.