Review Article

Current guidelines in the management of interstitial cystitis

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Abstract: Interstitial cystitis (IC) is a heterogeneous chronic disease of unknown etiology that impacts a very large number of women. Symptoms are highly variable: patients may suffer from pelvic pain that is exacerbated by bladder filling, and can be associated with a variety of lower urinary tract symptoms including frequency and urgency. Given the varying presentations and severities of corresponding treatment must be tailored to each specific patient. Current American Urological Association (AUA) guidelines separate the IC treatment recommendations into six tiers of increasing invasive therapies. These treatment guidelines begin with education and lifestyle modifications and progress through levels of physical, pharmacological, and ultimately surgical therapies for those that fail the less invasive therapies. The purpose of this review is to outline the recommendations for the treatment of IC and the evidence from which these recommendations arise. Furthermore, we examine the most up to date literature so that we may recognize future directions in the treatment of IC.

Keywords: Interstitial cystitis (IC); instillation therapy; neuromodulation

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Introduction

Interstitial cystitis (IC), also referred to as bladder pain syndrome (BPS), is a heterogeneous chronic disease of unknown etiology that impacts up to 8 million women in America (1). Patients suffer from pelvic pain that can be exacerbated by bladder filling, and is often associated with urinary frequency and urgency (2). Since Alexander Skene's inception of the term in 1887, research into the etiology and pathophysiology of this disease has not been successful in elucidating a specific mechanism, revealing more questions than answers. As a result, treatment is difficult.

The American Urological Association (AUA) breaks down the treatment recommendations into six tiers of treatment with the fundamental principle of using more conservative therapies first, with less conservative therapies employed if symptom control is inadequate for acceptable quality of life (*Table 1*) (3). These treatment guidelines begin with the simple clinical principles of education and lifestyle modifications and progress through levels of physical, pharmacological, and ultimately surgical therapies for those that fail the less invasive therapies.

The purpose of this review is to outline the recommendations for the treatment of IC and the evidence from which these recommendations arise.

Conservative therapy

As with most diseases first line therapy for IC is conservative management with techniques including education, behavioral modification, and stress control. Patient education as to the normal function of the bladder as well as what behaviors may lead to increased bladder pain is integral to symptom control. Behavioral modification strategies may include: altering diet to avoid known bladder irritants such as caffeine and spicy foods, altering urine volume to control concentration,

Table 1 Tiers of treatment for interstitial cystitis/bladder pain syndrome (IC/BPS)

First line treatments
General relaxation/stress management
Pain management
Patient education
Self-care/behavioral modification
Second line treatments
Manual physical therapy
Oral therapies
Intravesical therapies
Pain management
Third line treatments
Cystoscopy under anesthesia with hydrodistention
Pain management
Fulguration of Hunner's lesions if found
Fourth line treatments
Intradetrusor botulinum toxin A
Neuromodulation
Pain management
Fifth line treatments
Cyclosporine A
Pain management
Sixth line treatments
Diverson with or without cystectomy
Pain management
Substitution cystoplasty

Table 2 Pharmacological therapies for IC/BPS

Delivery method	Medication
Oral	Pain control
	Amitriptyline
	Hydroxyzine
	Cimetidine
	Pentosan polysulfate (PPS)*
	Cyclosporine A+
Intravesical	Dimethyl sufloxide (DMSO)
	Heparin
	Lidocaine

IC/BPS, interstitial cystitis/bladder pain syndrome; *, PPS is the only medication FDA approved for IC; +, cyclosporine A is fifth line therapy.

application of local heat or cold over the bladder or perineum and exercises that improve pelvic floor muscle relaxation and bladder training. IC flairs are also often associated with psychological stress, so stress reduction techniques such as meditation also play an important role in symptom control.

Beyond lifestyle changes, physical therapy is also playing an increasing role in the treatment of IC. Second line treatment begins with physical therapy, and the AUA recently upgraded appropriate manual physical therapy techniques that resolve abdominopelvic muscular trigger points and improve connective tissue restrictions as a standard of care with grade A evidence (4). These recommendations are based on a randomized clinical trial by Fitzgerald and colleagues that tested ten 60-minute sessions over 12 weeks of myofascial physical therapy (MPT) compared to global therapeutic massage (GTM) in IC patients. At 3 months, significantly more patients in the MPT group reported moderate or marked improvement compared to GTM group (59% versus 26%) (5). It should also be noted that these therapies are not pelvic floor strengthening therapy, and that such exercises may actually worsen IC symptoms (4).

Pharmacological therapy

Oral therapy

For those patients that fail conservative therapy, oral medications are the appropriate next line of treatment. *Table 2* demonstrates the currently accepted pharmacological therapies for IC. Introduction of pharmacological strategies should be done in parallel with continued conservative therapies and should involve pain control in addition to disease modifying agents (3). In terms of pain management, the principles for IC treatment should be similar to those for management of other chronic pain states. Beyond pain control, the following medications are recommended by the AUA.

Amitriptyline

Amitriptyline is a tricyclic antidepressant and has been demonstrated to be effective for various causes of neuropathic pain. One randomized controlled trial reported efficacy of oral amitriptyline to be superior to placebo with 63% of treatment group clinically significantly improved at 4 months versus 4% of placebo group (6). These benefits, however, must be weighed against adverse events. Although not life-threatening, observational studies

report up to a 79% adverse reaction rate with side effects including nausea, drowsiness, weight gain and sedation (7). For those patients that do not tolerate amitriptyline other neurological modifying agents such as gabapentin, pregabalin or serotonin-norepinephrine reuptake inhibitors like milnacipran and duloxetine can be substituted, though these treatments are less well studied.

Hydroxyzine/cimetidine

Hydroxyzine and cimetidine are an H1-receptor agonist and an H2-receptor antagonist, respectively. These drugs may affect IC by preventing mast cell degranulation and histamine release (one of the mechanisms that has been suggested in the pathophysiology of IC) (8). While both drugs have multiple observational studies that suggest their effectiveness, each only has one randomized clinical trial. For cimetidine, Thilagarajah and colleagues demonstrated a statistically significant improvement in patient symptoms after 3 months of treatment (9). For hydroxyzine, however, the only available randomized clinical trial demonstrated clinical, but not statistically significant improvement (10). As such the recommendation for cimetidine is grade B and the recommendation for hydroxyzine is grade C.

Pentosan polysulfate (PPS)

PPS is a polysulfated xylan and the only FDA-approved oral medication to treat IC (8). This medication is thought to exert its effect by repairing the glycosaminoglycan (GAG) layer of the bladder urothelium and reducing its permeability (11). PPS holds a grade B recommendation based on five clinical trials (four of which were randomized clinical trials). Of these trials, two demonstrated significant symptom improvement with PPS (12,13), while the other two did not (10,14). However, since publication of the guidelines update another randomized clinical trial by Nickel and colleagues found no difference between PPS (with two separate arms with different dosing regimens) and placebo (15), so the next iteration of the guidelines may see a change in the recommendations regarding this drug.

Cyclosporine A (CyA)

Unlike the other oral medications, CyA is actually a fifth line therapy and reserved for refractory patients. CyA inhibits calcineurin, which is necessary for the activation of T cells. As such it is generally used for immunomodulation in transplant recipients and certain autoimmune disorders. Given this mechanism of action it has also been proposed that this drug may benefit patients with bladder inflammation caused by IC.

The evidence for the use of CyA comes from one randomized control trial and four observational studies. For the randomized control trial Sairanen and colleagues randomized 64 IC patients to either CyA or PPS treatment over 6 months. What they found was that 75% of patients in the CyA group experienced clinically significant improvement compared to 19% of a PPS comparison group after the allotted time frame (16). The observational studies found similar efficacy, with particular efficacy noted in patients with active inflammation or Hunner's lesions (16-19). However, because of the relatively small numbers represented in these studies, the lack of long-term follow-up data, and the potential for serious side effects, the AUA lists CyA as an option with grade C evidence. They also recommend that, should this option be chosen, it only be done so by clinicians with significant experience dosing CyA (3).

Intravesicular therapy

Bladder instillation therapy refers to the direct introduction of a treatment agent into the bladder via a catheter (20). Although still considered second line therapy, these treatments are reserved for patients who fail conservative management as well as oral medications. *Table 2* shows the most commonly used intravesicular therapies.

Dimethyl sulfoxide (DMSO)

DMSO is an organosulfur compound with chemical formula $(CH_3)_2SO$. Although the exact mechanism by which DMSO alleviates IC is unknown, it is believed to work through several mechanisms: studies have suggested that it may act by reducing inflammation, causing detrusor relaxation, or dissolving collagen, as well as by acting as an analgesic (21). DMSO may also cause temporary urothelial injury (22) and therefore may allow for better penetration of other agents. As such, DMSO is often given as part of a "cocktail" in a multimodal regimen (23). These cocktails include some combination of DMSO, heparin, lidocaine, sodium bicarbonate, and/or steroid, but no combinations have been proven more effective than others. The general DMSO only regimen involves initial 50 mL doses weekly for 6-8 weeks, followed by 50 mL maintenance doses every 2 weeks for 3-12 months (21).

Heparin and GAGs

Heparin is the highly sulfonated GAG best known for its use as an anticoagulant. In addition to its hematological uses, heparin has also been adopted as an intravesicular treatment for IC. The theoretical benefit of heparin in these patients is derived from the histopathogical changes exhibited in IC: when diseased urothelium exhibits a loss of its endogenous proteoglycans (24,25). Like oral PPS, heparin has the potential to act as an exogenous GAG, and may be able to replace some of the urothelium's natural function (26,27). Heparin also demonstrates a variety of other potentially beneficial effects, including anti-inflammatory, fibroblast proliferation inhibition, angiogenesis, and smooth muscle cell proliferation, and therefore may act in IC by multiple mechanisms (28).

With the success of heparin, other GAGs have also been considered for use in treating IC, but none have proven successful. The most common is the nonsulfonated GAG hyaluronic acid. Although it sees some use in Europe and Canada, hyaluronic acid has not been proven to be effective in any randomized trials. The drug actually underwent two multi-center, double-blinded, placebo-controlled industry funded studies in 2003 and 2004, and neither demonstrated significant efficacy (29). Over the counter supplements containing the GAGs chondroitin and the GAG precursor glucosamine are available, but have never been subjected to randomized clinical trials.

Lidocaine

Lidocaine is a common topical anesthetic that has been used in a wide variety of pain syndromes, and the use of such anesthetics has long been practiced in the treatment of IC. It is given in a wide array of different formulations and concentrations, and recently has seen increasing use in combination with an alkalizing agent in order to avoid ionization within the acidic urine and better penetrate urothelium (30). Unfortunately, the relief granted by lidocaine is rarely long lasting (longer than 2 weeks). Currently researchers are attempting to remedy this problem with implantable lidocaine eluding devices, and initial results are positive (31).

Surgical therapy

For patients that continue to fail symptom control with a full course of pharmacological treatments more invasive treatment may be necessary. While the most extreme cases of IC may require removal or diversion from the bladder (sixth line therapy), the vast majority of surgical therapies are more benign.

Cystoscopy with hydrodistention/Fulguration of lesions

If conservative and pharmacological therapies have not provided acceptable symptom control, then third line therapy is to perform cystoscopy under anesthesia with low-pressure (60 to 80 cmH_2O), short duration (less than 10 minutes) hydrodistension. This procedure has multiple benefits. First and foremost it serves as a diagnostic tool by allowing the clinician to inspect the bladder for glomerulations and Hunner's lesions or any other bladder lesions. It also allows for staging by measuring anatomical capacity (rather than just functional capacity). Beyond the diagnostic properties of cystoscopy, hydrodistention is in itself a treatment for IC. Although the exact mechanism of action by which hydrodistention relieves pain is unclear, it has been theorized that hydrodistention allows for the break down and subsequent reconstruction of damaged nerve pathways, even in the absence of lesions (32). Regardless of the mechanism, hydrodistention has been demonstrated in multiple studies to be safe with relatively low rates of adverse events and to effectively relieve pain for up to 6 months (33,34).

Another important aspect to cystoscopy is that it allows for the examination of the bladder for Hunner's lesions. These lesions present as a reddened mucosal area with small vessels radiating towards a central scar, and have increased likelihood of bleeding, especially during hydrodistention. Although relatively rare (occurring in only 5-10% of patients), identification of Hunner's lesions is important because treatment appears to constitute one of the few IC therapies that results in significant prolonged improvement with only a single exposure to the procedure. Fulguration or sclerosing of Hunner's lesions has been demonstrated multiple times to result in complete or almost complete resolution of pain symptoms for durations of over a year (35,36). Intralesional injection of corticosteroids such as triamcinolone is also useful in reducing symptoms, though safety data on the maximum dose of such injections is lacking.

Intradetrusor botulinum toxin A (BTX-A)

Fourth line treatments for IC include intradetrusor BTX-A injections and neuromodulation. Botulinum

toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. Although it occurs in sever subtypes (A-G) in nature, in medical practice the only subtypes used are BTX-A and less commonly BTX-B. BTX-A has long been considered an efficacious treatment for various bladder pathologies such as overactive bladder (OAB) and neurogenic bladder, but is only recently being explored for the treatment of IC. For the treatment of IC current AUA guidelines list BTX-A as an option with grade C evidence. This option is based upon one randomized control trial and nine observational studies that demonstrated highly variable amounts of short and long efficacy rates (from 20% to 86% at 3 months) (37-41).

Given the novelty of using BTX-A for IC, there is still some debate as to the best strategy for treatment. The one randomized control trial for BTX-A in IC patients found significant improvement in patients who undergo hydrodistention with BTX-A than those who undergo hydrodistention alone: successful treatment response at 12 and 24 months was reported in 24 (55%) and 13 (30%) patients in BTX-A group, respectively, compared with only six (26%) and four (17%) in the hydrodistention only group (42). This suggests that BTX-A is best given in conjunction with hydrodistention, but more evidence is required to formulate the optimal regimen.

Neuromodulation

Neuromodulation through sacral nerve stimulation (SNS) involves an initial test phase with insertion of a test lead tunneled under the skin transmitted onto the nerve roots exiting the S3 foramen. The pelvic and pudendal nerves are stimulated by an external stimulator that is later exchanged for a permanent implant if successful. This technique has been shown to be effective in several disease states including fecal incontinence, urinary urgency, urge incontinence and urinary retention and has an FDA indication for these symptoms. Early studies investigating the efficacy of neuromodulation on pain secondary to IC have also been positive, but the research is scant and highly variable. Thus, patients must be advised that neuromodulation is to be used for the treatment of voiding symptoms and that pain relief may not occur.

Conclusions

Although the pathophysiology of IC is still poorly understood, a wide number of treatment options are available depending on severity of symptoms. As we better understand the disease process customized treatment should improve outcomes. Until personalized treatments become available application of the AUA guidelines is the best strategy to find the most beneficial and least invasive treatments for our patients in a timely fashion.

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Footnote

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