Current Clinical Management of Interstitial Cystitis

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Interstitial cystitis (IC) or painful bladder syndrome is a syndrome characterized by symptoms of urinary urgency, frequency, and chronic pelvic pain. The first epidemiology study of Interstitial cystitis(IC) was reported by Orvisto in 1975.[1] Since then several sporadic reports have been conducted with different prevalence from 17/100,00 to 510/100,00.[2] The main reason for the contradictory findings may be due to the lack of global accepted, objective diagnostic tests. At present the diagnostic approach to IC remains, if not for research purpose, empiric and physician specific. With increasing awareness of the IC prevalence and presentation, clinicians are identifying cases earlier in the disease process. A new consensus is emerging from the 2003 NIDDK/ICA research symposium and 2003 international Consultation on Interstitial Cystitis in Japan (ICICJ),[3] with regard to a revised diagnostic paradigm for IC. A symptom questionnaire to capture and record the presence of all IC symptoms is useful to establish the diagnosis. All other diagnostic measures are optional. From the evidence-based medicine point, either cystoscopy, urodynamic, potassium test, or biopsy does not require in the workup for IC.[4]

Because of uncurable nature of IC at present, the main goal of management is to control the symptoms. The pathogenesis of IC remains uncertain, and may consist of multiple coexisting and reinforcing mechanisms. It's known to include epithelial dysfunction and inflammatory events, allergic reaction, as well as peripheral and central nerve dysfunction. Animal and human research shows multiple neurological changes in IC as reviewed by Nazif et al.,[5] though whether the neural mechanisms and inflammation are the cause of IC or the results of other initiating events is unclear. It is evident that neural upregulation plays a role in the chronicity of pelvic pain, frequency, and urgency. Neural upregulation can help us better understand why patients typically present initially with urgency and frequency, and the pelvic pain tends to be a later picture.[6] In addition to the epithelial dysfunction theory, mast cell activation, neural upregulation in IC is an exciting area of research that may lead to additional treatments and a better understanding of IC.[7]

With advances in the understanding of IC in recent years, the ability to offer symptoms relief has increased significantly. The efficiency of the treatment depends on many factors, such as disease severity, disease status and the coexisting problems. Recently the impact of sexual function on IC patients has been addressed and deserves attention to it for the improvement of quality of life in IC patients.[8]

The surgical therapy of IC is an option after all trials have failed. After all, IC is a nonmalignant process and does not directly results in mortality. Patients should be informed all possibility of complication before the surgical treatment. It is beyond the scope this mini- review to discuss the surgical treatment for IC.

Guidelines for the management of IC are summarized in Table 1.

The successful management of IC should be patient oriented and multimodal.

A multimodal treatment regimen ,including medical (oral, intravesical), non medical and other adjuvant methods, are recommended to address the postulated path physiological processes such as dysfunctional epithelial, neural activation, mast cell activation, release of mediators, are summarized in Table 2.

HYDRODISTENTION

Among the various methods reported, hydrodistention under anesthesia was first used for the treatment of IC by Dunn et al. in 1977.[9] They postulated the efficacy is probably related to damage to mucosal nerve endings, resulting in decreased bladder pain or increased bladder capacity. The authors performed continuous distention

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for 2 hours to 3 hours, symptom-free was found in 16 of 25 patients with an average follow-up of 14 months (range, 3 months to 3.5 years). The study of Taub et al. found no difference in results among prolong (6hrs) and short (15-30 min.) duration of hydrodistention.[10] In the study of Yamada et al,[11] symptoms were complete recovered in 10% with only hydrodistention procedure and 60% were without symptoms for 3-12 months with hydrodistention under epidural anesthesia performed for 30 minutes on 2 consecutive days. Hydrodistention is useful because of its simultaneous diagnostic evaluation, histological analysis, and therapeutic effect. The mechanism how the procedure works remains unclear. However, acute hydrodistention does not seem to result in long-term bladder dysfunction.[12]

MEDICAL THERAPY

Oral medication

Heparin compounds

The reason of heparinoid compound as the basis of multimodal regimen is based on the hypothesis of epithelial dysfunction that causes irrigative materials in urine such as potassium, urea leak into interstitum and cause IC symptoms.[13] The glycosaminoglycan (GAG) rich bladder mucus appears to be the primary regulators of epithelial permeability.[14] With the use of structurally similar, exogenous sulfated polysaccharide is thought to augment or help restore the natural mucus.[15,16]

Table 1. Guidelines for management of IC

* Use medical therapies; single or combination; oral or intravesical
* Consider adjuvant therapy such as PFME, CAM, SNM, BOTOX
* Emphasize patient education, including diet modification, sexual consultation and realistic expectations.
* Surgery be final resort and with caution

PFME: pelvic floor muscle exercise
CAM: complementary and alternative medicine
SNM: sacral neuron modulation

Table 2. Summarized medical and non-medical treatment modalities and its purposes

	Medical therapy		Non-medical therapy
	Oral	Intravesical	
Restore epithelial function	PPS	* PPS * Heparin * Hyaluronic acid * Chondroitin sulfate	
Inhibit neural activation	Amitriptyline gabapentin	DMSO Capsaicin Resiniferatoxin (RTX) BOTOX	Sacral N. stimulation
Control allergies	Hydrolxyzine Cimetidine		
Others (neuroleptic)	Gabapentin NSAIDS	Alkalized lidocain Sodium bicarbonate Steroid.	* Hydrodistention * PFME (pelvic floor muscle exercise) * Biofeedback, E-stimulation * Dietary modification * Behavior modification including psychological treatment * Complementary medicine * Acupuncture
Others (immunotherapy)		BCG	* Nutraceuticals (herbal therapy)

PPS: pentosan polysulfate sodium

Pentosan polysulfate (PPS) to restore GAG layer

Pentosan polysulfate is the only oral medication approved by FDA for the treatment of IC/PBS. It is designed to replace the presumed defective GAG layer,. Studies have been contradictory. A randomized, double-blind, multicenter study of 380 patients with IC/PBS, reported that 45-50% of all patients were classified as responders (≥50% improvement on the Patient's Overall Rating of Improvement of Symptoms).[17] However the study was not placebo-controlled. Another randomized, placebo-controlled, double-blinded, multicenter trial in 136 patients, 300mg/day showed no better effect than placebo.[18]

There showed no dose-related efficacy study in the range of 300 to 900 mg daily, but adverse events were dose related.[17]

Antihistamine to control allergy

The use of antihistamine in treatment could be back to 1950 and stemmed from work of Simmons who postulated that the local release of histamine may be responsible for, or accompany the development of, IC. Beneficial effect of hydroxyzine seem to be associated with its anxiolytic, sedative, anticholinergic and mast cell inhibitory properties, along with its effect to reduce neurogenic bladder inflammation.[19] Hydroxyzine, pentosan polysulfate were compare with placebo in the study of Sant et al,[18] neither agent was effective when used alone, but their combination was associated with a 40% response rate compare with 31% with placebo (although not statistically significant). Why an H2-antagonist would be effective is unclear, but uncontrolled studies show no improvement of symptoms in two thirds of patients taking cimetidine 600mg per day in divided doses.[20] It also proved effective in double-blind, placebo-controlled trial, but histologic studies show no change of bladder mucosa before and after treatment, and the mechanism of any efficacy remained unexplained.[21]

Tricycle Antidepressants (Amitriptyline) to inhibit Neural Activation

Amitriptyline has become a main component of oral treatment for IC. The tricyclic agents have at least three major pharmacologic actions: central and peripheral anticholinergic actions at some sites; block reuptake of serotonin and noradrenaline; sedatives, an action presumably on central basis, but may be related to H1-antihistaminic properities. Tricyclic antidepressants are known to relieve pain, however, their mechanisms of analgesic action remain unknown.Tricyclic agents could stimulate bladder smooth B adrenergic receptors that would decrease excitability and facilitate urine storage.

Hanno et al reported a promising improvement in symptoms, with tricyclic antidepressant. dosage ranging form 25mg gradually increasing to 75mg within 4 weeks at bedtime.[22] Bladder capacities over 450 to 600 mL under anesthesia seemed to have the best results.[23] Amitryptyline has proven analgesic efficacy, with a median preferred dose of 75 mg in a range of 25 to 150 mg daily. A 19-month follow-up revealed little tachyphylaxis and good response rates but associated with sedation, dry mouth, and significant weight gain.[24]

Analgesics

The long-term, appropriate use of pain medications may be considered to an integral part of the management of a chronic pain condition such as IC. Chronic neuropathic pain syndromes could be helped markedly with medications, including antidepressants, anticonvulsants and opioids.[25] Gabapentin , as an anticonvulsant, demonstrates synergism with morphine in neuropathic pain, may give some benefit in IC.[26]

Other oral medications

Several oral medications for IC management have been tried and essentially been discarded, including systemic corticosteroids, hormones, vitamin E, anticholinergics, antispasmodics, immmunosuppression, chloroquine derivatives, opiate antagonist nalmefene, calcium channel antagonist nifedipine, cysteinyl leukotriene D4 receptor antagonist montelukast, oral L-arginine, Quercetin et al., although some are being reinvestigated.[27,28]

Intravesical medication

Intravesical drug delivery therapy y for IC has the established clinical efficiency and a perspective for future gene developments.[29] The intravesical therapeutic regimen including heparinoid drug , DMSO, hyaluronic acid, BCG., RTX, and Botox et al.

Heparinoid solution

Exogenous glycosaminoglycans have been showed to be effective in providing an epithelial permeability barrier.[30] Intravesical heparinoid therapy could be used as single or combination regimen, such as steroid, sodium bicarbonate, lidocain or DMSO.

Heparin

Because of the anti-inflammatory effects as well as actions that inhibit fibroblast proliferation, angiogenesis, and smooth muscle cell proliferation, the therapeutic

effect other than anticoagulation has been the subject of much inquiry and speculation.[30,31] Given intravesically, there is no systemic absorption, even in an inflamed bladder.[32] The dose of heparin from 10000U to 40000U, instillation daily or twice weekly, and duration for 3 to 6 months were noted in different studies.[32-34] However . there is not any placebo-controlled study conducted yet.

Pentosan polysulfate

A placebo-controlled study of intravesical pentosan polysulfate for the treatment of IC reported by Bade et al revealed that 4 of the 10 IC patients and 2 of the control group got significant improvement.[35]

Hyaluronic acid

Hyaluronic acid (marketed as Cystistat in Canada), a non-sulfated mucopolysaccharide component of the GAG layer, is believed to be presented in the subepithelium of urinary bladder and may protect it from irritating substances in the urine. Regimen with 40mg hyaluronic acid weekly for 4 weeks and then monthly achieved response rate 56% at week 4 and 71% at week 12, but decreased after week 24.[36] However, response rate of 30 % was noted in another study.[37] The use of intravesical hyaluronic acid in the treatment of IC has not been approved for use for IC in the United States.

Dimethyl sulfoxide (DMSO)

A mainstay of the treatment of IC is the intravescial instillation of DMSO.[38] DMSO (50% intravesical solution), approved for use in the United States in 1977. Pharmacologic properties include membrane penetration, enhanced drug absorption, anti-inflammatory action, analgesic action, collagen dissolution, muscle relaxation, and mast cell histamine release. Ek and colleagues reported a 70% success rate, but found relapse was not uncommon.[39] With its ease of administration, lack of significant side effect, and dependable symptomatic results, DMSO certainly merits its place as a useful treatment of IC.[40,41]

Vanilloids (capsaicin and resiniferatoxin, RTX)

Desensitizing the pain-mediating C-fiber in the bladder, regardless the cause, may be effective in the management of patients with IC. However, there is no sufficient data to support the benefit of capsaicin in IC at present. A recent placebo-controlled study revealed that RTX did not have definite activity in management of IC, but there is a possibility that alternative dosing regimes may be effective.[42] In the study of Kuo, multiple intravecical instillation of RTX at the concentration of 10 nM once weekly for 4 weeks are effective in relieving symptoms without serious adverse events in patient with refractory IC.[43] The role of these neurotoxins in the treatment of IC is still under investigation.

Bacillus Calmette-Guerin (BCG)

Immune system dysregulation with an imbalance of Th1 and Th2 cell may have a role in the pathophysiology.[44] Intravesical bacillus calmette-guerin (BCG) stimulate the Th1 cytokine, and pilot studies suggested that BCG may benefit patients with IC.[45] A double-blind, placebo-controlled study in 248 patients with IC showed that Global Response Assessment rate at 34 weeks was 21% for BCG compared with 12% of the placebo group after 6 weekly instillation of BCG(P=0.062).[46] The author concluded that intravesical BCG is not more effective than placebo in patients with moderate to severe IC. Because of the toxicity of BCG compared with other local agents, it should be used after other therapies failed. Parker et al reported a hypersensitivity reaction with intravesical BCG therapy, with complaints of systemic symptoms and arthritis, which resolved after steroid.[47]

Botulinum toxin type A (Botox, BTX-A)

In a study on rats, BTX-A was found to have an effect on visceral pain with a shorter time of latency,[48] and that support the application of BTX-A in the management of visceral pain as in IC. Two randomized studies reported different results after treatment with BTX-A in IC. The agent was administered by intradetrusor injection. One of the studies concluded that BTX is beneficial,[48,49] while the other showed no significant improvement.[50] Giannantoni et al reported with 85.7% improvement at 1 and 3 months in 14 patients after BTX-A injection at 20 sites in the trigone and bladder base.[51]

NON-MEDICAL THERAPY

The aim of non-medical therapies is designed to relieve the symptoms of IC. A variety of modalities were used which included sacral nerve modulation and complementary measures such as dietary modification, physical therapy, acupuncture behavior modification, and nutraceuticals materials (herbal therapy). At present, no large-scale evidence-base studies has been conducted in non-medical therapy for IC, and it should be emphasized that a given mode of therapy ought to be individualized.

Sacral Nerve Stimulation

Direct sacral nerve stimulation has been explored in the management of IC and urgency/frequency, which was referred to as neuromodulation.[52] Patients who do best with this treatment are those who have identifiable pain and dysfunction in pelvic muscles.[53] Although several studies has shown the efficacy of sacral nerve stimulation for the treatment of interstitial cystitis.[54-56] It's still not an approved indication for IC.

Overall, sacral nerve stimulation may be effective in treating the frequency component of IC, but it may not be effective in pain relief.[57]

Electrical Stimulation

Pain diversion by transcutaneous electrical nerve stimulation (TENS) is routine in a variety of painful condition. The intention is to relieve pain by stimulating myelinated afferents to activate segmental inhibitory circuits. Several studies have shown that electrical can modulate the neural behavior of bladder and pelvic floor. Several different approaches such as pudenda nerve stimulation,[58] sacral anterior root stimulation,[59] intravaginal electrical stimulation. The exact mechanisms are not clearly understood.

It is proposed that sacral nerve stimulation interrupts afferent inputs from bladder and modulates the voiding reflexes, thereby inhibiting activation of the reflex arc.[60] After all, sacral nerve stimulation may reset a balance between inhibitory and excitatory control to and from the pelvic organs at sacral and suprasacral levels, that is a balance between afferent pathways (pelvic pain and sensory urgency) and efferent pathways (motor frequency and urgency) that results in improved bladder function.[61]

Complementary and Alternative therapies for IC

Most patients with IC will use some form of complementary and alternative medicine therapy in their overall disease treatment procedure. The commonly used therapies included dietary modification, biofeedback and electrical stimulation, physical therapy, acupuncture, and herb medicine.

Dietary modification

Dietary modification was the fourth most common therapy reported in the Interstitial Cystitis Data Base (ICDB) study.[62] There is a large cohort of patients with IC in whom symptoms are exacerbated by the ingestion of specific comestibles. The most frequently reported and most bother some comestibles were coffee, tea, soda, alcoholic beverages, citrus fruits and juices, artificial sweeteners and hot pepper.[63]

The certain irritative foods and fluids cause a flare up of IC symptoms within 2 to 4 hours of ingestion.[64] It's a reasonable recommendation for patients to avoid the diet that will cause flare up of IC until symptoms begin to improve with medical therapy, and then to slowly reintroduce foods at each time as long as the symptoms under control.

Physical Therapy

The goal of physical therapy ,by stress reduction, exercise, warm tub baths, and biofeedback, is to relax the dysfunctional pelvic floor muscles that many IC patients accompanied with the dysfunction.[65] There are data that timed voiding and behavioral modification management can be helpful in the short-term, especially in patients in whom frequency rather than pain predominates.[66]

Although no standardized formula or studies have been undertaken to evaluate the effective of physical therapy for IC, physical therapy appears to most effective for those patients with concomitant pelvic floor muscle spasm.[67]

CONCLUSIONS

The information currently available in the literature does not lend itself to easily formulating a treatment pathway or guideline. Different groups of "experts" would propose their " best practice regimens" The compromise approach devised by experienced urologists and gynecologists from around the would at the International Consultation on Continence 2004 meeting in Monaco seem reasonable and allows physician broad choice in individual practice and to account for patient preference.[68]

It is important for the clinician to help the patients understand the possibility of long term course and what to expect from the treatment.

IC affects not only the patients themselves but also their family. Due to its chronic course, patient education and empowerment is an important initial step in therapy, patients should be encouraged to take responsibility for the management of their disease, and the support from their family also plays an important role in the treatment course. Because of the several possible pathophysiologies and the impact of disease on patients, a medical team, including urologist, gynecologist, psychologist, nutritionist and so on, is needed in the care of patients with IC.

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