Available online at www.sciencedirect.com

SciVerse ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 526–532

www.tjog-online.com

Review Article

Treatment of interstitial cystitis in women

Ching-Hung Hsieh [a,b,*], Wei-Chun Chang [c], Ming-Chao Huang [d], Tsung-Hsien Su [d], Yiu-Tai Li [e], Han-Sun Chiang [b]

[a] *Department of Obstetrics and Gynecology, Clinic of Fu Jen Catholic University, Taipei, Taiwan*
[b] *School of Medicine, Fu Jen Catholic University, Taipei, Taiwan*
[c] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[d] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[e] *Department of Obstetrics and Gynecology, Kuo General Hospital, Tainan, Taiwan*

Accepted 14 September 2012

Abstract

Interstitial cystitis (IC) has been described as a chronic debilitating sterile inflammatory multifactorial bladder syndrome of unknown etiology. IC is characterized by bladder pain (or suprapubic pain) associated with urgency, urinary frequency, and nocturia. Because the pathogenesis of IC remains unclear, it is still an enigma and represents a diagnostic and therapeutic challenge. The diagnosis of IC remains unclear and is based on exclusion of other diseases. Consequently, IC has usually been underdiagnosed, and the consensus on best available treatment for the disease is lacking. The current goal for the treatment of IC is usually symptomatic relief, and treatment protocols are based on empiricism. Multiple forms of therapy are available, and most patients can be managed conservatively. Nevertheless, the efficacy of most treatments is short term. This review article gives an overview of the available treatments for IC.

Keywords: bladder training; hydrodistention; interstitial cystitis; lower urinary tract symptoms; nocturia; painful bladder syndrome; urgency; urinary frequency

Introduction

Interstitial cystitis (IC) has been described as a chronic debilitating sterile inflammatory multifactorial bladder disease that results in severe impairment of quality of life (QOL). It is characterized by bladder pain, urinary frequency, urgency, and nocturia. In an epidemiologic study in Finland, the prevalence of IC was estimated to be 18.1 per 100,000 women [1]. Temml et al [2] considered women with high symptom and problem scores (≥12) on the O'Leary–Sant IC questionnaire [3] to be most likely to have IC. The Temml study revealed the overall prevalence of IC to be 306/100,000 women, with the highest value (464/100,000) in middle-aged women (40–59 years). About two-thirds of women with moderate to high risk for IC reported an impairment of QOL. In addition, the same study also showed that 35% of the IC patients reported an effect on their sexual life. However, the etiology of IC has not yet been clarified. Hence, IC has usually been underdiagnosed [4], and the consensus on best available treatment for this condition is lacking [5]. Treatment options for IC include conservative treatments, oral medications, intravesical therapy, intravesical botulinum toxin A injection, hydrodistention (HD), and surgeries. Oral or intravesical therapies are the mainstay treatment, whereas surgical managements are reserved for refractory cases. To date, clinical trials of individual therapies for IC have been limited in terms of size, quality, and duration of follow-up [6]. In addition, studies of combination or multimodal therapies are lacking. Owing to the paucity of randomized controlled trials (RCTs) on different treatments, an evidence-based management protocol has not yet been developed. This article therefore gives an overview of the treatments for IC in women.

* Corresponding author. Department of Obstetrics and Gynecology, Fu Jen Catholic University, P.O. Box 30-387, Taipei 100, Taiwan.
E-mail address: ug.doc@msa.hinet.net (C.-H. Hsieh).

1028-4559/$ - see front matter
http://dx.doi.org/10.1016/j.tjog.2012.10.002

Conservative treatment

Treatment strategies for IC should begin from more conservative therapies, and initial treatment type should depend on patient preferences, symptom severity, and the clinician's decision-making. The available conservative therapeutic options for treating IC are numerous, and include behavior therapy, dietary control, stress reduction, and physical therapy.

Behavioral therapy including bladder training, controlled fluid intake, and Kegel exercises improved symptoms in more than one-half of the IC patients [7,8].

IC patients afflicted with the chronic form of this disease will usually have a reduced-capacity bladder that is in part based on their constant urination at low volumes. The bladder holding protocol dictates keeping a voiding diary, carefully timing voiding, and gradually increasing the intervals between voiding. This behavior modification may be helpful in increasing bladder capacity.

Although controlled studies regarding the effect of dietary manipulation on IC are lacking, diet control is recommended as a first-line self-care treatment regimen for IC patients. More than 50% of IC patients can identify acidic foods that aggravate or cause a relapse in symptoms [9]. Dietary manipulation by avoiding acidic beverages, caffeine, alcohol, chocolate, tea, soda, spicy food, and artificial sweetener may be helpful [10,11]. Once offending foods are suspected, the use of an elimination diet might identify which foods or fluids contribute to flare symptoms, and the patient should then be counseled to avoid said foods [12,13]. However, not all patients need to try a restricted diet, and not every patient is sensitive to the same foods. Because many IC patients modify their diet and are also chronically ill, nutritional supplementation can be of benefit [10].

Stress is likely the most significant factor that aggravates the symptoms of IC. Patients should be encouraged to implement stress reduction techniques. The techniques might not only be very useful preventative management for patients in remission but also beneficial to patients with severe symptoms. For those with severe symptoms, stress reductions such as lifestyle changes, shortening working hours, choosing a less demanding workload, exercise, bathing, or joining support groups could be exceedingly helpful [9,14,15]. In addition, because psychological and emotional support from the family is crucial, patient education is necessary to give the patient and her family a good understanding of IC to help cope with the disease. Working against such stress reduction interventions are the stress-creating IC symptoms such as chronic bladder pain (or pelvic pain), urinary frequency, and sleep loss due to nocturia. These can cause anxiety and depression. Remission of these IC symptoms can help to reduce patient stress.

Physical therapy such as exercising regularly, learning self-relaxation of the pelvic floor muscles, using biofeedback, and using maneuvers that resolve pelvic or other connective tissue pains can help; one can also try the more mental techniques such as learning meditation [16–18]. Other adjuvant treatments reported to relieve IC symptoms include acupuncture, hypnosis, and soft tissue massage [19]. However, pelvic floor strengthening exercises, including Kegel exercises, should be avoided [20].

Oral medication

Oral pharmacologic therapies remain a mainstay for the treatment of IC. Oral medications include pentosan polysulfate sodium (PPS), amitriptyline (Elavil), hydroxyzine (Atarax), antimuscarinics, cyclosporine A (Cy A), antibacterial agents, and analgesics. To date, clinical trials of individual therapies with oral medication have been limited in terms of size, quality, and duration of follow-up, and studies of combination or multimodal therapies are lacking [6].

PPS (Elmiron) is the only oral therapy with U.S. Food and Drug Administration approval for the treatment of IC. The etiology of IC remains unclear; however, the most frequently discussed pathologic abnormality used to explain IC is a defect of the epithelial glycosaminoglycan (GAG) layer that separates and protects the transitional epithelium from urine [21]. PPS, a weak heparinoid similar to one of the components in the GAG layer, is believed to repair the damaged GAG layer and prevents leakage in the urothelium. It is the first oral medication for IC that has undergone randomized placebo-controlled trials [22–25]. Three trials showed modest symptom improvement [26–28]. However, the results of the placebo-controlled double-blind trials are contradictory [23,24,28]. This implies that some IC patients may have urothelial leakage, but not all IC is due to GAG layer deficiencies.

Chronic pelvic pain and sleep disturbances may cause stress in IC patients. Amitriptyline, a tricyclic antidepressant used to relieve the chronic pain associated with IC, may also have an effect on sleep disturbances because of its antihistamine sedation effects, and thus improve nocturia. van Ophoven et al [29] showed that amitriptyline provided symptomatic relief for 15 out of 24 patients in one RCT. However, the trial did not compare to placebo. Amitriptyline at different dosages showed a large effect size on standardized means of pain and urgency scales and on O'Leary–Sant Interstitial Cystitis Symptom Index and frequency [30]. The patients treated with this medication, starting at 10 to 25 mg daily, should be given increased dosages to increase the effect as long as the side effects, including dry mouth and drowsiness, remain tolerable. Long-term administration of amitriptyline is a feasible, safe, and effective treatment for IC provided that the drug is used judiciously to minimize adverse effects [31].

Hydroxyzine, a Hi-blocker, involves the theory of preventing mast cell degranulation with the release of neuroactive and vasoactive chemicals. However, in one RCT, hydroxyzine failed to show statistically significant benefits over placebo [32]. In addition, although the combination with PPS demonstrated a tendency toward a significant effect for the treatment of IC, there was still no statistical difference in efficacy as compared with placebo.

Antimuscarinics have been used to treat overactive bladders. There is a significant overlap between an overactive bladder and IC symptoms. Nevertheless, the efficacy of antimuscarinics for IC patients could be limited because the pathophysiology of IC and overactive bladder might be diversely different even if the symptoms overlap.

Cy A is a calcineurin inhibitor that inhibits T cell activation by blocking the transcription of cytokine genes, among other functions [33]. Cy A also stabilizes mast cells [34]. Thus, Cy A is a potent inhibitor of the immune system, and its efficacy has been reported in the treatment of IC patients [35]. In a prospective randomized study, Sairanen et al [36] showed that Cy A is more effective than PPS for the treatment of IC (with response rates of 75% and 19% for Cy A and PPS, respectively). However, there were more adverse events in the Cy A arm than in the PPS arm.

Antibacterial agents are not recommended for the treatment of IC. In a randomized placebo-controlled study, oral antibiotics were shown to have no statistically significant therapeutic effect over placebo, and adverse effects occurred more often in the antibiotics arm [37].

Pain is probably the most frequent driving symptom for an IC patient to void at lower voiding volume. Low-potency nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as first-line analgesics. Other drugs that may be useful are more potent NSAIDs, cyclooxygenase-2 selective drugs, phenazopyridine (Pyridium), oxybutynin chloride (Ditropan), or opioids. The use of opioids in urogenital pain is poorly defined. Interesting drugs that are potentially useful in controlling bladder pain include cannabinoid receptor agonists and purinergic receptor antagonist compounds. It is important to note that pain management alone is not considered to be sufficient treatment for IC and that pain management is just one part of treatment.

Intravesical therapy

Bladder instillation with different agents for the treatment of IC has been used for decades. The mechanism for this comprises the existing theories about urothelial dysfunction.

Intravesical pharmacotherapy is one of the mainstays in the treatment of IC. Intravesical therapy allows the administration of medication directly into the bladder and achieves a high drug concentration in the bladder. It also provides a potential low incidence of systemic side effects due to the relatively poor absorption from the bladder, provided that the time that the agent is kept in the bladder is short. Intravesical therapy could also eliminate the problem of low concentration of urinary excretion by oral medications and directly target the urothelium if the pathophysiology of IC is directly related to urothelial abnormalities. The drugs available for intravesical therapy are used singly or as a mixture of multiple medications (as a cocktail). The most commonly used agents include dimethyl sulfoxide (DMSO), heparin, hyaluronic acid, lidocaine, PPS, oxybutynin, chondroitin sulfate, steroid, and other agents mixed as a cocktail. Overall, the evidence base for treating IC using intravesical preparations is limited, and RCTs for the treatment of IC are still needed [38].

DMSO may be the most commonly used intravesical agent for IC, and it is the only intravesical therapy since 1978 with U.S. Food and Drug Administration approval for the treatment of IC. The mechanism of DMSO is not clear but it supposedly has an anti-inflammatory effect. The drug is also claimed to work as an analgesic, as a muscle relaxant, and to promote collagenolysis. The dose of DMSO used intravesically is 50 mL of a 50% solution instilled into and retained in the bladder for 10 to 20 minutes, given from one to two times a week to every few months. In a randomized double-blind placebo-controlled study, Perez-Marrero et al [39] showed a marked improvement of symptoms in 53% of DMSO-treated patients. In a recent study, Rossberger et al [40] reported that intravesical instillation therapy with DMSO appears to be a feasible treatment option for both subtypes of IC with the effect lasting 16–72 months and is associated with a reasonably low degree of discomfort. Additional treatments for the relapsed patients would be needed.

Heparin, an anionic polyelectrolyte, is a GAG derivative. Intravesical heparin, in a dose of 10,000–20,000 IU in 2–5 mL of solution introduced intravesically for a duration of 1 hour, thrice a week, is used because of the putative GAG layer deficiency in IC. Parsons et al [41] showed that 56% of IC patients had their symptoms relieved by heparin. However, the evidence for intravesical heparin for IC patients is still limited, and RCTs for the treatment are needed.

Hyaluronic acid, a glycoprotein, is the traditional agent used for GAG substitution.

Several studies have shown that hyaluronic acid has a place in the treatment for IC with comparable efficiency and without significant toxicity [42–44]. In a prospective study recently, Van Agt et al [45] treated the patients by administration of 40 mg (50 mL) intravesical hyaluronic acid three times weekly and obtained a positive response rate of 52% after 6 weeks of treatment.

Intravesical lidocaine (1%), usually 20–30 mL, may be used. A case report revealed that bladder pain and frequency could be controlled, but symptoms recurred within 3 months after treatment [46]. Other studies also reported that lidocaine instillation relieved pain for only a short term [47,48].

PPS has been administered intravesically and has been indicated to be effective. Pilot studies suggest a therapeutic benefit and with earlier responses than those observed with oral PPS [49]. The use of intravesical PPS simultaneously with oral PPS has been proposed to be a safe and effective therapeutic option [50]. These findings of Davis et al [50] might open a new option for patients with IC to reduce their symptom severity and to improve their QOL.

In a randomized trial of intravesical administration of oxybutynin in combination with bladder training versus placebo instillation plus bladder training, the oxybutynin group had a significant increase in bladder capacity, decrease in urinary frequency, pain relief, and did not have adverse events [51].

Chondroitin sulfate, a glycoprotein, is a major component of the GAG layer. GAG layer replenishment is a cornerstone in

the treatment of IC. A review of GAG layer intravesical replenishment therapy for IC in the small number of RCTs so far confirms that chondroitin sulfate (0.2%) is favorable for intravesical GAG layer replenishment therapy [52]. However, large-scale trials are urgently needed to further define the benefit of this type of therapy.

Corticotherapy can be given intravesically because of its anti-inflammatory effects, and bladder inflammation has been noted in some patients with IC [53]. Methylprednisolone, from 500 mg to 1 g, can be reconstituted in a small volume of liquid (10−15 mL) and mixed with DMSO.

Bladder instillation with different agents has been used for years in an attempt to treat IC. These agents are usually mixed as a cocktail because there are varying degrees of success for each drug. The selection of the regimen up to the present has mainly been based on empiricism. Patients usually undergo one treatment per week for a 6-week period once the treatment starts, and the maintenance schedule of treatment depends on the responses of patients [53].

Other agents that have been used for intravesical treatment of IC include silver nitrate, Clorpactin, cromolyn sodium, sodium bicarbonate, resiniferatoxin, and Bacillus Calmette−Guerin (BCG) vaccine. However, resiniferatoxin and BCG should not be offered to patients because the two drugs did not show efficacy in well-controlled trials [54,55]. Finally, the antiproliferative factor protein might be an important therapeutic target in the future because it might also have an important role as a urine marker for IC [56].

Intravesical botulinum toxin A injection

Botulinum toxin A, an inhibitor of acetylcholine release at the presynapse of neuromuscular junction, has well-known analgesic properties and has demonstrated some benefits in treating IC pain. The agent has been proved effective for refractory IC in an open, exploratory study [57]. There are also several studies that indicated symptom relief in the treatment of IC with intravesical botulinum toxin A injection, single or repeated, and did not have significant adverse events [58−62], However, evidence for botulinum toxin A in the treatment of IC is limited to small case series. In addition, a systematic review of reports on the agent for the treatment of IC concludes that the evidence from the studies so far suggests a trend toward short-term benefit in refractory patients, but also noted that further robust evidence should be awaited [63].

Hydrodistention

HD is recommended for the treatment of IC. The efficacy of HD of the bladder in the treatment of IC has been known since the first report appeared in 1930 [64]. Although the therapy has been the most common treatment for IC since then, there has been no randomized comparative study. The proportion of patients who, after bladder HD, show improvement and the duration of any such improvement remain uncertain. The report by Bumpus [64] in 1930 showed that HD improved the symptoms of IC and, as a result, this procedure has become a mainstay of IC patients' therapy. Most reports showed that IC symptoms in patients are improved following HD, but they suggest that the benefits are short-lived [65−68]. Furthermore, a study reported that HD provided little useful information above and beyond what was available from the patient's history and physical examination findings [69]. In addition, reports on the use of prolonged bladder HD for the treatment of patients with IC remain controversial [70,71]. Nevertheless, Hsieh et al [72] showed that HD followed by bladder training, when there was good patient compliance, was able to produce both a good efficacy and long-term benefits [72]. There is no standard method for HD, nor is there a significant difference in efficacy among current HD methods. The safest method is to fill the bladder with normal saline to maximal capacity at a pressure of 80 cm H_2O, at which point the full bladder is emptied immediately, without repetition of the procedure. Bladder rupture and sepsis may be associated with HD, especially when high-pressure, long-duration HD has been offered [66,70,71].

Surgery

The role of major surgery in patients with IC is not fully established. Surgical intervention is not a mainstay in the treatment of IC symptoms and should be considered the last resort for severe IC refractory to other therapies. Before surgery, the patient should be informed of all surgical procedures and should understand the possible outcomes and possible side effects of this type of intervention.

Less invasive surgeries to treat IC include sacral neuromodulation to control the symptoms of IC. Sacral neuromodulation should be considered before any major invasive surgical intervention is undertaken and after conservative therapies have failed. Several retrospective studies indicate that sacral neuromodulation provides an effective long-term outcome [73−76]. The use of the neodymium−yttrium aluminum garnet (YAG) laser to fulgurate Hunner's ulcers to alleviate IC symptoms has been reported; however, repeated treatment is usually required [77,78].

The major surgical interventions that have been described to treat IC include bladder augmentation, urinary diversion, and cystectomy [79−86]. Although some studies have reported that major surgery is associated with good symptom relief in strictly selected patients with disabling IC, surgical intervention for IC has been demonstrated to be of limited use and failed to achieve long-term remission of symptoms in the majority of patients.

Conclusion

IC is a complex disease with a constellation of symptoms such as urinary urgency, urinary frequency, and pelvic pain affecting urine storage in the bladder. Many physicians still do not believe that IC exists because IC remains a mysterious syndrome in female urology. In addition, limited evidence exists for the few IC treatment options available to doctors.

However, IC is indeed a chronic, debilitating disease for the patient. Patients should first be encouraged to implement stress management practice to manage and to cope with symptom exacerbations induced by stress.

Because the etiology of IC is thought to be multifactorial, multimodal therapies might be considered if the initial treatment does not result in a significant remission of symptoms. In addition, the predisposing etiologies inducing the development of IC should all be ruled out. In women, uterine prolapse may cause bladder compression, and the long-term effect of the pathophysiology of uterus−bladder compression may result in a reduced-capacity bladder. Furthermore, the bladder may enter a status of disuse and atrophy. The famous words "use or disuse" by La March, a French biologist (1744−1829), may help to explain the reduced bladder capacity of IC patients. Hence, it is important to first help reconstruct the pelvis, especially with uterine suspension when uterine prolapse has occurred, before the bladder problems in IC patients are treated.

The "gold standard" IC treatment of cystoscopy with HD is now being questioned. However, the majority of reports about HD for IC patients revealed a short-term effect. This fact reveals that HD is a good method to enlarge the bladder, but IC patients could not keep their enlarged bladder for a long time after treatment. Bladder training may be an option to help post-HD IC patients to reverse their bladder from a state of disuse/atrophy into a functional state and to create a bladder big enough to obtain a long-term effect [72]. The theory about HD plus bladder training keeping the bladder large for the long term is similar to consciously sitting up straight in order to correct one's posture. The simultaneous implementation of HD and bladder training is important in order to achieve long-term remission among IC patients. Hence, HD of the bladder and concomitant bladder training should be recommended as the first treatment choice for patients with IC, once IC is suspected, because it provides significant remission, is a conservative therapy, and avoids extirpative surgeries.

References

[1] Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chirur Gynaecol Fenn 1975;64:75−7.

[2] Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol 2007; 51:803−8.

[3] O'Leary MP, Sant GR, Fowler Jr FJ, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. Urology 1997; 49:58−63.

[4] Parsons CL. Interstitial cystitis. In: Ostergard DR, Bent AE, editors. Urogynecology and urodynamics. Theory and practice. 4th ed. Baltimore, MD: Williams & Wilkins; 1996. p. 409−25.

[5] Propert KJ, Payne C, Kusek JW, Nyberg LM. Pitfalls in the design of clinical trials for interstitial cystitis. Urology 2002;60:742−8.

[6] French LM, Bhambore N. Interstitial cystitis/painful bladder syndrome. Am Fam Physician 2011;83:1175−81.

[7] Chaiken DC, Blaivas JG, Blaivas ST. Behavioral therapy for the treatment of refractory interstitial cystitis. J Urol 1993;149:1445−8.

[8] Parsons CL, Koprowski PF. Interstitial cystitis: successful management by increasing urinary voiding intervals. Urology 1991;37:207−12.

[9] Koziol JA, Clark DC, Gittes RF, Tan EM. The natural history of interstitial cystitis: a survey of 374 patients. J Urol 1993;149:465−9.

[10] Whitmore KE. Self-care regimens for patients with interstitial cystitis. Urol Clin North Am 1994;21:121−30.

[11] Shorter B, Lesser M, Moldwin RM, Kushner L. Effect of comestibles on symptoms of interstitial cystitis. J Urol 2007;178:145−52.

[12] Webster DC, Brennan T. Self-care strategies used for acute attack of interstitial cystitis. Urol Nurs 1995;15:86−93.

[13] Erickson DR, Davies MF. Interstitial cystitis. Int Urogynecol J 1998;9: 174−83.

[14] Webster DC, Brennan T. Self-care effectiveness and health outcomes in women with interstitial cystitis: implications for mental health clinicians. Iss Ment Health Nurs 1998;19:495−519.

[15] Rothrock NE, Lutgendorf SK, Kreder KJ, Ratliff T, Zimmerman B. Stress and symptoms in patients with interstitial cystitis: a life stress mode. Urology 2001;57:422−7.

[16] Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency−frequency syndrome. J Urol 2001; 166:2226−31.

[17] Markwell SJ. Physical therapy management of pelvi/perineal and perianal pain syndromes. World J Urol 2001;19:194−9.

[18] Lukban JC, Whitmore KE. Pelvic floor muscle re-education treatment of the overactive bladder and painful bladder syndrome. Clin Obstet Gynecol 2002;45:273−85.

[19] Oyama IA, Rejba A, Lukban JC, Fletcher E, Kellogg-Spadt S, Holzberg AS, et al. Modified Thiele massage as therapeutic intervention for female patients with interstitial cystitis and high-tone pelvic floor dysfunction. Urology 2004;64:862−5.

[20] Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, FitzGerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 2011;185:2162−70.

[21] Parsons CL, Boychuk D, Jones S, Hurst R, Callahan H. Bladder surface glycosaminoglycans: an epithelial permeability barrier. J Urol 1990;143: 139−42.

[22] Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987;138:513−6.

[23] Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology 1990;35:552−8.

[24] Holm-Bentzen M, Jacobsen F, Nerstrøm B, Lose G, Kristensen JK, Pedersen RH, et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol 1987;138: 503−7.

[25] Parsons CL. Current strategies for managing interstitial cystitis. Expert Opin Pharmacother 2004;5:287−93.

[26] Parsons CL, Schmidt JD, Pollen JJ. Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. J Urol 1983;130:51−3.

[27] Fritjofsson A, Fall M, Juhlin R, Persson BE, Ruutu M. Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. J Urol 1987;138:508−12.

[28] Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol 1993; 150:845−8.

[29] van Ophoven A, Pokupic S, Heineke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004;172:533−6.

[30] Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol 2012;61:29−53.

[31] Hertle L, van Ophoven A. Long-term results of amitriptyline treatment for interstitial cystitis. Aktuelle Urol 2010;41(Suppl. 1):S61−5.

[32] Sant GR, Propert KJ, Hanno PM, Burks D, Culkin D, Diokno AC, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003;170:810−5.

[33] Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology 2000;47:119−25.
[34] Krishnaswamy G, Kelley J, Johnson D, Youngberg G, Stone W, Huang SK, et al. The human mast cell: functions in physiology and disease. Front Biosci 2001;6:1109−27.
[35] Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol 2004; 171:2138−41.
[36] Sairanen J, Tammela TL, Leppilahti M, Multanen M, Paananen I, Lehtoranta K, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 2005;174:2235−8.
[37] Warren JW, Horne LM, Jebel JR, Marvel RP, Keay SK, Chai TC. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol 2000;163:1685−8.
[38] Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/interstitial cystitis. Cochrane Database Syst Rev 2007 (4):CD006113.
[39] Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 1988;140:36−9.
[40] Rossberger J, Fall M, Peeker R. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. Scand J Nephrol 2005;39:73−7.
[41] Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994;73:504−7.
[42] Kallestrup EB, Jorgensen SS, Nordling J, Hald T. Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. Scand J Urol Nephrol 2005;39:143−7.
[43] Iavazzo C, Athanasiou S, Pitsouni E, Falagas ME. Hyaluronic acid: an effective alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis? Eur Urol 2007;51: 1534−40.
[44] Riedl CR, Engelhardt PF, Daha KL, Morakis N, Pfluger H. Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogynecol J 2008;19:717−21.
[45] Van Agt S, Gobet F, Sibert L, Leroi AM, Grise P. Treatment of interstitial cystitis by intravesical instillation of hyaluronic acid: a prospective study on 31 patients. Prog Urol 2011;21:218−25.
[46] Asklin B, Cassuto J. Intravesical lidocaine in severe interstitial cystitis: case report. Scand J Urol Nephrol 1989;23:311−2.
[47] Rosamilia A, Dwyer PL, Gibson J. Electromotive drug administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis. Int Urogynecol J 1997;8:142−5.
[48] Gurpinar T, Wong HY, Griffith DP. Electromotive administration of intravesical lidocaine in patients with interstitial cystitis. J Endourol 1996;10:443−7.
[49] Sant GR, LaRock DR. Standard intravesical therapies for interstitial cystitis. Urol Clin North Am 1994;21:73−83.
[50] Davis EL, El Khoudary SR, Talbott EO, Davis J, Regan LJ. Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. J Urol 2008;179:177−85.
[51] Barbalias GA, Liatsikos EN, Athanasopoulos A, Nikiforidis G. Interstitial cystitis: bladder training with intravesical oxybutynin. J Urol 2000; 163:1818−22.
[52] Madersbacher H, van Ophoven A, van Kerrebroeck PE. GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans — a review. Neurourol Urodyn 2012. http://dx.doi.org/10.1002/nau.22256.
[53] Swift SE, Chai TC, Bent AE. Painful conditions of the lower urinary tract including painful bladder syndrome. In: Bent AE, Cundiff GW, Swift SE, editors. OSTERGARD'S urogynecology and pelvic floor dysfunction. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. p. 106−32.
[54] Mayer R, Propert KJ, Peters KM, Payne CK, Zhang Y, Burks D, et al. Interstitial Cystitis Clinical Trials Group. A randomized controlled trial of intravesical bacillus Calmette−Guerin for 12 treatment refractory interstitial cystitis. J Urol 2005;173:1186−91.
[55] Payne CK, Mosbaugh PG, Forrest JB, Evans RJ, Whitmore KE, Antoci JP, et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol 2005;173:1590−4.
[56] Keay S, Kaczmarek P, Zhang CO, Koch K, Szekely Z, Barchi Jr JJ, et al. Normalization of proliferation and tight junction formation in bladder epithelial cells from patients with interstitial cystitis/painful bladder syndrome by D-proline and D-pipecolic acid derivatives of anti-proliferative factor. Chem Biol Drug Des 2011;77:421−30.
[57] Pinto R, Lopes T, Frias B, Silva A, Silva JA, Silva CM, et al. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. Eur Urol 2010;58:360−5.
[58] Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin A has antinociceptive effects in treating interstitial cystitis. Urology 2004;64:871−5.
[59] Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, Porena M. Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: a pilot study. Eur Urol 2006;49:704−9.
[60] Liu HT, Kuo HC. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. Urology 2007;70:463−8.
[61] Giannantoni A, Porena M, Costantini E, Zucchi A, Mearini L, Mearini E. Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year follow up. J Urol 2008;179:1031−4.
[62] de Miquel F, Chancellor MB. Pittsburgh experience with botulinum toxin A injection. Actas Urol Esp 2006;30:310−4.
[63] Tirumuru S, Al-Kurdi D, Latthe P. Intravesical botulinum toxin A injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review. Int Urogynecol J 2010;21:1285−300.
[64] Bumpus HJ. Interstitial cystitis: its treatment by over-distention of the bladder. Med Clin North Am 1930;13:1495−8.
[65] Hanno PM, Wein AJ. Conservative therapy of interstitial cystitis. Semin Urol 1991;9:143−7.
[66] Yamada T, Murayama T, Andoh M. Adjuvant hydrodistension under epidural anesthesia for interstitial cystitis. Int J Urol 2003;10:463−8.
[67] Tomoe H, Kobayashi H, Nakazawa H, Toma H. The efficacy of hydrodistention of the bladder for interstitial cystitis. J Interst Cyst 2004;2: 24−31.
[68] Parsons M, Toozs-Hobson P. The investigation and management of interstitial cystitis. J Br Menopause Soc 2005;11:132−9.
[69] Ottem DP, Teichman JMH. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005;66:494−9.
[70] McCahy PJ, Styles RA. Prolonged bladder distention: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol 1995; 28:325−7.
[71] Glemain P, Riviere C, Lenormand L, Karam G, Bouchot O, Buzelin JM. Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. Eur Urol 2002;41: 79−84.
[72] Hsieh CH, Chang ST, Hsieh CJ, Hsu CS, Kuo TC, Chang HC, et al. Treatment of interstitial cystitis with hydrodistention and bladder training. Int Urogynecol J 2008;19:1379−84.
[73] Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol 2001;165: 884−6.
[74] Peters KM. Neuromodulation for the treatment of refractory interstitial cystitis. Rev Urol 2002;4:S36−43.
[75] Gajewski JB, Al-Zahrani AA. The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int 2011;107:1258−64.
[76] Ghazwani YQ, Elkelini MS, Hassouna MM. Efficacy of sacral neuromodulation in treatment of bladder pain syndrome: long-term follow-up. Neurourol Urodyn 2011;30:1271−5.
[77] Shanberg AM, Baghdassarian R, Tansey LA. Treatment of interstitial cystitis with neodymium−YAG laser. J Urol 1985;134:885−8.
[78] Rofeim O, Hom D, Freid RM, Moldwin RM. Use of the neodymium:YAG laser for interstitial cystitis: a prospective study. J Urol 2001;166:134−6.

[79] Nielsen KK, Kromann-Andersen B, Steven K, Hald T. Failure of combined supratrigonal cystectomy and Mainz ileocecocystoplasty in intractable interstitial cystitis: is histology and mast cell count a reliable predictor for the outcome of surgery? J Urol 1990;144: 255–8.

[80] Kontturi MJ, Hellstrom PA, Tammela TL, Lukkarinen OA. Colocystoplasty for the treatment of severe interstitial cystitis. Urol Int 1991;46:50–4.

[81] Irwin PP, Galloway NT. Surgical management of interstitial cystitis. Urol Clin North Am 1994;21:145–51.

[82] Linn JF, Hohenfellner M, Roth S, Dahms SE, Stein R, Hertle L, et al. Treatment of interstitial cystitis: comparison of subtrigonal and supratigonal cystectomy combined with orthotopic bladder substitution. J Urol 1998;159:774–8.

[83] Peeker R, Aldenborg F, Fall M. The treatment of interstitial cystitis with supratrigonal cystectomy and ileocystoplasty: difference in outcome between classic and nonulcer disease. J Urol 1998;159:1479–82.

[84] van Ophoven A, Oberpenning F, Hertle L. Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. J Urol 2002;167:603–7.

[85] Rossberger J, Fall M, Jonsson O, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology 2007;70:638–42.

[86] Andersen AV, Granlund P, Schultz A, Talseth T, Hedlund H, Frich L. Long-term experience with surgical treatment of selected patients with bladder pain syndrome/interstitial cystitis. Scand J Urol Nephrol 2012; 46:284–9.