Int Urogynecol J (2000) 11:23–32

International Urogynecology Journal

Review Article

Treatment Guidelines for Classic and Non-Ulcer Interstitial Cystitis

R. Peeker and M. Fall

Department of Urology, Sahlgrenska University Hospital, Göteborg, Sweden

Abstract: Interstitial cystitis (IC) is a chronic disease of as yet unknown etiology. It commonly affects females, presenting with symptoms of pain on bladder filling, and urinary frequency. Accumulated evidence indicates that IC is a heterogeneous syndrome. Compared to classic IC, the non-ulcer type appears different concerning symptomatic, endoscopic and histological findings, as well as the response to various forms of treatment. This review gives an introduction to the syndrome of IC, concerning epidemiology, clinical characteristics, diagnostic criteria and etiological considerations. A variety of treatment modalities have been suggested and are assessed and reviewed, such as hydrodistension of the bladder, intravesical instillation therapy, oral medication, transcutaneous electrical nerve stimulation, transurethral resection of diseased bladder tissue, and supratrigonal cystectomy followed by enterocystoplasty and urinary diversion. Our algorithm on non-surgical and surgical treatment for classic and non-ulcer IC is presented.

Keywords: Classic; Interstitial cystitis; Non-ulcer; Treatment

Introduction

Interstitial cystitis as a descriptive term, was first used in 1887 by Skene [1]. However, the ulcer which is a constant finding in the classic subtype of the disease was not recognized until described by Hunner some 30 years later [2,3]. The disease was also called 'submucous ulcer', but the term interstitial cystitis was reappraised in 1930 by Bumpus, who considered this to be more appropriate because of the disease's general involvement of the bladder [4].

Correspondence and offprint requests to: R. Peeker, Department of Urology, Sahlgrenska University Hospital, Göteborg, Sweden.

Epidemiology

There is increasing evidence that interstitial cystitis is a heterogeneous syndrome and the disease is frequently subdivided into two different subtypes: the classic 'ulcerous' form, which was first described by Hunner [2], and 'early' [5] or 'non-ulcer' interstitial cystitis [6,7].

The prevalence of interstitial cystitis has been estimated to be approximately 8–16 cases per 100 000 population [8,9]. However, it has been proposed that this is a gross underestimation [10] and that it might exceed 0.5% among adults in the United States [11].

There is a clear female predominance of about 10:1 [9,12–14] and it seems as if the disease is more common in caucasians than in other races [14]. Furthermore, interstitial cystitis is considered to be very rare in the developed countries.

The percentages of classic and non-ulcer disease in the total number of patients with interstitial cystitis is under debate. Messing and Stamey reported classic interstitial cystitis to account for about half of all patients with interstitial cystitis [5]. Later, the Hunner type has been considered a rare finding, accounting for 5%–10% of cases of interstitial cystitis [15]. However, Koziol et al. recently presented a very large series in which classic interstitial cystitis accounted for approximately 20% [7].

Interstitial cystitis causes significant economic costs. Not taking into account indirect costs (e.g. loss of income, etc.), the incremental medical cost in the United States attributable to interstitial cystitis has been estimated at more than $100 million per year [10].

Diagnostic Criteria and Clinical Characteristics

Over the years different diagnostic criteria have been used in interstitial cystitis, mainly because of difficulties in defining the disease. However, some 10 years ago the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIDDK) managed to establish consensus criteria, principally in order to ensure that groups of patients studied would be relatively comparable [16]. However, the issue of subtyping has not yet been addressed in clinical guidelines.

In the following presentation, the subdivision of patients into two different groups of interstitial cystitis is based on clinical (according to the discussion above), endoscopic and histopathologic criteria [6].

Endoscopy

Classic Interstitial Cystitis. Single or multiple reddened mucosal areas are seen, with small vessels radiating towards a central scar, fibrin deposit or coagulum; this site ruptures with increasing bladder distension, with petechial oozing of blood from the ulcer and the mucosal margins. A rather typical, slightly bullous edema develops post distension.

Non-Ulcer Interstitial Cystitis. There is a normal bladder mucosa on initial cystoscopy and the development of small, multiple glomerulations and multiple superficial petechial bleedings during or after hydrodistension. In some patients multiple, confluent, superficial mucosal cracks develop during distension. The degree and location of the glomerulations are recorded during and after bladder distension. The abundance of glomerulations has been found to be associated with a bloody effluent and bladder capacity under anesthesia [17].

Histopathology

Classic Interstitial Cystitis. Histological specimens obtained from such lesions display urothelial spongiosis and detachment, subepithelial, perineural and perivascular deposits of mononuclear cells, and a characteristic mast cell response, with increase of such cells in the detrusor muscle and in the lamina propria [6,18].

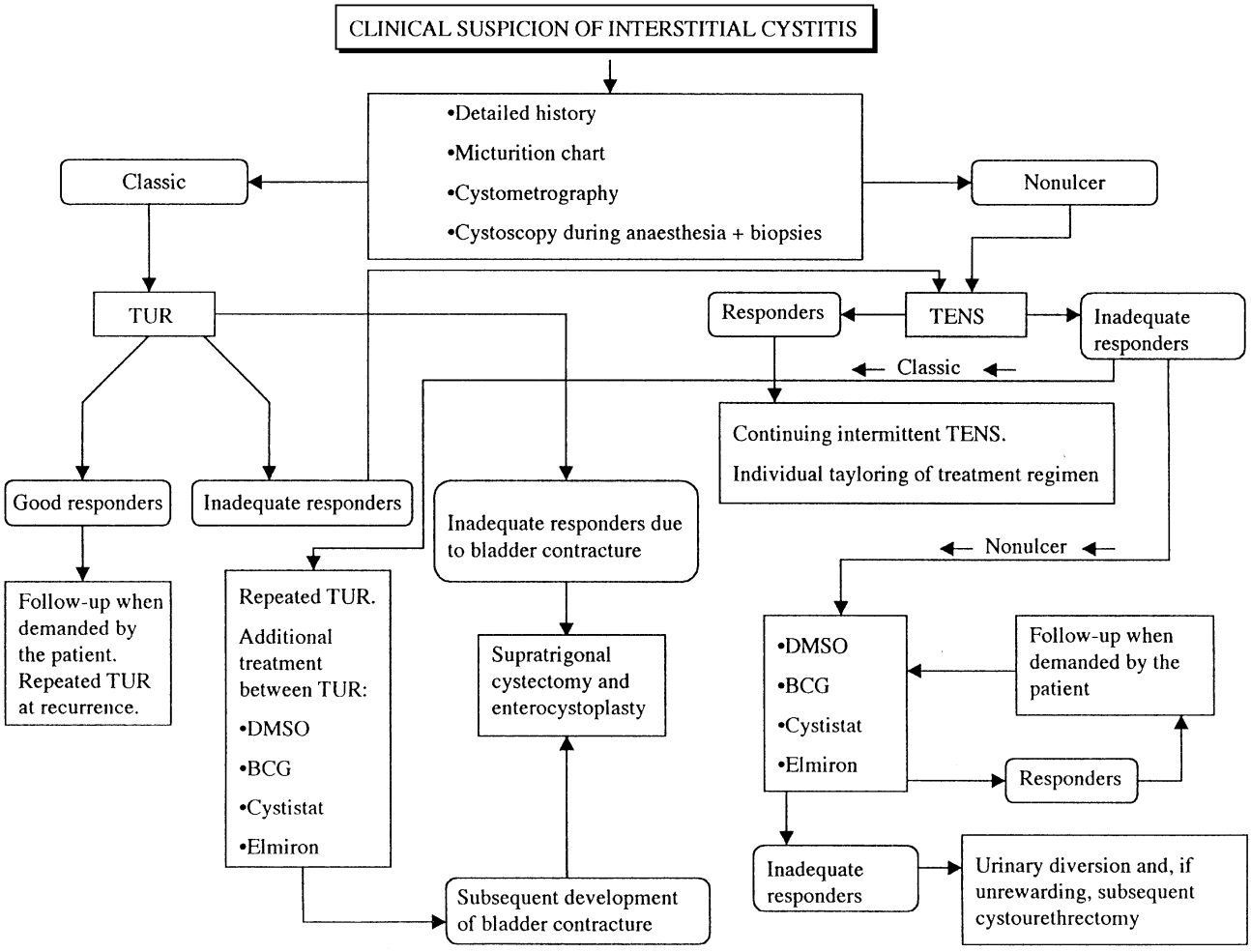

Fig. 1. Algorithm for diagnosis and treatment of classic and non-ulcer interstitial cystitis.

Non-Ulcer Interstitial Cystitis. Inflammatory signs like those found in classic IC, including the mast cell reaction, are lacking. In particular there is only slight or no mast cell involvement. Small suburothelial bleedings and tiny cracks in the mucosa may be seen in accordance with the cystoscopic findings [6,18].

Interstitial cystitis may show remissions and exacerbations or have a constant course. Some patients with classic interstitial cystitis eventually develop a small-capacity fibrotic bladder. As the disease progresses, the symptoms may become severe enough to force the patient into social incapacitation [19]. Urinary frequency of up to 100 times a day may severely disturb the patient's personal and professional life. Travelling may prove difficult or even impossible. Some patients must work reduced schedules, and others are forced to go on a disability pension. Many abstain from sex rather than risk exacerbation of their symptoms. Many give up sport and leisure activities, and others are unable to fulfil essential family obligations [20].

General Aspects of Interstitial Cystitis

Etiological Considerations

In spite of the fact that IC was described more than 100 years ago, it remains a disease of unknown and probably complex etiology. A comprehensive presentation of all current hypotheses as its etiology lies beyond the scope of this paper. However, we have chosen to briefly discuss a few contemporary theories, as there is still no common denominator for all hypotheses proposed and as the perception of the origin of the symptoms obviously influences the choice of therapy.

Inflammation and Mast Cells

Inflammation seems to be an essential part of the picture in classic interstitial cystitis. Histological examination of bladder lesions has revealed mucosal ulceration, pancystitis and perineural inflammatory infiltrates [21].

Mast cells and basophilic granulocytes are bone marrow-derived cells which contain high-affinity surface receptors for IgE, which is the immunoglobulin of allergy. In contrast to the basophilic granulocytes, which complete their maturation in the bone marrow prior to circulating in the blood, mast cells circulate as primitive lymphocyte-like cells in the blood and then migrate into the tissues, where they complete their maturation and acquire phenotypic properties strictly regulated by the local microenvironment [22–24]. Mast cells and basophilic granulocytes also contain granular glycosaminoglycan. The glycosaminoglycan (heparin in mast cells) characteristically stains metachromatically with certain thiazine dyes, such as toluidine blue. Highly potent inflammatory mediators, such as histamine, leukotrienes, cytokines and the angiogenic and fibroblast stimulatory bFGF (basic fibroblast stimulatory factor), are also found in these cells [25,26], along with distinct proteinases [27,28]. These cells are thus the repository of many potent inflammatory factors, all of which are of importance not only in allergic inflammation but also in chronic inflammatory diseases such as rheumatoid arthritis [29], and probably also interstitial cystitis [30–36]. Many of the symptoms and findings in classic interstitial cystitis, such as pain, frequency, edema, fibrosis and the production of new vessels in the lamina propria, could possibly be explained by the release of mast cell-derived factors. Hence, the mast cell–IgE system and its interaction with other inflammatory cells seems to be of importance when it comes to the etiology and pathogenesis of interstitial cystitis.

Neurobiology

The S-100 family of proteins are acidic calcium- and zinc-binding low molecular weight proteins located mainly in astrocytes and a population of oligodendrocytes of the CNS. They also appear in Schwann cells of the peripheral nervous system [37,38]. In a recent study, we found significantly decreased levels of S-100 protein in the non-ulcer group compared to controls [39], which is consistent with an altered pattern of innervation of the bladder. S-100 in the bladder wall most likely has its origin in periaxonal glial cells. Thus, a decrease of S-100 in the bladder wall of patients with non-ulcer IC would indicate a decreased amount of this type of cell, and probably also of axons. Several authors have described autonomic nerve changes [40–43], but the findings of patterns are far from uniform.

The lower levels of S-100 in non-ulcer patients suggest a decreased nerve content in patients with non-ulcer IC. These findings are in contrast to those of Hohenfellner et al. [41], who used polyclonal antihuman protein gene product 9,5 antibody and found the overall nerve content increased in IC patients compared to controls. However, their study did not include subtyping of the disease into the classic and non-ulcer types.

Tyrosine hydroxylase is the rate-limiting enzyme for all catecholamine synthesis, dopamine as well as norepinephrine and epinephrine [44,45]. In a recently conducted study we noted a prominent increase of tyrosine hydrolase immunoreactivity in bladder tissue in IC patients compared to controls [46]. This can presumably be interpreted as a sign of generally increased sympathetic outflow, which in turn lends further support to the notion of a neurogenic etiology, even though the pathophysiological mechanisms remain speculative at this stage. Further neurobiological studies will hopefully further define and characterize alterations in neural activity in IC. By means of such knowledge the etiology of subgroups of IC may be explored, in turn providing the means for the search for more specific therapy.

GAG Layer

Parsons and coworkers have proposed an important function for cell surface glycosaminoglycans (GAG), and that a defect in this epithelial permeability barrier may contribute to the pathogenesis of interstitial cystitis by exposing the submucosal tissue, including intramural nerve fibers, to noxious substances in urine [47]. This led to the hypothesis that exogenous polysaccharides may be of value in treating this disease, and sodium pentosanpolysulfate has been found to alleviate symptoms in interstitial cystitis [48,49]. The GAG theory stipulates that the bladder surface proteoglycans play a physiological role in maintaining the impermeability of the bladder epithelium, and that a functional deficiency of such proteoglycans is related to the etiology of as many as 60%–70% of interstitial cystitis cases [50].

Autoimmunity

There are numerous reports on autoantibodies in patients with IC [51–55]. However, the precise identity of these autoantibodies is not yet determined. Neither viruses nor bacteria have been proved to be the causative agent in IC. Some of the common clinical and histopathological characteristics present in IC patients show certain similarities with other known autoimmune phenomena, and this is the background to the theory that IC may arise from autoimmune disturbances.

Moreover, independent studies on autoantibodies in IC have shown that they mainly consist of antinuclear antibodies [53,56] and these findings are in turn similar to the autoantibody profiles in some systemic diseases well known to be of autoimmune origin [57,58].

The role of autoimmunity in IC is controversial and the disease is not thought to arise from a direct autoimmune attack on the bladder. Rather, some of the autoimmune symptoms and pathologic findings arise indirectly as a result of tissue destruction and inflammation from other, as yet unknown, causes. This is considered to explain the fact that not all IC patients have autoantibodies. It has also been proposed that the titers or presence of autoantibodies in IC patients could be a reflection of disease severity [59]. Interestingly, the pattern of immune cell involvement differs between the classic and non-ulcer subtypes [60].

Heterogeneity in Interstitial Cystitis

The classic and non-ulcer types of interstitial cystitis share the same symptom pattern and the same chronic course. As previously mentioned, however, the two subtypes differ in a number of important respects: the histopathologic features, the age distribution (patients with the non-ulcer subtype being younger than those with classic disease), the complication pattern and the response to treatment [6,61]. Furthermore, there is a significant difference in the nerve axon marker S-100 between the two subtypes [39]. Koziol et al. recently supported the contention of heterogeneity of interstitial cystitis by observations based on epidemiological data relating to demographics, risk factors, symptoms, pain and psychosocial factors [7].

Treatment Options

Oral Medication

The factors causing interstitial cystitis have yet to be identified. Therefore, the therapy for this disease is either empiric or symptomatic. Oral medication is frequently used as first-line treatment because of its simplicity and low complication rate.

As previously mentioned, mast cells are considered to play a pivotal role in interstitial cystitis. Among the substances released by mast cells is histamine, a well recognized inflammatory mediator. Thus, histamine receptor antagonists have been used to block the H_1-receptor subtype [62] as well as the H_2-receptor subtype [63], with mixed results. Hydroxyzine, a histamine receptor antagonist with effect on the peripheral as well as the central nervous system, has been claimed to have a very good clinical effect in IC [62].

Amitriptyline is a tricyclic antidepressant which is also known to block the previously discussed histamine H_1 receptor. The drug is thought to act via various mechanisms, such as blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and norepinephrine, and also sedation, possibly via its H_1 antagonism [64]. Several authors have reported amelioration after oral treatment with amitriptyline [65–67].

Corticosteroids are frequently used in a variety of inflammatory disorders and have also been tried as treatment for interstitial cystitis. Reports on outcome have been both promising [68] and discouraging [69]. Nowadays, urologists are reluctant to use chronic medication with corticosteroids for interstitial cystitis as the effect is unpredictable and the side effects, such as fluid retention and osteoporosis, are considerable.

As the GAG-layer model emerged, controlled studies with sodium pentosanpolysulfate (PPS, Elmiron, Pharmacia, Piscataway, NJ) were undertaken. In a double-blind placebo-controlled trial subjective improvements in pain, urgency, frequency and nocturia were seen in the patients taking the drug rather than placebo [70]. Furthermore, this study also demonstrated an objective improvement in average voided volume in the patients who took the active drug. The frequency remained unaffected by the medication, however. In an open multicenter study Fritjofsson et al. found that the classic subtype responded more favorably to Elmiron than did non-ulcer IC [48]. An even larger double-blind placebo-controlled study reported an improvement greater than 25% in 28% of the patients taking Elmiron and 13% of placebo patients. In these studies the patients received 150 mg orally b.i.d. for 6–24 months. A good response is expected 4–12 months after initiation of therapy, and

may occur in up to 50% of patients [71]. The higher the dose and the longer the treatment, the better the response (Parsons L., personal communication).

Denervation Procedures

Both subtypes of interstitial cystitis are associated with an abnormal sensory function. Therefore, various surgical and non-surgical approaches have been suggested to interrupt neural transmission. First, local treatment of ulcers and/or bladder epithelium, examples of which are presented below, might very well be looked upon as primarily interfering with the peripheral innervation. For example, removal of nerve endings engaged in the inflamed bladder tissue has been proposed as an explanation for symptomatic control in patients with interstitial cystitis subjected to TUR [72].

Hydrodistension has also been advocated to relieve symptoms in interstitial cystitis [73], and its mechanism of action is suggested to be destruction of the submucosal nerve plexus and tension receptors in the bladder wall [74]. It has been reported to reduce pain and frequency, although symptomatic relief is sometimes not achieved or only in the short term [73]. In fact, some authors have found that IC responds less favorably to bladder distension than do other irritative bladder disorders [75].

The effect of short-term urinary bladder distension on cholinergic innervation has been studied in rats, where distension was induced for 3 hours by forced diuresis and balloon outlet obstruction [76]. Cholinergic hypoinnervation was observed 7 days after the distension, persisting up to 21 days. The findings indicate transient damage to the cholinergic innervation, and the short-lasting effect of bladder dilatation therapy used to treat interstitial cystitis may be due to the fairly rapid regeneration of innervation.

Open surgical denervation includes cystolysis [77,78] and sacral rhizotomy [79–82], methods rarely used nowadays. The long-term results of cystolysis appear discouraging [83], and the method is therefore now used only occasionally.

Intravesical Instillation Therapy

This approach is based on a variety of theoretical mechanisms. Intravesically administered agents are frequently classified as either cytoprotective or cytodestructive. Among the former can be mentioned heparin and sodium pentosanpolysulfate, and among the latter DMSO, silver nitrate and BCG.

DMSO (dimethylsulphone) remains the cornerstone of intravesical therapy for IC. This substance has numerous effects, but its mechanism of action in IC is not fully elucidated. DMSO is a scavenger of the intracellular OH radical believed to be an important trigger of the inflammatory process [84]. The compound also has local anesthetic properties.

Lidocaine, a local anesthetic, has been reported to give long-lasting symptom relief in a pilot study [85] and is another option for intravesical treatment. Although the initial response to instillation may be excellent, this modality is hampered by the need to make instillations very frequently, sometimes three or four times a day. Catheterization may be painful in this group of patients and hence difficult to perform repeatedly.

Self-instillation with heparin is a further option. Parsons used a dose of 20000 IE in 10 ml water [71]. Some authors advocate multidrug intravesical treatment, including heparin and methylprednisolone, in patients who do not respond adequately to standard therapy [86].

Chondroitin sulphate (Cystistat), to substitute for the GAG-layer defect, has recently been introduced as a treatment for IC [87]. It is administered as instillations of 50 ml into the bladder twice weekly, decreasing to weekly. This treatment has so far only been tested on a pilot basis.

Bacillus Calmette–Guérin (BCG) instillation therapy has recently been introduced as a symptomatic treatment for IC [88,89]. It is thought to modulate urothelial immune responses, in analogy with what is seen when treating superficial bladder tumors, and its beneficial effect is claimed to be superior to, for example, DMSO. So far, observations are preliminary. It has to be remembered that BCG has more potential risks than does DMSO.

Electrical Stimulation

Transcutaneous electrical nerve stimulation (TENS) is being used extensively in many pain conditions. In interstitial cystitis suprapubic TENS is proposed to relieve pain by stimulation of myelinated afferents in order to activate segmental inhibitory circuits, according to the theory of Melzack and Wall [90] of blockade of afferent impulses by a gate control mechanism [91]. By stimulating more easily excitable afferents from the painful area, the artificial stimulus competes with and blocks the pain impulses. The stimulus may simultaneously elicit autonomic nerve effects, such as inhibition of detrusor activity [61]. Another mechanism is the release of opiates, especially endorphins.

In a follow-up study, 33 patients with classic IC and 27 with non-ulcer disease were treated by means of suprapubic, high- or low-frequency TENS for 1–2 hours twice daily at maximum non-painful intensity [92]. Treatment periods ranged from 1 month to 16 years. The effect of treatment on pain was more marked than on frequency of urination. In classic IC 9 patients had a remission of symptoms after treatment of more than 1 year's duration. Remarkably, local lesions that had been present for 13 and 23 years in 4 women who were re-examined under anesthesia had disappeared in 2 and were hardly visible at careful examination and were not bleeding in the other 2, who had had the same duration of symptoms when starting TENS. A further 9 patients experienced good pain relief during continuing treat-

ment, but could not stop TENS. Thus, 54% of patients with classic IC had a good or excellent effect of treatment. The outcome of therapy differed markedly between the two categories of IC. Of 27 patients with non-ulcer disease, only 4 reported remission and 3 had good pain palliation during continuing TENS, that is, 26% had an excellent or good effect. The differing response to TENS in patients with classic and non-ulcer IC further supports the idea of fundamental differences between the two subtypes.

Application of electrodes at the acupuncture site at the medial malleolus was found successful in a pilot group of IC patients [93]. In a recent study devoted to non-ulcer IC, little effect was registered with genuine Chinese acupuncture or electroacupuncture [94].

Intravaginal electrodes are too uncomfortable to wear for most women with IC, although there is an effect with this modality also [61]. There have been some trials with other electrostimulation techniques. In a pilot series, Eriksen [95] used the conventional outpatient clinic device for so-called maximal electrical stimulation designed for the treatment of motor urge incontinence. In a series of 15 women with the non-ulcer type of IC he found an effect on pain and urinary urgency in 8, with an effect lasting up to 4 years. To our knowledge, there have so far been no further trials with this modality.

Direct sacral nerve stimulation has recently been tested in the treatment of interstitial cystitis [96]. In this method, which is preceded by trial stimulation via a temporary percutaneous electrode, a permanent electrode is implanted, most frequently at the S3 nerve, and connected to a subcutaneous pacemaker. As yet, only a limited number of patients with interstitial cystitis have been subjected to this form of electrical stimulation therapy.

Conservative Surgical Treatment

Transurethral resection (TUR), as well as laser fulguration of ulcers, has been reported to result in a favorable symptomatic outcome in patients with classic interstitial cystitis [12,72,97].

We have recently updated our own clinical experience from 259 transurethral resections on 103 patients with classic IC [98]. After TUR, 92 individuals experienced considerable amelioration. Seven were not relieved of pain. As for frequency, 11 patients, including the latter 7, had no symptom relief.

A possible mode of action of TUR might be the removal of intramural nerve endings engaged by the inflammatory process, as has been suggested previously to explain symptom relief in patients with IC [72]. In a recent article we reported that TUR was successful in the treatment of nephrogenic adenoma, a metaplastic lesion of the urinary tract mucosa [99]. We have previously suggested that the symptoms of classic interstitial cystitis can be explained by the release of mast cell-derived factors and, interestingly, nephrogenic adenoma displays high numbers of mast cells in the epithelium, whereas other types of urothelial metaplastic transformations (cystitis cystica, cystitis glandularis, colonic metaplasia) do not [100]. In fact, the presentation of intraepithelial mast cells is a rare finding in humans, occurring in only a few conditions, such as seasonal rhinitis [101], but also in classic IC [35].

There is some evidence that mast cells are innervated [102]. Speculatively, the explanation for a good symptomatic response to TUR, in interstitial cystitis as well as nephrogenic adenoma, could be sought in the occurrence of mast cells and their interaction with the peripheral nervous system. A more thorough evaluation of mast cell distribution, phenotype expression and recruiting factors is under way, as these cells seem to play a pivotal role in the fundamental disease process in classic IC.

Focal aggregates of lymphocytes and plasma cells are also a characteristic feature of classic IC [21], and resection of areas with an intense inflammatory reaction would in fact decrease the local production of a large number of inflammatory mediators of importance for the distressing symptoms. Fibrous and granulation tissue, including epithelial defects, is also removed. Thus, several explanations can be given for the beneficial effect of TUR on bladder lesions.

Major Open Reconstructive Surgery

Apparently there is no gold standard method for the treatment of interstitial cystitis, and the regimen for these patients usually has a trial-and-error character. In some patients, or at some stages of the disease, IC does not respond to conservative treatment at all. Reconstructive surgery has been reported to be successful in such cases. Among the methods advocated is supratrigonal cystectomy, followed by ileocystoplasty [103,104] or colocystoplasty [78,105].

In a recent paper we showed that supratrigonal cystectomy and ileocystoplasty led to a good outcome in all patients with classic IC, whereas it consistently failed to help patients with non-ulcer disease [106]. The importance of resection of all supratrigonal bladder tissue has been emphasized [103,105], and we fully agree. In fact, we resect part of the trigone too, leaving a trefoil including the two ureteral orifices and the urethra. If lesions close to the trigone are not resected it is a possible reason for continuing pain and frequency [107]. Furthermore, we advocate conservative treatment until bladder contracture develops. At that end-point there are very few inflammatory changes, as the process seems to burn out and the risk of continuing pain seems less.

It has been claimed that poor results occur more often in patients with large preoperative bladder capacities [108–110], and this is consistent with the findings in our study [106]. Large bladder capacities during anesthesia are more often found in the non-ulcer type of IC [5,6].

Urinary Diversion

In the past the therapeutic options were far more limited and the urinary diversion seemed at first to be the method of choice, not only after pelvic evisceration [111], but also to overcome severe symptoms associated with interstitial cystitis [5]. A more modern way of performing urinary diversion is the construction of a continent reservoir [112], a procedure which, with or without associated removal of the entire bladder, also has been used for interstitial cystitis in recent years [108].

Diversionary procedures subsequently turned out to be associated with significant long-term morbidity. Stomal problems, an increased incidence of stone formation and a high risk of progressive loss of renal function became apparent [113]. Still, there is apparently a place of urinary diversion in some patients with interstitial cystitis refractory to all other kinds of treatment.

In our expeirence, patients with classic disease that has resulted in bladder contracture respond very well to urinary diversion. Of course, in this patient group supratrigonal cystectomy and enterocystoplasty is preferable, and hence we only perform a conduit diversion in elderly patients or patients at high operative risk.

In non-ulcer disease, however, supratrigonal cystectomy and enterocystoplasty does not appear to be the treatment of choice [106]. Moreover, these patients are often younger than the patients with classic disease. Therefore, patients with non-ulcer IC refractory to all other kinds of treatment receive a continent reservoir. We recommend that the procedure be performed without simultaneous cystectomy, which may be performed extraperitoneally at a later stage should the patient's symptoms remain unaffected by the diversion. Unfortunately, this is sometimes the case. In the great majority of cases we have been able to overcome persisting distress by supplementing the diversion procedure with cystourethrectomy. However, in line with previous reports [114], we have seen occasional cases in which even this ablative surgery has been in vain.

Practical Guidelines

Electrical Stimulation

Suprapubic transcutaneous electrical nerve stimulation is administered by means of carbon rubber electrodes positioned 10 cm apart immediately above the pubic bone. The electrodes are applied with a broad tape to enable the patient to be ambulant during treatment for 1–2 hours twice daily. Treatment is initiated using an intensity as high as possible, starting with high-frequency stimulation (50–100 Hz). If the effect is inadequate or lacking, low-frequency stimulation is tested as well (2–10 Hz). The trial should go on for at least 2 months before evaluation.

Oral Treatment

Sodium pentosan polysulfate (Elmiron) 150–200 mg twice daily between meals. Absorption is incomplete.

Hydroxyzene (Atarax) 25–50 mg daily for 14 days. This is especially valuable in patients with increasing mast cell counts.

Tricyclic antidepressants (amitriptyline) 25 mg before bedtime, when needed, with a gradual increase to 75 mg over a 3-week period.

Intravesical Treatment

According to our routine DMSO is administered twice weekly as 50 ml sterile filtered 50% solution. It is sometimes combined with heparin and bicarbonate for local application (RIMSO-50).

BCG (OncoTICE) intravesically 12.5 mg (50 ml) weekly for 4–6 weeks.

Glycosaminoglycane hyaluronic acid (Cystistat) 40 mg weekly for 4 weeks, followed at remission by monthly administration.

Transurethral Resection

Bladder capacity under general anesthesia is measured after distension to full capacity at a pressure of 70–80 cmH_2O. TUR is performed with a low-pressure continuous irrigating cystoscope, thereby avoiding prolonged bladder distension and allowing continuous resection of lesions, which are sometimes extensive. All lesions should be carefully outlined for complete resection, and all involved areas should be removed with the diathermy equipment preset for pure cutting at as low an intensity as possible. The resection should include half or more of the muscular coat underlying the lesions. Direct pinpoint coagulation of bleeding vessels is recommended to ensure adequate hemostasis, avoiding broad fulguration. Postoperatively an indwelling catheter should be left in place until the urine becomes clear.

Supratrigonal Cystectomy and Ileocystoplasty

Access to the abdominal cavity is obtained via a lower midline laparotomy incision. After cystotomy the ureters are intubated with two baby feeding catheters anchored to the ureteral ridge with 4/0 catgut sutures. Subtotal resection of the bladder is performed, leaving only the internal urethral meatus and both ureteral orifices. A 40 cm segment of the ileum is isolated, taking care to preserve the vascular supply, and with the distal transection margin located 30–40 cm proximal to the ileocecal valve. The segment is detubularized antimesenterically, double-folded to a spherical shape and anastomosed to the trigone remnant using an uninterrupted resorbable 3/0 suture. Postoperatively, an external drain tube should be left in place for 1–3 days,

depending on the amount of discharge. The baby feeding tube ureterostomies are extracted after 1 week. An indwelling evacuation catheter should be left open, inside the cystoplasty, for 10 days, after which clamping of the catheter may begin, with the intervals between the emptying initially being 1 hour and increasing gradually. The catheter is removed after approximately 2 weeks.

Acknowledgments. This study was supported by The Swedish Medical Research Council, project numbers 09902 and 02235, the Regional Health Authority of West Sweden, Märtha and Gustaf Ågrens Research Foundation, the Swedish Society for Medical Research, the Göteborg Medical Society and the Medical Faculty, Göteborg University.

References

1. Skene AJC. Diseases of bladder and urethra in women. New York: Wm Wood, 1887:167
2. Hunner GL. A rare type of bladder ulcer in women; report of cases. *Boston Med Surg J* 1915;172:660–664
3. Hunner GL. Elusive ulcer of the bladder: further notes on a rare type of bladder ulcer with report of 25 cases. *Am J Obstet* 1918;78:374–395
4. Bumpus HC. Interstitial cystitis: its treatment by over-distension of the bladder. *Med Clin N Am* 1930;13:1495–1498
5. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology and treatment. *Urology* 1978;12:381–392
6. Fall M, Johansson SL, Aldenborg F. Chronic interstitial cystitis: a heterogeneous syndrome. *J Urol* 1987;137:35–38
7. Koziol JA, Adams HP, Frutos A. Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. *J Urol* 1996;155:87–90
8. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences [see comments]. *J Urol* 1995;154:2035–2037
9. Oravisto KJ. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Finn* 1975;64:75–77
10. Held PJ, Hanno PM, Wein AJ, Pauly MV, Cann MA. Epidemiology of interstitial cystitis 2. In: M. HP, R. SD, Krane RJ, Wein AJ, eds. Interstitial cystitis. New York: Springer-Verlag, 1990:29–48.
11. Jones CA, Harris M, Nyberg L. Prevalence of interstitial cystitis in the United States. *J Urol* 1994;151:423A
12. Greenberg E, Barnes R, Stewart S, Furnish T. Transurethral resection of Hunner's ulcers. *J Urol* 1974;111:764–766
13. Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). *J Urol* 1949;61:291–310
14. Koziol JA. Epidemiology of interstitial cystitis. *Urol Clin N Am* 1994;21:7–20
15. Parsons CL. Interstitial cystitis: clinical manifestations and diagnostic criteria in over 200 cases. *Neurourol Urodyn* 1990;9:241–250
16. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28–29, 1987, *J Urol* 1988;140:203–206
17. Nigro DA, Wein AJ, Foy M et al. Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. *Urology* 1997;49:86–92
18. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol* 1990;143:1118–1124
19. Koziol JA, Clark DC, Gittes RF, Tan EM. The natural history of interstitial cystitis: a survey of 374 patients. *J Urol* 1993;149:465–469
20. Ratner V, Slade D. Interstitial cystitis: a women's health perspective. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997;257–260
21. Fall M, Johansson SL, Vahlne A. A clinicopathological and virological study of interstitial cystitis. *J Urol* 1985;133:771–773
22. Galli SJ. New insights into 'the riddle of the mast cells': microenvironmental regulation of mast cell development and phenotypic heterogeneity. *Lab Invest* 1990;62:5–33
23. Kitamura Y, Go S, Hatanaka K. Decrease of mast cells in W/Wv mice and their increase by bone marrow transplantation. *Blood* 1978;52:447–452
24. Kitamura Y, Hatanaka K, Murakami M, Shibata H. Presence of mast cell precursors in peripheral blood of mice demonstrated by parabiosis. *Blood* 1979;53:1085–1088
25. Qu Z, Liebler JM, Powers MR et al. Mast cells are a major source of basic fibroblast growth factor in chronic inflammation and cutaneous hemangioma. *Am J Pathol* 1995;147:564–573
26. Stevens LR, Austen KF. Recent advances in the cellular and molecular biology of mast cells. *Immunol Today* 1989;10:381–386
27. Irani A-MA, Schechter NM, Craig SS, DeBlois G, Schwartz LB. Two types of human mast cells that have distinct neutral protease composition. *Proc Natl Acad Sci USA* 1986;83:4464–4468
28. Irani A-MA, Bradford TR, Kepley CL, Schechter NM, Schwartz LB. Detection of MCT and MCTC types of human mast cells by immunohistochemistry using new monoclonal anti-tryptase and anti-chymase antibodies. *J Histochem Cytochem* 1989;37:1509–1515
29. Tetlow LC, Woolley DE. Distribution, activation and tryptase/chymase phenotype of mast cells in the rheumatoid lesion. *Ann Rheum Dis* 1995;54:549–555
30. Aldenborg F, Fall M, Enerback L. Mast cells in interstitial cystitis. *Ann Urol Paris* 1989;23:165–166
31. Boucher W, el-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. *Br J Urol* 1995;76:94–100
32. Enerbäck L, Fall M, Aldenborg F. Histamine and mucosal mast cells in interstitial cystitis. *Agents Actions* 1989;27:113–116
33. Frenz AM, Christmas TJ, Pearce FL. Does the mast cell have an intrinsic role in the pathogenesis of interstitial cystitis? *Agents Actions* 1994;41:C14–15
34. Sant GR, Theoharides TC. The role of the mast cell in interstitial cystitis. *Urol Clin N Am* 1994;21:41–53
35. Aldenborg F, Fall M, Enerbäck L. Proliferation and transepithelial migration of mucosal mast cells in interstitial cystitis. *Immunology* 1986;58:411–416
36. Theoharides TC, Sant GR. Bladder mast cell activation in interstitial cystitis. *Semin Urol* 1991;9:74–87
37. Stefansson K, Wollmann RL, Moore BW. Distribution of S-100 protein outside the central nervous system. *Brain Res* 1982;234:309–317
38. Sugimura K, Haimoto H, Nagura H, Kato K, Takahashi A. Immunohistochemical differential distribution of S-100 alpha and S-100 beta in the peripheral nervous system of the rat. *Muscle Nerve* 1989;12:929–935
39. Peeker R, Aldenborg F, Haglid K, Johansson SL, Rosengren L, Fall M. Decreased levels of S-100 protein in nonulcer interstitial cystitis. *Scand J Urol Nephrol* 1998;32:395–398
40. Christmas TJ, Rode J, Chapple CR, Milroy EJ, Turner-Warwick RT. Nerve fibre proliferation in interstitial cystitis. *Virchows Arch A Pathol Anat Histopathol* 1990;416:447–451
41. Hohenfellner M, Nunes L, Schmidt RA, Lampel A, Thuroff JW, Tanagho EA. Interstitial cystitis: increased sympathetic innervation and related neuropeptide synthesis. *J Urol* 1992;147:587–591
42. Palea S, Artibani W, Ostardo E, Trist DG, Pietra C. Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis. *J Urol* 1993;150:2007–2012
43. Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibres in interstitial cystitis. *Br J Urol* 1995;75:744–750
44. Goldstein M. Enzymes involved in the catalysis of catecholamine biosynthesis. In: Ubell RN, ed. Methods in neurochemistry. New York: Plenum Press, 1972:317–340

45. Goldstein M, Fuxe K, Hökfelt T. Characterization and tissue localization of catecholamine synthesizing enzymes. *Pharmacol Rev* 1972;24:298–309
46. Peeker R, Aldenborg F, Johansson SL, Li J-Y, Dahlström A, Fall M. Increased tyrosine hydroxylase immunoreactivity in bladder tissue from patients with classic and nonulcer interstitial cystitis. *J Urol*. In press
47. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol* 1991;145:732–735
48. 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;138:508–512
49. 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;150:845–848
50. Parsons CL, Stein PC, Bidair M, Lebow D. Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. *Neurourol Urodyn* 1994;13:515–520
51. Oravisto KJ. Interstitial cystitis as an autoimmune disease. A review. *Eur Urol* 1980;6:10–13
52. Silk MR. Bladder antibodies in interstitial cystitis. *J Urol* 1970;103:307–309
53. Jokinen EJ, Alfthan OS, Oravisto KJ. Antitissue antibodies in interstitial cystitis. *Clin Exp Immunol* 1972;11:333–339
54. Anderson JB, Parivar F, Lee G et al. The enigma of interstitial cystitis – an autoimmune disease? *Br J Urol* 1989;63:58–63
55. Mattila J, Linder E. Immunoglobulin deposits in bladder epithelium and vessels in interstitial cystitis: possible relationship to circulating anti-intermediate filament antibodies. *Clin Immunol Immunopathol* 1984;32:81–89
56. Ochs RL, Stein T Jr, Peebles CL, Gittes RF, Tan EM. Autoantibodies in interstitial cystitis. *J Urol* 1994;151:587–592
57. Tan EM. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. *Adv Immunol* 1989;44:93–151
58. von Mühlen CA, Tan EM. Autoantibodies in the diagnosis of systemic rheumatic diseases. *Semin Arthritis Rheum* 1995;24:323–358
59. Ochs RL, Tan EM. Auotoimmunity and interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997;47–52
60. Harrington DS, Fall M, Johansson SL. Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. *J Urol* 1990;144:868–871
61. Fall M, Carlsson CA, Erlandson BE. Electrical stimulation in interstitial cystitis. *J Urol* 1980;123:192–195
62. Theoharides TC. Hydroxyzine in the treatment of interstitial cystitis. *Urol Clin N Am* 1994;21:113–119
63. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. *Urology* 1994;44:614–616
64. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Rall TW, eds. The pharmacological basis of therapeutics, 7th edn. New York: Macmillan, 1985:387–445
65. Hanno PM, Buehler J, Wein AJ. Use of amitriptyline in the treatment of interstitial cystitis. *J Urol* 1989;141:846–848
66. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. *Urol Clin N Am* 1994;21:89–91
67. Kirkemo AK, Miles BJ, Peters JM. Use of amitriptyline in interstitial cystitis. *J Urol* 1990;143:279A
68. Badenoch AW. Chronic interstitial cystitis. *Br J Urol* 1971;43:718–721
69. Pool TL. Interstitial cystitis: clinical considerations and treatment. *Clin Obstet Gynecol* 1967;10:185–191
70. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. *J Urol* 1987;138:513–516
71. Parsons CL. Epithelial coating techniques in the treatment of interstitial cystitis. *Urology* 1997;49:100–104
72. Fall M. Conservative management of chronic interstitial cystitis: transcutaneous electrical nerve stimulation and transurethral resection. *J Urol* 1985;133:774–778
73. Dunn M, Ramsden PD, Roberts JBM, Smith JC, Smith PJB. Interstitial cystitis, treated by prolonged bladder distension. *Br J Urol* 1977;49:641–645
74. Hanno PM, Wein AJ. Conservative therapy of interstitial cystitis. *Semin Urol* 1991;9:143–147
75. Lloyd SN, Lloyd SM, Rogers K, Deane RF, Kirk D, Kyle KF. Is there still a place for prolonged bladder distension? *Br J Urol* 1992;70:382–386
76. Lasanen LT, Tammela TL, Kallioinen M, Waris T. Effect of acute distension on cholinergic innervation of the rat urinary bladder. *Urol Res* 1992;20:59–62
77. Freiha FS, Stamey TA. Cystolysis: a procedure for selective denervation of the bladder. *J Urol* 1980;123:360–363
78. Webster GD, Galloway N. Surgical treatment of interstitial cystitis. Indications, techniques, and results. *Urology* 1987;29:34–39
79. Mason TH, Haines GL, Leversee BW. Selective sacral neurectomy for Hunner's ulcer. *J Neurosurg* 1960;17:22–26
80. Milner WA, Garlick WB. Selective sacral neurectomy in interstitial cystitis. *J Urol* 1957;78:600–604
81. Bohm E, Franksson C, Petersén I. Sacral rhizopathies and sacral root syndromes. *Acta Chir Scand* 1956;Suppl 216:5–49
82. Meirowsky AM. The management of chronic interstitial cystitis by differential sacral neurotomy. *J Neurosurg* 1969;30:604–607
83. Albers DD, Geyer JR. Long-term results of cystolysis (supratrigonal denervation) of the bladder for intractable interstitial cystitis. *J Urol* 1988;139:1205–1206
84. Childs SJ. Dimethyl sulfone (DMSO2) in the treatment of interstitial cystitis. *Urol Clin N Am* 1994;21:85–88
85. Asklin B, Casuto J. Intravesical lidocaine in severe interstitial cystitis. Case report. *Scand J Urol Nephrol* 1989;23:311–312
86. Ghoniem GM, McBride D, Sood OP, Lewis V. Clinical experience with multiagent intravesical therapy in interstitial cystitis patients unresponsive to single-agent therapy. *World J Urol* 1993;11:178–182
87. Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *J Urol* 1996;156:45–48
88. Peters KM, Diokno AC, Steinert BW, Gonzales JA. The efficacy of intravesical Bacillus Calmette–Guérin in the treatment of interstitial cystitis: long-term followup. *J Urol* 1998;159:1483–1487
89. Zeidman EJ, Helfrick B, Pollard C, Thompson IM. Bacillus Calmette–Guérin immunotherapy for refractory interstitial cystitis. *Urology* 1994;43:121–124
90. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971–979
91. Fall M. Transcutaneous electrical nerve stimulation in interstitial cystitis. Update on clinical experience. *Urology* 1987;29:40–42
92. Fall M, Lindstrom S. Transcutaneous electrical nerve stimulation in classic and nonulcer interstitial cystitis. *Urol Clin N Am* 1994;21:131–139
93. McGuire EJ, Shi-Chun Z, Horwinski R, Lytton B. Treatment of motor sensory detrusor instability by electrical stimulation. *J Urol* 1983;129:78–79
94. Geirsson G, Wang YH, Lindstrom S, Fall M. Traditional acupuncture and electrical stimulation of the posterior tibial nerve. A trial in chronic interstitial cystitis. *Scand J Urol Nephrol* 1993;27:67–70
95. Eriksen BC. Painful bladder disease in woman: effect of maximal electric pelvic floor stimulation. *Neurourol Urodyn* 1989;8:362–363
96. van Kerrebroeck PEV. Electric stimulation in the management of interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997;219–222
97. Shanberg AM, Malloy T. Treatment of interstitial cystitis with neodymium: YAG laser. *Urology* 1987;29:31–33
98. Peeker R, Aldenborg F, Fall M. Complete transurethral resection of ulcers in classic interstitial cystitis. *Int Urogynecol J*. In press
99. Peeker R, Aldenborg F, Fall M. Nephrogenic adenoma – a study

with special reference to clinical presentation. *Br J Urol* 1997;80:539–542
100. Aldenborg F, Peeker R, Fall M, Olofsson A, Enerbäck L. Metaplastic transformation of urinary bladder epithelium: effect on mast cell recruitment, distribution and phenotype expression. *Am J Pathol* 1988;153:149–157
101. Juliusson S, Aldenborg F, Enerback L. Proteinase content of mast cells of nasal mucosa; effects of natural allergen exposure and of local corticosteroid treatment. *Allergy* 1995;50:15–22
102. Newson B, Dahlstrom A, Enerback L, Ahlman H. Suggestive evidence for a direct innervation of mucosal mast cells. *Neuroscience* 1983;10:565–570
103. Bruce P, Buckham G, Carden A, Salvaris M. The surgical treatment of chronic interstitial cystitis. *Med J Aust* 1977;1:581–582
104. Christmas TJ, Holmes SA, Hendry WF. Bladder replacement by ileocystoplasty: the final treatment for interstitial cystitis. *Br J Urol* 1996;78:69–73
105. Kontturi MJ, Hellstrom PA, Tammela TL, Lukkarinen OA. Colocystoplasty for the treatment of severe interstitial cystitis. *Urol Int* 1991;46:50–54
106. 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;159:1479–1482
107. Fall M, Nilsson S. Volume augmentation cystoplasty and persistent urgency. *Scand J Urol Nephrol* 1982;16:125–122
108. Hohenfellner M, Linn J, Hampel C, Thüroff JW. Surgical treatment of interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997;223–233
109. 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;144:255–258
110. Webster GD, Maggio MI. The management of chronic interstitial cystitis by substitution cystoplasty. *J Urol* 1989;141:287–291
111. Bricker EM. Bladder substitution after pelvic evisceration. *Surg Clin N Am* 1950;30:1511–1521
112. Kock NG, Nilson AE, Nilson LO, Norlén LJ, Philipson BM. Urinary diversion via a continent ileal reservoir: clinical results in 12 patients. *J Urol* 1982;128:469–475
113. Pitts R, Muecke E. A 20-year experience with ileal conduits: the fate of the kidneys. *J Urol* 1979;122:154–157
114. Baskin LS, Tanagho EA. Pelvic pain without pelvic organs. *J Urol* 1992;147:683–686