

# **Bladder Pain Syndrome/Interstitial cystitis: Aspects on outcome after intravesical and surgical treatment**

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2010**



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*To my children Augusta and Bernard*



# Bladder Pain Syndrome/Interstitial cystitis: aspects on outcome after intravesical and surgical treatment

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## Abstract

### Background

BPS/IC is a chronic syndrome with bladder pain, divided into two main types: one with so called Hunner's lesions (classic type) and one without (nonulcer type). In the recently presented ESSIC classification system the classic type, in focus of the present work, has the designation Type 3C BPS/IC. Symptoms are characterized by bladder pain, urgency, frequency and nocturia. The aetiology and pathophysiology of BPS/IC remain obscure and treatment is directed towards symptom relief. Intravesical instillation of dimethyl sulfoxide, DMSO, is an established treatment for BPS/IC and can be proposed as first-line treatment for patients with nonulcer BPS/IC. For patients with Type 3C, transurethral resection of lesions in the bladder, TURB, may render satisfactory symptomatic effect. Myofibroblasts might have a role in the evolution towards bladder contracture in patients with Type 3C BPS/IC and high levels of cytoplasmatic  $\alpha$ -smooth muscle actin,  $\alpha$ -SMA, are consistent with a typical myofibroblast phenotype. In patients with Type 3C, fibrosis of the bladder may represent end-stage disease. At this stage conservative treatment is often no longer effective and reconstructive surgery may be necessary.

### Aim and methods

The aims of this thesis were to investigate side-effects and outcome with first-line treatments for BPS/IC, especially in Type 3C BPS/IC. Data on patients were obtained from medical records and by telephone interviews. Immunohistochemical techniques were employed to visualize mast cells and possible myofibroblasts.

### Results

I. Side-effects after instillations of DMSO were common but transitory. Maintenance treatment with DMSO may offer long-term symptom improvement.

II. For patients with end-stage Type 3C BPS/IC, the initial major surgical procedure resulted in complete symptom resolution in 82 per cent, in contrast to only 23 per cent of the patients with nonulcer BPS/IC.

III. No statistically significant correlation between mast cell density in the lamina propria, urothelium or the detrusor and duration of symptom amelioration could be seen after the first, second or third TURB. There was a positive correlation between a high mast cell number in the urothelium at the third TURB and the risk of developing end-stage disease.

IV. No statistically significant increase or decrease in  $\alpha$ -SMA positive or  $\alpha$ -SMA negative fibroblast-like cells could be seen with increased number of TURB. An overweight of  $\alpha$ -SMA positive fibroblast-like cells compared to  $\alpha$ -SMA negative fibroblast-like cells was identified at the third TURB, but only reaching a statistical significance in the group with patients who had not yet reached end-stage.

### Conclusions

Intravesical instillation with DMSO appears to be associated with a reasonable degree of discomfort, when considering the potential benefit of the treatment in both subtypes of BPS/IC.

For patients with Type 3C BPS/IC, TURB is potentially quite an effective treatment option. However, mast cell density does not appear to predict the duration of symptom amelioration after complete transurethral resection of Hunner's lesions, neither in the lamina propria nor in the urothelium or the detrusor.

The findings of an overweight of  $\alpha$ -SMA positive fibroblast-like cells in patients with signs of active disease, expressed by repeated TURB's, might represent a time dependent factor of myofibroblast activation eventually resulting in a contracted bladder.

When conventional therapies no longer offer any symptom amelioration, in the patient with bladder contracture and/or intolerable symptoms, reconstructive surgery can be an appropriate last resort, however only in patients with Type 3C BPS/IC. The most important determinant in the decision to embark upon major reconstructive surgery is the assessment of subtype and stage of the disease.

**Keywords:** interstitial cystitis, bladder pain syndrome, dimethyl sulphoxide, mast cells, myofibroblasts, transurethral resection, bladder substitution

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## LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

- I. Rössberger, J. ; Fall, M. ; Peeker, R.  
Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome.  
*Scand J Urol Nephrol.* 2005; 39 (1) s. 73-77.
  
- II. Rössberger, 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 (4) s. 638-42.
  
- III. Rössberger, J. ; Fall, M. ; Kåbjörn-Gustafsson, C. ; Peeker, R.  
Does mast cell density predict the outcome after transurethral resection of Hunner's lesions in patients with type 3C bladder pain syndrome/interstitial cystitis?  
*Scand J Urol Nephrol.* *In press.*
  
- IV. Rössberger, J. ; Fall, M. ; Kåbjörn-Gustafsson, C. ; Peeker, R.  
TURB and bladder contracture in BPS/IC. Does myofibroblast activity play a role?  
*In manuscript.*

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## **ABBREVIATIONS**

APF	anti-proliferative factor
$\alpha$ -SMA	alfa-smooth muscle actin
BCG	bacillus calmette-guerin
BPS	bladder pain syndrome
CP	chronic prostatitis
CPP	chronic pelvic pain
CPPS	chronic pelvic pain syndrome
DNA	deoxyribonucleic acid
EGF	epidermal growth factor
ELISA	enzyme-linked immunosorbent assay
ESSIC	Former European Society for the Study of Interstitial Cystitis, now International Society for the Study of Bladder Pain Syndrome
FDA	food and drug administration
GAG	glycosaminoglycans
GP-51	glycoprotein 51 (molecular weight 51 kD)
GRA	global response assessment
H1R	histamine receptors 1
H2R	histamine receptor 2
HB-EGF	heparin-binding epidermal-like growth factor
HC gp-39	human cartilage glycoprotein-39
Htx-Eo	hematoxylin-eosin
IBS	irritable bowel syndrome
IC	interstitial cystitis
ICPI	interstitial cystitis problem index
ICSI	interstitial cystitis symptom index
IGFBP3	insulin-like growth factor binding protein 3
IGF-1	insulin-like growth factor 1
IPG	implanted pulse generator
MAP kinase	mitogen-activated protein kinases
MC <sub>TC</sub>	mast cell tryptase-positive, chymase-positive
MC <sub>T</sub>	mast cell tryptase-positive, chymase-negative
Nd:YAG	neodymium-doped yttrium aluminium garnet
NIDDK	national institute of diabetes and digestive and kidney diseases
NIH	national institute of health
NO	nitric oxide
OAB	overactive bladder syndrome
PCR	polymerase chain reaction
PI3K	phosphatidylinositol 3-kinase
PRV	pseudo rabies virus
PUF	pelvic pain and urgency/frequency questionnaire
SNS	sacral nerve electrical stimulation
TENS	transcutaneous electrical nerve stimulation
TNF	tumour necrosis factor
TUR	transurethral resection
VEGF	vascular endothelial growth factor
WICI	wisconsin interstitial cystitis inventory
YKL-40	Y (tyrosine)K (lysine) L(leucine) 40 kD
ZO-1	tight junction protein 1 (zona occludens 1)

## **INTRODUCTION**

### **HISTORY**

The name interstitial cystitis (IC) was given to the disease by A.J.C. Skene, who described a condition characterized by “inflammation that destroyed the urinary bladder mucous membrane partly or wholly and extended to the muscular parity”, in his book on Diseases of Bladder and Urethra in Women published in 1887<sup>1</sup>.

Some time earlier in 1808, Philip Syng Physick had described an inflammatory condition of the bladder, and in 1836 the Philadelphian surgeon Joseph Parrish used the description "tic douloureux" of the bladder, a term used for painful neurological conditions such as trigeminal neuralgia. However, the person whose name has been most commonly linked with this syndrome is Guy Hunner, a Boston surgeon who described this inflammatory bladder disorder in a number of patients in 1915<sup>2</sup>. He popularized the disease with the description of characteristic bladder wall ulcers and these lesions became to be known as Hunner's ulcers although the term “ulcer” is now considered to be a misnomer since in fact it is not a true ulcer. The first widespread epidemiological description of IC was done by Hand in 1949<sup>3</sup>, who published an article on interstitial cystitis with a report on 223 cases, describing the widespread, small, submucosal bladder haemorrhages and the significant variation in bladder capacity.

### **DEMOGRAPHICS AND CLINICAL PRESENTATION**

BPS/IC is a chronic disease affecting the function of the bladder. It predominantly affects middle-aged women but occurs in all age groups. It is rare in men<sup>4</sup> but from the Mayo clinic a series of 123 cases in men over a 15 year period has been reported<sup>5</sup>. The disease may also be diagnosed in children<sup>6</sup>. Most studies also report the disease to be rare in black people<sup>7,8</sup>. Familial occurrence of BPS/IC has been reported<sup>9</sup>. A hereditary aspect to incidence has been suggested by Warren et al<sup>10</sup> in a pioneering study. He found that adult female first-degree relatives of patients with BPS/IC may have a prevalence of the syndrome 17 times that found in the general population. This together with previous reported evidence showing a greater concordance of BPS/IC among monozygotic than dizygotic twins suggests, but does not prove, a genetic susceptibility that could partially explain the discord in prevalence rates in different populations<sup>10,11</sup>. There is a delay between the onset of urinary symptoms and the diagnosis typically being about 5 years<sup>4,12,13</sup>. The most obvious signs of BPS/IC are pain, urgency and urinary frequency (day and night). The pain is usually located supra- or retropubically. Occasionally the pain can be described to radiate into the loins or into the urethra or the vagina. In many cases voiding relieves the pain.

The urgency is sensory and often, but not always, due to the pain. Variability of urinary symptoms is common; with symptoms worsen periodically in 40–50 per cent of premenopausal women. Common triggers include psychological or physical stress<sup>14</sup>. Incontinence is rare and motor urge incontinence nearly excludes the disease. However, considerable amount of clinical characteristics are shared between BPS/IC and several other disease states, including; overactive bladder syndrome (OAB) (especially “OAB-dry”), chronic cystitis/urethral syndrome, chronic pelvic pain syndrome (CPPS) in women and CPP syndrome (CPPS)/chronic prostatitis (CP) in men<sup>15-17</sup>.

There is increasing evidence that BPS/IC is a heterogeneous syndrome and owing to a new classification described later, patients with Hunner’s lesion on cystoscopy are referred to Type 3C BPS/IC. In this group of patients some develop contracted bladder. There is little known and described about this in the literature, although well known for decades. Some patients develop end-stage disease rapidly, characterized by fibrosis and fat involution on histopathological examination, but more commonly this result of the disease evolves over several years<sup>18</sup>.

## **PREVALENCE**

Prevalence estimates for BPS/IC vary significantly due to how the studies are made; based on hospital record review, based on a mailed survey of board certified urologists or based on participant self-report. Estimates have ranged from 18.6/100,000 women older than 20 years in Finland<sup>4</sup> to approximately twice that in the United States<sup>19</sup>. In studies, with reported prevalence rates as high as 25 per cent<sup>16,20</sup>, investigators have moved toward prediction of BPS/IC prevalence based on symptoms consistent with the disease, rather than positive cystoscopic findings. Some argue that traditional epidemiologic studies have significantly underestimated BPS/IC prevalence, because they surveyed populations for diagnosed cases rather than screening for BPS/IC symptoms and evaluating suspected cases. The percentage of Type 3C BPS/IC of the total number of patients with BPS is not uniformly reported. Messing and Stamey reported Type 3C BPS/IC to account for about half of all cases<sup>12</sup>. Later, Type 3C BPS has been considered a rare finding, accounting for only 5-10 per cent of diagnosed cases<sup>21</sup>, whereas in our centre 50 per cent, a figure stable over years<sup>86</sup>. Later in a very large US series, Type 3C BPS/IC comprised approximately 20 per cent<sup>22</sup>.

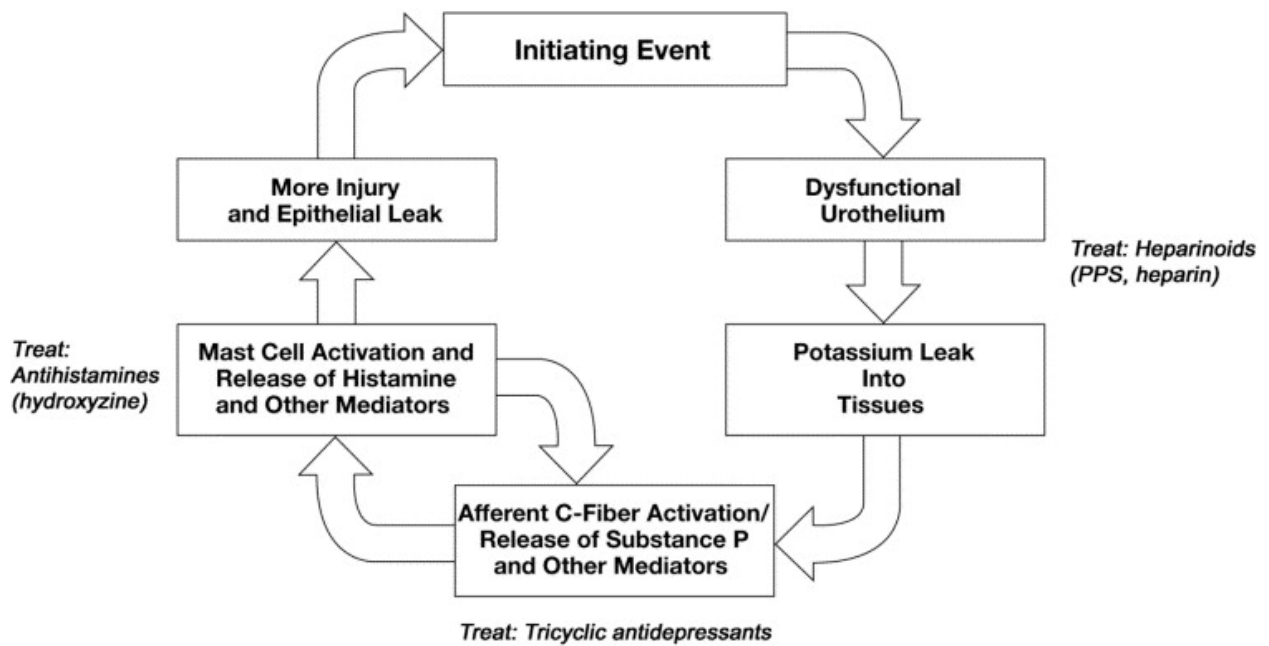
## **COMORBIDITY AND NONBLADDER RELATED SYMPTOMS**

High risks of impairment of quality of life are reported, commonly affecting sexual life. Also, bowel disorders and psychological stress are correlated to the probability of BPS/IC<sup>23</sup>.

In several epidemiological studies an increase of other conditions, including the irritable bowel syndrome, anxiety disorders, allergies, fibromyalgia and rheumatological disorders, has been shown in patients with BPS/IC<sup>24-28</sup>. In a case-control study Erickson found that patients with BPS/IC had higher scores than controls for pelvic discomfort, backache, dizziness, chest pain, aches in joints, abdominal cramps, nausea, palpitations and headache<sup>29</sup>. Buffington theorizes that a common stress response pattern of increased sympathetic nervous system function in the absence of comparable activation of the hypothalamic-pituitary-adrenal axis may account for some of these related symptoms<sup>30</sup>. Common factors associated with BPS/IC, such as sleep deprivation and chronic pain, can possibly lead to some of the nonbladder related symptoms. It is unknown whether these symptoms share a common pathophysiology or whether they are results of having BPS/IC. However, several studies have concluded that patients with BPS/IC do not indiscriminately report high scores for multiple somatic complaints<sup>29, 31, 32</sup>. No reports have ever documented a relationship to suggest that BPS/IC is a premalignant disorder.

## **PATHOLOGY/AETIOLOGY AND HYPOTHESIS**

The underlying pathophysiology of BPS/ IC is still incompletely understood. A number of theories of its pathogenesis have been suggested, but none entirely explain manifestations of the syndrome, and its exact aetiology is still unknown. It seems as if BPS/IC may have pluricausal aetiology and multifactorial pathogenesis. The previously explored aetiologies of IC include increased bladder epithelial permeability, mast cell activation, release of inflammatory mediators, subclinical infection, neuropathic changes, toxic compounds in the urine, impaired bladder vascular supply and autoimmunity. Pathophysiologic concepts focus on increased permeability of the urothelium, neurotransmitter/neuropeptide release by the urothelial cells, bladder sensory nerve upregulation secondary to nerve inflammation and neuroimmunoendocrine inflammation with mast cell involvement. A possible starting event are thought to be an infective or other inflammatory insult that lead to loss of integrity at the epithelial surface of the bladder. Secondary to this, sensory nerve up-regulation and enhanced mast cell activation may occur. The closing stages of this process would be a form of regional neuropathy that can result in pain and voiding symptoms, as well as other manifestations, e.g. gynaecological and gastrointestinal. As indicated above, the aetiology of interstitial cystitis is unknown, but there are many theories concerning its aetiology and pathogenesis, some of which are discussed briefly below.



**Fig 1** Hypothesis of possible pathophysiological events in BPS/IC.

### *Leaky epithelium*

The urothelium has a number of levels of defences against low and high molecular weight solutes, including the dense layer of glycosaminoglycans and glycoproteins on the luminal layer, tight junctions, hydrophobic uroplakin plaques and active ion pumps. Mucus provides the immediate interface between urine and bladder wall and represents the primary barrier in the bladder for controlling interactions with urine. Bladder surface mucus is composed of glycosaminoglycans (GAGs) and proteoglycans on the outer surface of the transitional cell apical membrane, with about 80 to 90 per cent of the total surface glycosaminoglycan bound as integral membrane proteins<sup>33, 34</sup>.

The role of mucus was first investigated in studies on the antibacterial defence mechanism of the bladder. With the use of acid or detergents containing solutions, mucus was removed and a marked rise in bacterial adherence and a resultant increase in bacterial infection could be seen<sup>35</sup>.

Further studies showed that an anti adherence effect could be regenerated by exogenous substances after mucus removal<sup>36, 37</sup>. In a study by Parsons et al this hypothesis was confirmed by showing more than 22 per cent increased urea movement in patients with BPS/IC compared with normal individuals<sup>38</sup>. In patients with Type 3C BPS/IC it was even more increased. This was taken as strong evidence for an existing abnormal regulation of mucosal permeability in BPS/IC patients and that mucus is an important regulator of permeability to urinary cations and is dysfunctional in most patients with BPS/IC.

Urine potassium is by some considered to play a pivotal role in BPS/IC pathogenesis, being a potentially toxic component to the bladder muscles and nerves. The urine levels are quite high, ranging from 24 to 133 mEq/L, compared to normally only 4 mEq/L inside the bladder wall. When intravesical potassium was compared to sodium in a blinded fashion, normal subjects had no reaction to sodium or potassium before injury of the mucus with protamine. After protamine treatment 90 per cent of normal subjects reported urgency, compared to only 10 per cent of normal subjects who had any reaction to sodium<sup>39</sup>. These data was considered as evidently supporting the theory that potassium is the primary toxin accountable for causing the symptoms of BPS/IC.

An excess of potassium ions in the suburothelial space is then accountable for the strong urge sensation in BPS/IC, originating from the chemosensitive C fibers. Typically, anticholinergics are ineffective in the treatment of these urge sensations since C fibers are not governed by the cholinergic system. Further verification for the potassium hypothesis is that evaluated levels of urinary potassium in normal patients versus those in newly diagnosed untreated patients with BPS/IC, show significantly lower levels of potassium in patients with BPS/IC. Urine potassium levels in patients with BPS/IC who were successfully treated were significantly higher than in newly diagnosed untreated patients with BPS/IC<sup>40</sup>.

#### *-Defect differentiation*

The apical layer of cells, the so-called umbrella cell layer, is known to be impermeable, but the molecular mechanisms that constitute this impermeability are far from completely identified. E-cadherin, which has a crucial role in urothelial differentiation<sup>41</sup>, ZO-1, which contributes to the impermeability of the bladder urothelium by forming tight junctions<sup>42, 43</sup>, as well as uroplakin, the major hydrophobic urothelial protein found on the surface of umbrella cells and also contributes to bladder impermeability,<sup>42, 44</sup> has been studied. In the same study<sup>45</sup> chondroitin sulphate, a component of the so-called glycosaminoglycan GAG layer that has been implicated to have a role in maintaining bladder impermeability and previously shown to be decreased in IC<sup>46</sup> was also examined. Immunohistochemical labelling for ZO-1 tight junction protein, uroplakin, chondroitin sulphate and E-cadherin was performed and evidence was found for widespread abnormalities in the expression of proteins associated with urothelial defences and differentiation in 24 of 27 biopsy specimens. There is further evidence of the failure of the urothelium to generate the entire set of defence molecules normally produced by a mature urothelium; the GP51 glycoprotein (molecular weight, 51 kDa) is a major component of the bladder mucous layer that is produced mainly by bladder uroepithelial cells<sup>47</sup>, with 97 per cent of all GP51

produced within the bladder<sup>48</sup>. GP51 covers the epithelium and is secreted into the urine, as detected by immunohistochemistry and enzyme-linked absorbent assay (ELISA), respectively<sup>48, 49</sup>. GP51 also binds to gram-positive and gram-negative uropathogens and encapsulates or aggregates them<sup>50</sup>. Immunohistochemical studies of bladder biopsy specimens comparing patients with BPS/IC versus normal controls reveal absent or decreased levels of GP51 in patients with BPS/IC versus a normal quantity of GP51 in the controls<sup>51</sup>. Interestingly, urine levels of GP51 are also noticeably decreased in patients with BPS/IC, with values similar to those in patients who undergo cystectomy<sup>48</sup>.

Other evidence for abnormal epithelial cell growth factor levels in BPS/IC exists. Keay et al<sup>52, 53</sup> have demonstrated that BPS/IC patient urine specimens have significantly abnormal levels of some epithelial cell growth factors, including decreased levels of heparin-binding epidermal-like growth factor (HB-EGF), increased levels of epidermal growth factor (EGF), insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3), compared with asymptomatic controls or patients with other urogenital disorders. These findings could explain the histological changes, with e.g. bladder epithelial thinning, seen on biopsy. In the same studies an inhibition of 3H-thymidine incorporation by normal human bladder epithelial cells, in response to urine from BPS/IC patients, was seen in 94 per cent compared with 9 per cent of urine from asymptomatic controls and 9 per cent of patients with other urogenital disorders. This then giving rise to evidence for a urinary toxin in BPS/IC that inhibits the proliferation of normal bladder epithelial cells in vitro significantly more often than specimens from controls<sup>53</sup>.

When bladder epithelial cells from BPS/IC patients are grown in vitro, the same abnormal production in growth factors are seen, indicating that these changes are not a result from an extrinsic stimulus<sup>54</sup>.

### *-Autoimmunity*

With BPS/IC being a non-infectious inflammatory disorder, coexisting with allergic disorders and affecting predominantly women, theories of an immunologic aetiology on autoimmune basis seem logical. IgM antibodies and complement have been identified in areas of endothelial cell damage<sup>55-57</sup> as well as IgA antibodies on the surface of bladder epithelium in BPS/IC patients, but the antigenic specificity of these antibodies is unknown. BPS/IC patients also do display, to a greater extent than in control, auto-antibodies in the sera but the specificity of these auto-antibodies has differed between reports<sup>58, 59</sup>. Harrington et al<sup>60</sup> examined local and peripheral immune response in bladder biopsies and peripheral blood, using a panel of monoclonal antibodies. Type 3C BPS/IC patients had ulcers, intense inflammation with focal sheets of

plasma cells, aggregates of T cells, B cell nodules including germinal centers, a decreased or normal helper-to-suppressor cell ratio and suppressor cytotoxic cells in germinal centers. However, no statistically significant difference between control and nonulcer group was identified. Flow cytometry analysis of peripheral blood lymphocyte subsets showed normal patterns in controls, but increased numbers of secretory Ig positive B cells and activated lymphocytes in both the Type 3C BPS/IC and nonulcer group.

Studies, showing a common autoantigen in serum from patients with BPS/IC and those with atopic dermatitis (a Th-2-mediated skin disease)<sup>61</sup> or an increase in interleukin(IL)-6 in urine of patients with BPS/IC (a known stimulus of the Th-2 response)<sup>62</sup>, are by some thought to suggest that BPS/IC may be driven by a group of Th-2 cytokines leading to an immunopathologic response. In general, a Th-2 response is thought to be associated with disease states, supporting antibody development and tissue necrosis. In summary, data show that anti-epithelial cell auto-antibodies are present in the urine of BPS/IC patients, but suggest that these antibodies may simply be the manifestation of non-specific antigenic products of cellular/tissue damage and probably not the primary cause of the disease.

### *-Infection*

Urinary tract infection and BPS/IC share some features, such as predominance in women, irritative bladder symptoms, rapid onset and episodic course and nonspecific inflammatory histopathologic characteristics. A prospective, controlled study by Keay et al<sup>63</sup> did not reveal the presence of a uniform bacterial species or of any Mycoplasma, Ureaplasma, Chlamydia, mycobacteria, anaerobic bacteria, or fastidious bacteria (including Gardnerella sp, Helicobacter sp, Campylobacter sp, Haemophilus sp, or Neisseria sp). Nor did any patient have evidence of active infection with herpes viruses (herpes simplex, cytomegalovirus, and varicella zoster), enteroviruses (poliovirus, coxsackie virus groups A and B, echovirus, and others), measles, mumps, rubella, or respiratory viruses (adenovirus, influenza A and B, respiratory syncytial, parainfluenza, and rhinovirus). These results concur with those of others<sup>64-66</sup>.

Keay et al<sup>63</sup> did find proof for the hypothesis that BPS/IC patients have a higher prevalence than controls of various microorganisms in their urine. However, that BPS/IC would be a result of the direct effect of virulence factor or factors of these organisms is somewhat questionable due to the fact that several different species of microorganisms were isolated, showing that no common factor or cluster of factors characterizes BPS/IC-associated organisms. Also, the organisms are non-pathogenic in normal hosts because of deficiency in known virulence factors.



Therefore, it seems more likely that these organisms may be pathogenic owing to an abnormal host response, either epithelial, inflammatory, or immune response.

In a large study patients with BPS/IC/CPSP were screened for bacterial DNA and viral DNA sequences using PCR. Common urogenital pathogens such as eubacteria, cytomegalovirus, herpes simplex I, herpes simplex II, adenovirus, human papilloma virus (HPV) and *Chlamydia trachomatis*, which could be implicated in the aetiology of BPS/IC/CPSP, were selected. However, PCR were negative in all samples and the authors draw the conclusions that BPS/IC/CPSP is not associated with persistence of viral and bacterial DNA in the bladder and that a chronic infective aetiology for the condition is excluded<sup>67</sup>.

#### *-Nerve inflammation and mast cells*

Most studies in humans have shown an increase in mast cell numbers and activation in bladder biopsies from patients with BPS/IC<sup>55, 68-71</sup> and the partial efficacy of neuromodulatory therapies suggests that neural-immune interactions are engaged in BPS/IC associated pelvic pain<sup>72, 73</sup>.

Based on the presence or absence of tryptase and chymase in their granules, mast cells are classified as MC<sub>T</sub> (tryptase-positive, chymase negative mast cell) and MC<sub>TC</sub> (tryptase-positive, chymase-positive mast cell)<sup>74</sup>. The MC<sub>T</sub> is mainly observed in the bronchial and nasal mucosa and MC<sub>TC</sub> in the skin. The type of mast cell dominantly present in the bladder of BPS/IC patients may be MC<sub>TC</sub>. In nonulcer BPS/IC, reports on bladder mast cells show large standard deviations while mast cells are more consistently increased in Type 3C BPS/IC<sup>75</sup>. The hypothesis is that activated mast cells are multifunctional cells competent of secreting a wide variety of preformed stores of immune mediators, such as vasoactive, nociceptive and proinflammatory mediators. Vasoactive and inflammatory mediators secreted by mast cells may explain many BPS/IC symptoms and produce neuronal sensitization and secretion of neurotransmitters that further stimulates mast cells. Mast cells and histamine receptors 1, H1R, and 2, H2R, have been demonstrated in a murine interstitial cystitis model, to cause pelvic pain originating from the bladder<sup>76, 77</sup>. In a limited trial of BPS patients, the H2R antagonist cimetidine produced significant improvement in pain and nocturia<sup>78</sup> but in contrast to this clinical trials present with varying results, on patients receiving the old-line H1R antagonist hydroxyzine<sup>79</sup>.

## **DIAGNOSING**

Diagnostic criteria have varied widely in the past. Historically, the strictest diagnostic criteria are those developed in 1987 and 1988 by the National Institute of Health (NIH), the so called NIDDK (National Institute of Diabetes, Digestive and Kidney Diseases) criteria, used in research definition of interstitial cystitis. To meet these criteria, both cystoscopy and cystometry are needed to exclude other possible causes for patient symptoms.

### **Automatic inclusions**

Hunner's ulcer

### **Positive factors**

Pain on bladder filling relieved by emptying

Pain (suprapubic, pelvic, urethral, vaginal, or perineal)

Glomerulations on endoscopy

Decreased compliance on cystometrogram

### **Automatic exclusions**

Bladder capacity > 350 mL on awake cystometry using either gas or liquid as filling medium.

Absence of intense urge to void with bladder filled to 100 mL of gas or 150 mL of water during cystometry, using a fill rate of 3-100 mL/mm

Demonstration of phasic involuntary bladder contractions during cystometry using fill rate described above

Duration of symptoms less than 9 months

Absence of nocturia

Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics (muscle relaxants)

Frequency of urination while awake < 8 times per day

Diagnosis of bacterial cystitis or prostatitis within 3 month period

Bladder or lower ureteral calculi

Active genital herpes

Uterine, cervical, vaginal, or urethral cancer

Urethral diverticulum

Cyclophosphamide or any type of chemical cystitis

Tuberculous cystitis

Radiation cystitis

Benign or malignant bladder tumors

Vaginitis

Age < 18 years

**Table 1** *NIDDK criteria*

These criteria have allowed a reasonably homogeneous group of patients to be identified for research purposes but they have not been generally accepted as standard criteria and, as a consequence, prevalence estimates for BPS/IC vary significantly. The NIDDK criteria have also generally been considered too strict to be used in clinical settings<sup>80</sup>. In fact, the diagnosis has been based on quite varying expert opinions. Therefore, ESSIC (International Society for the study of Bladder Pain Syndrome) have recently decided upon a new nomenclature, new diagnostic criteria and a new classification for the syndrome formerly called interstitial cystitis (IC). The new nomenclature for the disease is bladder pain syndrome, with the advantage of not having a name of the disease implying inflammation. However, a patient with the Hunner type of disease actually fulfils the requirements of the original term of IC, displaying lesions and bladder interstitial inflammation of the bladder. With the new ESSIC nomenclature patients who displays Hunner`s lesions on cystoscopy are referred to as Type 3C BPS/IC.

**Patient selection**

Patients with pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency



**Exclusion of confusable diseases**

Medical history, physical examination, urinalysis, urine cultures, PSA in males over 40 yrs, uroflowmetry, post-void residual urine volume by ultrasound scanning, cystoscopy and biopsy



**Classification of BPS**

cystoscopy with hydrodistension and biopsy if indicated

**Cystoscopy findings**

- x: not done
- 1: normal
- 2: glomerulations grade II or III
- 3: Hunner`s lesion (with or without glomerulations)

**Biopsy findings**

- x: not done
- A: normal
- B: inconclusive
- C: inflammatory infiltrates, granulation tissue, detrusor mastocytosis or intrafascicular fibrosis

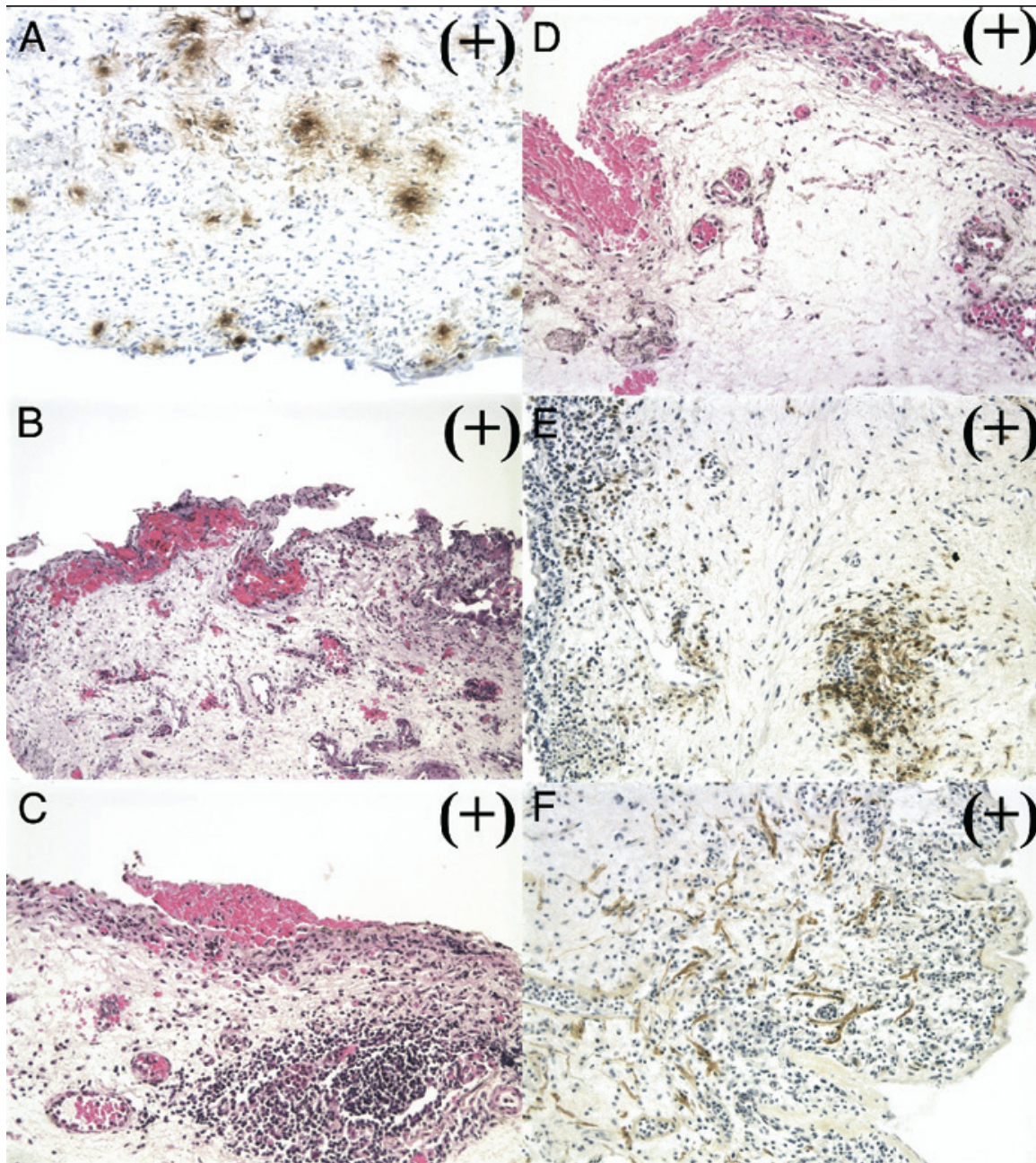
**Table 2** ESSIC nomenclature, diagnostic criteria and classification

### *Symptoms*

Earlier distinction was made between two subtypes: ulcerative (classic, Type 3C BPS/IC) and non-ulcerative variants<sup>81, 82</sup>. Type 3C BPS/IC is generally being reported as being more uncommon, with prevalence ranges from 3,5 to 56 per cent in different studies<sup>3, 12, 82-85</sup>. Patients with nonulcer subtype are younger at diagnosis and symptom onset. Both average functional bladder capacity and average bladder capacity under general anaesthesia are significantly larger for patients with nonulcer disease. Nonulcer disease does not progress into Type 3C BPS/IC<sup>82</sup>. The two entities usually do not differ in symptom pattern, but e.g. sharp pain, pain relieved by urinating and hematuria, are all symptoms being more common in Type 3C BPS/IC. Pain relieved by standing, IBS, dull aching pain and dyspareunia are all symptoms being more common in nonulcer IC. However, no variable alone can discriminate between the two subtypes with high sensitivity and specificity and are therefore just epidemiological data that can support cystoscopic findings<sup>22</sup>. Logadottir et al has demonstrated that a subclassification between classic and non-ulcer disease, without cystoscopy, can be made by measuring a difference in intraluminal nitric oxide (NO) evaporation in patients meeting the NIDDK criteria<sup>86</sup>. Hosseini et al<sup>87</sup> showed a statistically significant correlation between changes in symptom/problem IC index score and changes in luminal bladder NO in each patient after treatment with oral prednisolone for 8 weeks, suggesting that NO also can be used to evaluate treatment responses in individual patients with Type 3C BPS/IC objectively.

### *Cystoscopy and biopsy*

In Type 3C BPS/IC single or multiple reddened mucosal areas are seen with small vessels radiating towards a central scar, fibrin deposit or coagulum. With increasing bladder distension this site ruptures, resulting in petechial oozing of blood from the ulcer and the mucosal margins. Post distension a rather typical, bullous oedema develops. 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<sup>55, 88</sup>.



**Fig 2** Distinct mastocytosis of lamina propria on tryptase stain (A), complete denudation of urothelium (B), granulation tissue in lamina propria (C), edema in lamina propria (D), dense lymphocytosis of lamina propria on leukocyte common antigen stain (E) and small nerve proliferation in lamina propria on S100 stain (F).

In contrast, in patients with nonulcer BPS/IC a normal bladder mucosa is seen at initial cystoscopy. During or after hydrodistension small, multiple glomerulations and multiple superficial petechial bleedings occur. However, glomerulations have been reported to be present in healthy women after bladder distension<sup>89</sup>. In some patients, confluent, superficial mucosal cracks develop during distension. Histopathological changes like those found in Type 3C BPS/IC

are absent. Mainly, there is slight or no mast cell involvement. Small suburothelial bleedings and tiny cracks in the mucosa may be seen in accordance with the cystoscopic findings<sup>55, 88</sup>.

#### *Urine markers*

The finding that cells from the bladder lining of normal controls grow significantly more rapidly in culture than cells from BPS/IC patients led Keay et al<sup>90</sup> to the discovery of an anti-proliferative factor, APF, produced by the urothelium of BPS/IC patients. Normal bladder cells were cultured in the presence of urine from patients with BPS/IC, asymptomatic controls, bacterial cystitis and vulvo-vaginitis. Only urine from BPS/IC patients inhibited bladder cell proliferation. The presence of APF was found to be a sensitive and specific biomarker for BPS/IC<sup>53</sup>. APF activity dropped significantly in BPS/IC patients within two hours after hydrodistension<sup>91</sup> and after five days of sacral neuromodulation<sup>92</sup>. APF has been purified and proved to be a frizzled 8 protein that belongs to a newly discovered family of proteins which seem to be important in the development of nerve tissues, skin, and the linings of organs<sup>93</sup>.

#### *Questionnaires*

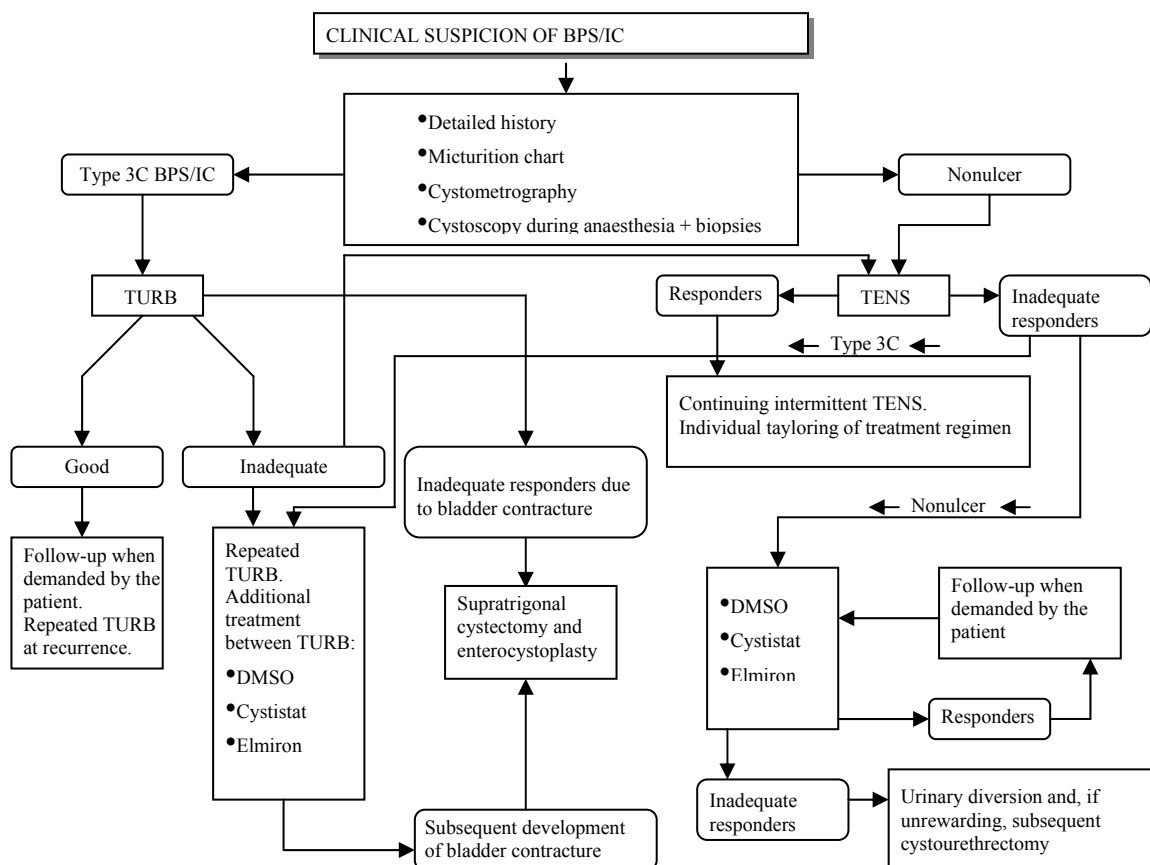
The O'Leary-Sant IC Symptom (ICS) and O'Leary-Sant IC Problem Indexes (ICPI) and the Wisconsin IC Inventory (WICI)<sup>31, 94</sup> are the most commonly used instruments to assess overall symptoms in BPS/IC. The two O'Leary-Sant indexes are intended to assess symptoms and their impact on patients' quality of life, respectively. The WICI is implanted in a longer questionnaire, including other body systems, and is based on seven questions associated to urinary symptoms. Measures of pain, urgency and frequency are also used as outcomes in BPS/IC research. The three scales have been validated.<sup>31, 94, 95</sup> The ICS, ICPI, and WICI have also been shown to be responsive to change over time as measured by global response assessment (GRA) in patients with BPS/IC and are therefore suggested as secondary endpoints for future clinical trials<sup>96</sup>.

#### *"Screening-tools"*

Two validated symptom-based tools can be used to screen the general patient population for BPS/IC; the Pelvic Pain and Urgency/Frequency (PUF) questionnaire and O'Leary-Sant (OLS) IC symptom and problem index. The PUF questionnaire consists of a symptom component and a problem component, which together yield a total score<sup>16</sup>, while the latter focuses on four symptoms, namely, urgency, frequency, nocturia, and pain. The problems arising from each of these four symptoms is scored and a total score is then calculated<sup>94</sup>.

## TREATMENT

Because of various theories of pathogenesis proposed for BPS/ IC, a large range of treatments have developed. These include oral medication, intravesical or bladder instillation therapy, dietary changes, lifestyle interventions, peripheral or transcutaneous nerve stimulation, hyperbaric oxygen therapy and surgical intervention. The guidelines for BPS/IC primarily recommend the use of medical therapies, including heparinoids, tricyclic antidepressants and antihistamines. These are often used in combination. Intravesical therapies and sacral neuromodulations are considered as adjuncts and surgery should be preceded by a methodical preoperative assessment, stressing evaluation of subtype. The benefits of combination therapy, with simultaneous addressing of a number of pathophysiological steps described in the disease, are recommended by some. Although lack of proof of knowledge in the literature, synergisms between medical therapies are theoretically probable, because many medications aim at treat different symptoms (e.g., pain, sleep difficulties, associated allergic phenomena).



**Fig 3** Treatment algorithm for BPS/IC

## ORAL MEDICATIONS

### *Sodium pentosanpolysulphate, PPS*

The mechanism of PPS is believed to substitute for a defect in the glycosaminoglycane (GAG) layer. Sodium pentosanpolysulphate (PPS) (Elmiron®) has been evaluated in double-blind, placebo-controlled studies and is the only oral medication approved by the US Food and Drug Administration (FDA) for use in the treatment of patients with BPS/IC. Subjective improvement of pain, urgency, frequency but not nocturia was reported in patients taking the drug as compared to placebo<sup>97,98</sup>. However, conclusions from different studies on PPS are difficult due to differences among study designs, end points, missing data handling and furthermore, data are contradictory. In a later multicenter placebo controlled study, low global response rates for sodium PPS as well as for hydroxyzine suggest that neither provided benefit for the majority of the patients<sup>79</sup>. In this context it is also worth noting that, because of lack of rigorous inclusion criteria in various studies, severe obstacles remain when trying to extract valid conclusions. PPS is routinely administered at 300 mg/day in 2 or 3 separated doses and the response appears to be associated with the duration of therapy rather than the dosage<sup>99</sup>.

### *Hydroxyzine*

The hypothesis behind treatment with hydroxyzine, a tricyclic, H<sub>1</sub>-receptor antagonist, is that the activation of mast cells seen with seasonal allergies may provoke symptom flares in individuals with BPS/IC and that antihistamine therefore could be an option in the treatment. The first report on treatment with hydroxyzine was in 1958<sup>100</sup>. Hydroxyzine is the only antihistamine that has the capacity to prevent mast cell activation and when used continuously, it suppresses mast cell degranulation<sup>101</sup>. The effect of hydroxyzine has not been evaluated in placebo-controlled studies except for the one previously mentioned, where no significant improvement was seen with treatment of hydroxyzine compared to placebo. This study was impaired by a probable type II error due to under-powering. However, because of lack of major side effects, wide availability and low cost it still has a role in the arsenal of BPS/IC treatments.

The standard starting dose is 25 mg daily, taken in the evening to minimize the sedative effects.

### *Cimetidine*

Cimetidine is a H<sub>2</sub>-blocker that has been evaluated clinically in a double-blind study with oral cimetidine versus placebo for three months. Those receiving cimetidine had a significant improvement in symptom scores, pain and nocturia. However, histologically the bladder mucosa showed no qualitative changes in either group<sup>78</sup>.



### *Amitriptyline*

Tricyclic antidepressant such as amitriptyline is thought to be effective in BPS/IC for mechanisms beyond its anxiolytic effect, such as blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and norepinephrine and blockade of the histamine H<sub>1</sub> receptor. The first report on amitriptyline in the treatment for BPS/IC was promising, showing a significant improvement in pain and daytime frequency but also resulting in virtually total remission of symptoms in 32 per cent of the patients (8/25), after being on the drug for 4 to 28 months<sup>102</sup>. In a more recent prospective, randomized, placebo controlled, double-blind study by van Ophoven, a statistically significant change in the O'Leary-Sant IC symptom and problem index and statistically significant improvement of pain and urgency intensity compared with placebo could be seen<sup>103</sup>. In another study by the same researchers, considering patients reporting improvement in a global response assessment questionnaire as responders, the response rate was 64 per cent (60 patients) with an overall mean dose of 55 mg. Likewise, the therapeutic response to amitriptyline was observed in patients fulfilling the NIDDK criteria as well as in those with a clinical diagnosis of BPS/IC<sup>104</sup>.

Amitriptyline can be given at a starting dose of 10 to 25 mg daily in the evening. After several weeks, the dose can be titrated up in an attempt to maintain a balance of pain/irritative symptom reduction and adverse effects (i.e. fatigue, constipation, palpitations, weight gain, and urinary retention). Satisfactory results are usually achieved with doses in the range of 10 to 75 mg daily taken at night.

### INTRAVESICAL INSTILLATIONS

#### *Dimethyl sulphoxide, DMSO*

The chemical solvent DMSO is a lipid and water-soluble liquid that penetrates cell membranes. Its mode of action is not fully understood but has been suggested to be, except for purely analgesic, also anti-inflammatory, collagenolytic and muscle relaxant. It is also a scavenger of the intracellular OH radical believed to be an important trigger of the inflammatory process. In a crossover trial<sup>105</sup>, patients were randomly allocated to instillations with 50 per cent DMSO solutions and placebo. Subjective improvement was noted in 53 per cent versus 18 per cent and objective improvement in 93 per cent versus 35 per cent, following DMSO and placebo treatment, respectively. DMSO is contraindicated during urinary tract infections or shortly after bladder biopsy and it temporarily causes a garlic-like odour. A case of pigmented eye lens deposits possibly caused by DMSO treatment has been reported<sup>106</sup>.

DMSO is typically given at an initial dose of 50 mL weekly for 6 to 8 weeks, followed by a maintenance regimen of 50 mL every 2 weeks for 3 to 12 months. To potentially enhance the beneficial effects of the DMSO solution other compounds, such as methylprednisolone and heparin sulphate, can be added<sup>107</sup>.

#### *Bacillus Calmette-Guèrin*

BCG treatment involves marked elevation of IL-1, IL-2, interferon-gamma, and tumour necrosis factor, known stimulants of the Th-1 response<sup>108, 109</sup>. Thus, the efficacy of BCG in treating BPS/IC has speculatively been thought to be due to stimulation of Th-1 cytokines, allowing for correction of the underlying abnormal immunologic event, and promoting reparative conditions. In a study by Peters et al in 1997, BCG was shown to be safe and efficacious in the treatment of BPS/IC and therefore BCG was put forward as a potential promising treatment option for patients with IC<sup>110</sup>. In a follow-up study of the patients who responded favourably, 89 per cent (8/9) continued to have an excellent response with follow-up ranging from 24 to 33 months and BCG did not worsen symptoms in nonresponders<sup>111</sup>. However, in a later prospective, double-blind crossover trial of BCG and DMSO, BCG treatment seemed not to be of any benefit of the patient<sup>112</sup>. These negative results were later corroborated in a large placebo study including 265 subjects, showing that the treatment was tolerable but with quite low response rate<sup>113</sup>.

#### *Pentosanpolysulphate*

Pentosanpolysulphate (PPS) is a glycoprotein aimed at repairing the glucosaminoglycan (GAG) layer in BPS/IC bladders and is thereby thought to potentially diminish the effects that noxious agents in urine have on underlying sensory nerves of the bladder wall (C- and A- $\delta$  fibers). The bioavailability of PPS is poor after oral administration, hence the intravesical application. The efficacy of PPS has been studied in a double-blind placebo-controlled study including 20 patients. At three months, the only parameter showing a statistically significant increase in patients treated with PPS was the cystometric bladder capacity<sup>114</sup>. PPS was given as 300 mg in 50 mL OF 0, 9% saline, and twice a week for three months.

#### *Hyaluronic acid*

Treatment with hyaluronic acid, a natural proteoglycan, is aimed at repairing defects in the GAG layer. A wide range of epithelial-coating techniques including the use of heparin, sodium pentosan polysulfate, and hyaluronic acid have been used. Many reports suggested a long-lasting moderate efficacy with no significant toxicity<sup>115-121</sup>. However, available studies are limited in

number and quality and no randomized, placebo-controlled trials evaluating the use of intravesical hyaluronic acid exists. Patients usually receive four to six weekly intravesical installations of hyaluronic acid at a dose of 40 mg in a volume of 50 ml of phosphate-buffered saline. Responders then receive monthly doses.

#### *Chondroitin Sulphate*

Chondroitin sulphate, to substitute for the GAG layer defect, has been evaluated in two non-randomized, uncontrolled pilot studies, both of them reporting improvements in patient-reported symptoms after the use of chondroitin sulphate. In one of the studies, a total of 6/13 (46.2 per cent) showed a good response, and 1/13 (7.7 per cent) showed no response<sup>122</sup>. Sorensen et al<sup>123</sup> seemed to show more promising results, with average symptom improvement of 73.1 per cent (range 50 to 95 per cent) reported in 20 patients completing the trial, when using high dose (2.0 per cent) chondroitin sulphate instillations in some patients instead of 0.2% solution.

#### *Vanilloids/ Resiniferatoxin (RTX)*

RTX is derived from a cactus named *Euphorbia resinifera*, and is an ultra potent analogue of the chili pepper extract capsaicin. RTX are vanilloid agonists that perform their action by activating the transient receptor potential vanilloid type 1 (TRPV1) receptor. They are meant to desensitize the TRPV1 receptor so pain transmission through C-fibers is prevented<sup>124</sup>. RTX is more potent than capsaicin in desensitizing C-fibers with less irritation. Clinical efficacy was demonstrated clearly in studies of small sample size<sup>125, 126</sup>. In a placebo-controlled trial on patients with pain and hypersensitive bladder disorder, RTX reduced symptoms such as nocturia, pain and frequency by approximately 50 per cent<sup>127</sup>. However, in a more recent study with the same design, RTX was not found to be effective in BPS/IC<sup>128</sup>.

## SURGICAL TREATMENT

#### *Bladder distension*

Hydrodistension of the bladder was first reported as an effective treatment of IC by Bumpus et al in 1930<sup>129</sup>, but the mode of action is still unknown. The initial intention with the procedure was to increase bladder capacity simply by stretching the detrusor and simultaneously inducing ischemic necrosis of sensory nerve fibers, accomplishing decreased bladder pain.

Although many of the following series were small with dissimilarities in techniques, inclusion criteria and follow-up, the treatment regimen was accepted maybe mostly due to the fact that it represents a simple method with few complications. Complete absence of symptoms was claimed

to be achieved in 64 per cent (16/25) using the Helmstein method<sup>130</sup>, where an intravesical balloon is distended at the level of systolic blood pressure for three hours. However, bladder rupture occurred in two cases. This, together with the results of others, not using the Helmstein method, though, who failed to demonstrate any improvement later led to rejection of the treatment because of lack of efficacy and a high complication rate<sup>131, 132</sup>.

### *Electrical stimulation*

The bladder wall contains visceral parasympathetic afferents in the form of lightly myelinated A $\delta$  fibers and unmyelinated C fibers, possessing predominantly mechanosensitive (tension) and chemosensitive (nociception) properties, respectively<sup>133</sup>. Upon bladder filling, A $\delta$  fibers respond to physiologic low-threshold intravesical pressure, whereas C fibers are typically silent. In animal models, unmyelinated bladder afferents exhibit impulse transmission following chemical irritation, and in the presence of significant epithelial inflammation may exhibit both spontaneous activity and novel mechanosensitivity<sup>134, 135</sup>. Such C fiber plasticity may play a role in the evolution of BPS/IC symptoms. Physiologic bladder filling in the presence of chronic inflammation could produce an afferent storm resulting in frequency, urgency and pain.

Electrical stimulation is thought to function in part through the inhibition of C fiber impulse transmission to the central nervous system. Inhibition of C fiber transmission by sacral neuromodulation may occur as a result of primary somatic afferent activation, as typically employed SNS impulse parameters exhibit an affinity for somatic (versus visceral) and afferent (versus efferent) nerve fibers<sup>136, 137</sup>. Somatic afferent inhibition of C fiber transmission may be explained by the 'gate theory', introduced in 1965 by Melzak and Wall<sup>138</sup>. 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 like inhibition of detrusor activity<sup>139</sup>. Another possible mechanism is the release of opiates, especially endorphins.

Transcutaneous electrical nerve stimulation, TENS, is administered with high frequency stimulation (50-100 Hz) by electrodes above the pubic bone, and is applicable at the outpatient clinic. Patients with Type 3C BPS/IC have shown to respond more favourably than patients with nonulcer BPS/IC<sup>140, 141</sup>.

Sacral nerve electrical stimulation, SNS, involves application of electrodes within the sacral foramina three or four, S3 or S4. As a first step an electrode is inserted into a relevant sacral foramen and stimulation is given by an external pulse generator. If good subjective effect is

achieved under a test period of some days or weeks, the sacral nerve electrode is connected to a subcutaneously implanted pulse generator, IPG, for long-term use.

In a study including 78 patients with BPS/IC, with a median follow up was 61.5 months, a good long-term success was seen in 72 per cent of the patients<sup>142</sup>. The revision rate was 50 per cent and the explantation rate was 28 per cent, with the most common reason for explantation being poor outcome (54 per cent of the failed patients). Even better long-term results have been reported by others with similar follow up<sup>143</sup>. Also, both reduced symptoms and narcotic requirement in refractory BPS/IC patients have been achieved with long-term treatment<sup>144</sup>.

### *Transurethral resection and coagulation*

Peeker et al<sup>18</sup> retrospectively evaluated 103 patients with Type 3C BPS/IC and their response to complete transurethral resection of visible lesions in the bladder. In that series, a satisfactory symptomatic effect in 9 of 10 patients could be seen. This was in concordance with earlier fairly small studies on TURB and laser fulguration, that also resulted in favourable symptomatic outcome<sup>145-148</sup>. Interestingly, the included patients seemed to be suitable for division into four relatively distinct groups; long-term good responders (long-term remission for 3 years or more with a maximum of three resections), short-term good responders (need for repeated resections to stay symptomatically relieved and follow up less than 3 years), patients with bladder contracture (developed over more than 2 years) and end-stage disease (within 2 years after diagnosis). TURB has been suggested to result in symptom improvement by the removal of intramural nerve endings engaged by the inflammatory process. Surgical complications are rare, the most common being bladder perforation and prolonged postoperative hematuria. Neodymium (Nd):YAG laser has been used in urology since the 1960`s and Shanberg et al initially used it in 1985 for treatment of interstitial cystitis<sup>148</sup>. Laser ablation penetrates approximately 5 mm, heating tissue to 60-70°C, thought leaving the underlying elastic fibers undamaged. Laser is among some considered advantageous over TURB since the operation is easier to perform with this technique and since it is debated which technique, if repeated, entails the greater risk of inducing bladder contracture. In the treatment of superficial bladder carcinoma, a cost analysis of Nd-YAG laser versus transurethral resection treatment showed that the main savings of laser versus TURB were a significantly shorter hospitalization and the elimination of the need for catheter drainage in almost all of the patients treated with laser therapy<sup>149</sup>.

### *Supratrigonal/ subtrigonal cystectomy or urinary diversion*

In patients no longer responding to conservative treatment, reconstructive surgery has been reported to be successful in some cases. However, surgical therapy of BPS/IC should never be considered as a first-line therapy, and is only applicable in 2 to 10 per cent of patients with BPS/IC who fail to respond adequately to conservative management<sup>26, 150, 151</sup>. Initially, simple augmentation of the bladder with enterocystoplasty was carried out, similar to the “clam” enterocystoplasty used in the treatment of neurogenic and idiopathic detrusor overactivity. However, this procedure frequently failed, with recurrence of symptoms, and this led to the idea that the diseased bladder should be removed prior to augmentation of bowel. Assessment of bladder capacity will provide a good indication as to the progression of inflammation-induced contraction of the bladder as a whole, as bladder capacity is the best prognostic indicator for major surgical intervention in BPS/IC. Performing reconstructive surgery in patients with large bladder capacity, a finding typical of nonulcer BPS/IC, has been questioned<sup>152</sup>. In a small study, Peeker et al<sup>153</sup> showed that in patients with Type 3C BPS/IC, supratrigonal resection and subsequent augmentation is often successful, but typically patients with nonulcer BPS/IC have residual symptoms after this sort of procedure.

## AIMS

1. To describe the degree of discomfort with intravesical DMSO instillations and long-term efficacy results associated with the treatment  
(Paper I)
2. To evaluate the outcome in patients, with long follow-up, after various types of reconstructive surgery in patients with Type 3C and nonulcer BPS/IC  
(Paper II)
3. To assess mast cell density in lamina propria for correlation with duration of symptom amelioration after TURB in patients with Type 3C BPS/IC  
(Paper III)
4. To describe prevalence and change in density of possible myofibroblasts in native resections and following repeated resections from patients with Type 3C BPS/IC  
(Paper IV)

## **PATIENTS**

### **Paper I:**

Twenty-eight patients, 13 (eleven women and two men, mean age at diagnosis 63, range 36 - 80 years) with Type 3C BPS/IC and 15 (13 women, two men, mean age at diagnosis 45, range 24 – 61 year) with nonulcer disease, who had received at least six instillations with DMSO were included. Bladder capacity at diagnosis under general anaesthesia was 568 ml and 863 ml for the two subtypes. Functional capacity at the beginning of treatment was 209 ml and 315 ml, respectively. The patients had been diagnosed according to the NIH-NIDDK criteria and were subdivided into the two different subtypes.

### **Paper II:**

Thirty-four patients with Type 3C BPS/IC and 13 patients with nonulcer BPS/IC who had undergone reconstructive surgery during a 25 year period were included. Patients diagnosed before 1987 were included if found to conform to the NIDDK criteria. There was a typical female predominance. Patients with nonulcer disease were significantly younger than patients with Type 3C BPS/IC, both at symptom onset and at surgery. Preoperative functional capacities and bladder capacities under general anaesthesia were significantly larger in nonulcer patients compared to those with Type 3C BPS/IC.

Patients were preoperatively assessed by interviews, visual analogue pain scales, 48h micturition diaries, urinalysis, intravenous urography, urethro-cystoscopy and bladder distension during anaesthesia including biopsies and in selected cases urodynamic evaluation.

<b>Initial surgery</b>	<b>Type 3C</b>	<b>Nonulcer</b>
Supratrigonal cystectomy and ileocystoplasty	20	3
Noncontinent uretero-entero-cutaneostomy	11	1
Continent cutaneous stoma	1	9
Caecocystoplasty	1	0
Continent orthotopic diversion	1	0

**Table 3** *Surgical methods*

### **Paper III/IV:**

The study included twelve patients, eight women and four men, diagnosed and treated between June 2003 and June 2009. All had undergone three consecutive complete transurethral resections,



the first one also being diagnostic. Bladder capacity at diagnosis under general anaesthesia was measured after distension to full capacity at 70 cm water. All patients fulfilled the NIH-NIDDK criteria<sup>154</sup> and the ESSIC BPS/IC Type 3C criteria; they had Hunner`s lesions and biopsy findings with inflammatory infiltrates, granulation tissue and detrusor mastocytosis. After the first TURB the patients were instructed to report symptom relapse. If so, they were scheduled for repeated TURB.

## **METHODOLOGICAL CONSIDERATIONS**

*All patients were diagnosed according to the NIH-NIDDK criteria and subdivided into the two different subtypes on the basis of clinical, endoscopic and histopathological criteria (Paper I -IV).*

### **Paper I:**

In order to assess the most prevalent side effects of DMSO instillation treatment, a score system was adopted with one point given for every side effect (fever, hematuria, shivering, nausea and urethral irritation) reported and zero point if no side effect was experienced. Sensation of urethral burning/pain subsiding within 24 hours was also given one point, whereas if lasting more than one day, two points were given. Side effects were evaluated after each instillation; hence, maximal score after one instillation was 6 and minimal score 0. The scores after each instillation was added up resulting in a maximal total score of 36 during one series including six instillations. From the total scores a median side effect score was calculated. Attention is to be drawn to the unfortunate fact that the sum resulting in the total score of 42, described in the published article, is wrong.

Six weekly instillations of 50 ml DMSO-solution, 500 mg dimethyl-sulfoxide per ml, were administered. A Lofric Ch 8 catheter or a Conveen Easi Ch 10 catheter was used.

Data were obtained by retrospectively surveying the clinical records. Evaluation included two micturition diaries, before as well as after the series, VAS of pain and registration of side effects after each instillation in every series. Three patients received only three instillations and one patient four instillations because of a marked aggravation of symptoms or failure to experience any symptom resolution. A follow-up telephone interview was conducted for patients who were successfully treated with DMSO and these patients were asked to fill in VAS and micturition diaries for two consecutive days.

### **Paper II:**

Data were retrospectively obtained by surveying the clinical records. Various surgical procedures were made; noncontinent ureteroenterocutaneostomy, supratrigonal cystectomy and ileocystoplasty, continent urinary diversion (Kock pouch), continent orthotopic diversion and caecocystoplasty, depending on the patient's age, health status, symptoms and to some extent also on when, during the 25 year period, the procedure was performed. The type of surgical procedure was dictated primarily by subtype classification. For patients with BPS/IC and normal bladder capacity, supravescical diversion procedures were chosen and primarily patient's age determined whether a continent or noncontinent type of diversion was to be performed. Five patients were excluded because they were lost from follow-up.

## Reconstructive surgery- surgical techniques

### *Supratrigonal cystectomy and ileocystoplasty/ Caecocystoplasty*

Via lower midline laparotomy incision the bladder is dissected free from peritoneum, while partially filled to facilitate the dissection. The bladder is incised and the ureteric orifices identified and catheterized for protection and for easier identification of the intramural portion of the urether. Subtotal resection of the bladder is then performed, leaving only the internal urethral meatus and both urethral orifices. A 40-cm segment of the ileum is isolated, approximately 30 to 40 cm from the ileocaecal valve. Alternatively, an ileocolic segment cystoplasty can be fashioned. The isolated bowel, on its mesentery, is then detubularized along its antemesenteric border, sutured and double-folded to a spherical shape and anastomosed to the trigone remnant.

### *Noncontinent uretero-entero-cutaneostomy*

A 15-25 cm length of ileum is chosen for a conduit, approximately 30 cm from the ileocecal valve, and removed from continuity with the bowel, maintaining the conduit's vascular pedicle. The ureters are identified and cut. Both ureters are mobilized, and as the conduit is classically brought out on the right side of the abdominal wall, the left ureter is passed below the mesentery of the descending colon to the right side of the abdomen. Both ureters are then anastomosed to the afferent end of the conduit and its efferent end is brought through the abdominal wall to form a cutaneous stoma.

### *Continent urinary diversion*

A 70 cm ileum segment is isolated approximately 50 cm proximal to the ileocecal valve. Approximately fifteen centimetres of the distal portion of the isolated loop are preserved for the outlet and continence nipple valve. The proximal fifteen centimetres of the segment are preserved for the construction of the afferent intestinal segment and the reflux nipple valve. The 40 cm-long segment in-between is detubularized antimesenterically and used for the construction of the reservoir.

### *Continent orthotopic diversion*

This technique is performed much like the one described above for continent urinary diversion, with the exception that the distal portion is anastomosed to the urethra.

## **Paper III/IV**

### *TURB*

Bladder capacity under general anaesthesia was measured after distension to full capacity at 70-80 centimetres of water. An arbitrary value of 250 ml was set as the upper limit for bladder contracture (Paper IV). The median time of improvement in months after each TURB was measured and the entire group of patients was thereafter dichotomized based on the median value of symptom amelioration, referred to as fair responders or short-term responders (Paper III). Complete TURB of all lesions and the adjacent zone of oedema reaction were performed using a low-pressure continuous irrigating resectoscope. Complete resections, at as low current intensity as possible, were made with care taken to include adjacent zone of post-distension oedema and obtain large strips to include half or more of the underlying detrusor muscle. In this way, prerequisites for obtaining sufficient material for histological examination were obtained.

### *Histological examination and immunohistochemistry*

The histological examinations were made on series of 4  $\mu\text{m}$  tissue sections and were cut from paraffin embedded bladder biopsies that were deparaffinised and stained with mouse monoclonal anti-human antibody against mast cell tryptase (Paper III) and smooth muscle cell actin (Paper IV). Counterstaining with Htx-Eo and Van Gieson was performed prior to dehydration and mounting with cover slips. The histologic specimens were examined and evaluated in a blinded fashion by two examiners including one specialized uropathologist.

Mast cells were counted at 100 x magnification. The mast cells were scored according to their location in the urothelium, lamina propria or detrusor musculature. Mast cells residing in the stroma were counted per square mm, using a grid. Three different areas in each resection were counted and a mean value was calculated. When possible, mast cells located in the detrusor were also counted by the same technique. The urothelial mast cells were counted using a line width of 1 mm (Paper III).

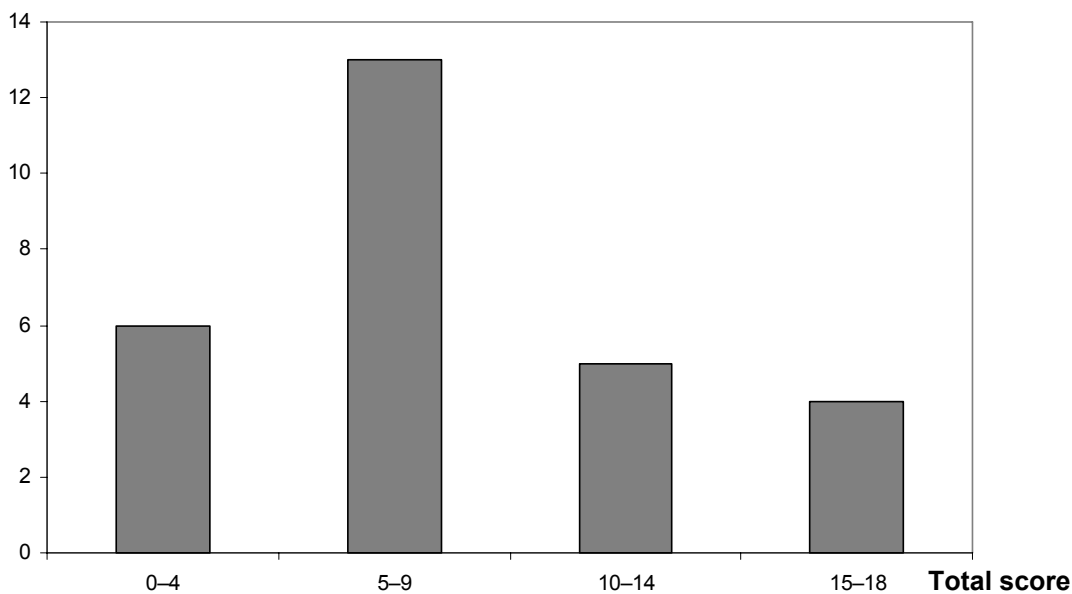
$\alpha$ -SMA-positive and  $\alpha$ -SMA-negative fibroblast-like cells were counted at 400 x magnification per 4x250  $\mu\text{m}$ , using a grid. All round cells, mast cells, endothelial cells and smooth muscle cells were avoided in the counting process. The  $\alpha$ -SMA-positive fibroblast-like cells were counted in the subepithelial compartment, in urothelial covered tissue, above the lamina muscularis mucosa, avoiding the most ulcerated areas (Paper IV).

## **RESULTS**

### **Paper I:**

The median side effect score after six instillations were 7 and 6, out of maximum 36, in patients with Type 3C BPS/IC and nonulcer BPS/IC, respectively. Side effects after instillations of DMSO were common, the most frequent being sensation of urethral irritation/pain in 48 % of the patients after the first instillation. For patients with Type 3C BPS/IC a significant difference could be seen when comparing experienced side effects during the first three instillations with the three following. When comparing patients, who responded well to treatment with those who did not, neither a difference in the character of side effects nor a relation of side effects to efficacy could be seen. With exception of one sepsis episode, no serious side effects or complications were noted. We were not able to demonstrate a difference in side effects between the two subtypes of BPS/IC.

**Patients**



**Fig 4** *Distribution of total side-effect scores for the six instillations.*

**Paper II:**

In 28 out of 34 patients with Type 3C BPS/IC did the initial surgical procedure result in complete symptom resolution. Of the remaining six patients, four could successfully be managed by a supplementary diversion procedure, cystectomy or transurethral resection of lesions in the trigonal remnant, respectively.

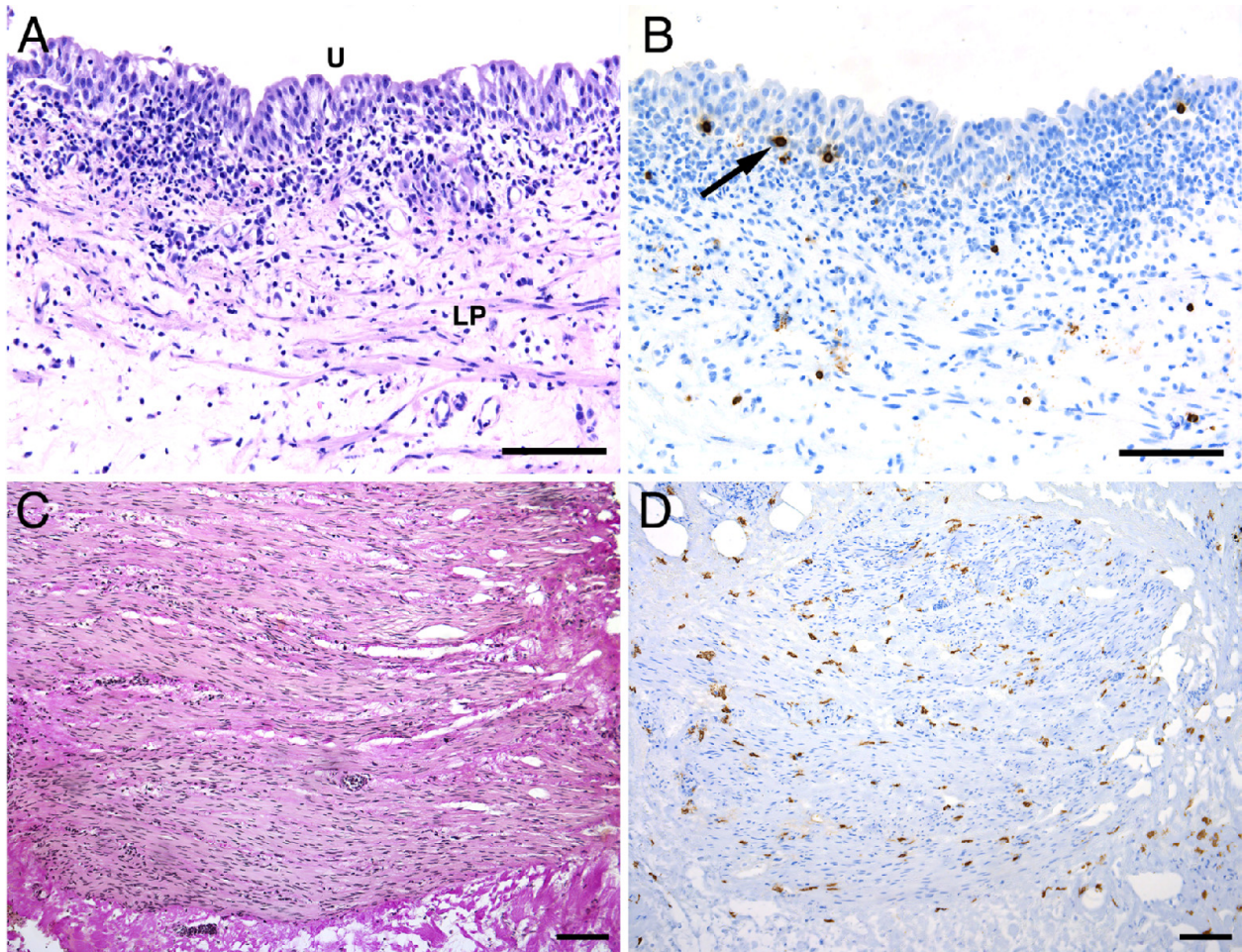
Only three of the 13 patients with nonulcer BPS/IC experienced symptom resolution after reconstructive surgery and two out of these required a supravescical diversion procedure.

Eight patients had a supplementary secondary simplex cystectomy in an attempt to treat persistent suprapubic pain, without improvement. Out of the 25 patients with initial ICP, continent orthotopic urinary diversion or caecocystoplasty, 13 required clean intermittent self-catheterization at various stages during follow-up.

Early intra- and postoperative complications were few. However, the need for reoperations in patients with nonulcer BPS/IC having undergone continent urinary diversion was high, mainly related to nipple valve problems. Widened ureteral orifices with vesicoureteral reflux seem very common following ICP, however not resulting in discernible clinical consequences. There was no finding of malignant change.

### Paper III:

The median time of improvement in months after each TURB was four, two and six and a half months, respectively. Although single patients responded well to treatment, in this limited series there was no homogeneous good responder group. Median mast cell density in the lamina propria was high.



**Fig 5** A and B: Adjacent sections of urinary bladder from patient with Type 3C BPS/IC. Intact urothelium (U) and inflammatory cells in lamina propria (LP) as demonstrated with staining by Hematoxylin and eosin (A). Occasional mast cells are seen within the urothelium (arrow) but more frequent in the lamina propria identified by tryptase immunohistochemical staining (B). Original magnification  $\times 200$ . Bar is  $100 \mu\text{m}$ . C and D: Detrusor muscle shows intrafascicular fibrosis, van Gieson (C). Frequent mast cells within the muscle fiber identified by tryptase immunohistochemical staining (D). Original magnification  $\times 100$ . Bar is  $100 \mu\text{m}$ .

No statistically significant correlation between mast cell density in the lamina propria and the duration of symptom could be demonstrated. After the third TURB, five of the 12 patients were offered major reconstructive surgery due to end-stage disease with a small contracted bladder, since a response to TURB could no longer be expected. Bladder reconstruction was performed in one case. There was a positive correlation between a high mast cell numbers in the urothelium at the third TURB and the risk of developing end-stage disease.

TURB 1				TURB 2			TURB 3		
Gender	MC dens	Duration	F/SR	MC dens	Duration	F/SR	MC dens	Duration	F/SR
m	68	0,5	SR	64	0,5	SR	83	5	SR
m	105	14	F	55	14	F	80	24	F
f	78	2	SR	94	1	SR	56	2	SR
f	77	4	F	88	1,5	SR	52	29	F
m	69	5	F	104	2	F	62	4	SR
m	80	12	F	68	3	F	55	2	SR
f	68	8	F	83	0,5	SR	75	13	F
f	48	1	SR	41	0	SR	47	12	F
f	90	14	F	78	36	F	71	6	SR
f	118	1	SR	134	2	F	79	3	SR
f	128	1,5	SR	33	11	F	107	32	F
f	161	4	F	96	6	F	51	7	F

**Table 4** Mast cell density and outcome after TURB. TURB 1,2 3= first, second and third TURB. MC dens=mast cell density, Duration=duration of symptom amelioration after TURB. F=fair responders. SR=short-term responders. m=male. f=female.



## Paper IV

Density of  $\alpha$ -SMA+/  $\alpha$ -SMA- fibroblast-like cells seemed constant and no statistically significant change in density with increasing number of TURB's could be seen, *see Table 5*.

However, when comparing distribution of  $\alpha$ -SMA+ fibroblast-like cells contra  $\alpha$ -SMA- fibroblast-like cells at each TURB, an overweight of  $\alpha$ -SMA + fibroblast-like cells compared to  $\alpha$ -SMA - fibroblast-like cells was identified statistically significant only in patients with normal bladder capacity and not in patients with end-stage disease.

	$\alpha$ -SMA+1	$\alpha$ -SMA-1	$\alpha$ -SMA+2	$\alpha$ -SMA-2	$\alpha$ -SMA+3	$\alpha$ -SMA-3	End-stage
M	18	18	5	12	3	6	X
M	8	14	19	15	11	3	
F	8	11	23	10	22	21	
F	19	2	23	26	38	12	
M	28	7	14	6	21	14	X
M	20	17	20	19	12	6	X
F	26	25	44	32	14	8	
F	69	15	7	8	12	20	
F	24	9	6	8	34	6	
F	10	16	11	22	31	13	X
F	36	4	33	16	19	6	
F	18	14	27	10	27	17	

**Table 5** Density of  $\alpha$ -SMA+ and  $\alpha$ -SMA- fibroblast-like cells (per  $mm^2$ ) at first ( $\alpha$ -SMA+1 and  $\alpha$ -SMA-1), second ( $\alpha$ -SMA+2 and  $\alpha$ -SMA-2) and third ( $\alpha$ -SMA+3 and  $\alpha$ -SMA-3) TURB. M= male, F= female. X= end-stage

## **DISCUSSION**

Several factors have limited progress in the understanding of BPS/IC, including lack of objective diagnostic criteria, unpredictable symptom fluctuation, and the variability of symptoms, objective findings and treatment outcomes. Furthermore, although a feline model has been used in some studies<sup>155-157</sup> no ideal animal model mimics the evaluation of symptoms in humans, limiting our understanding of pathophysiology. In recent publications, the need for subdivision of BPS/IC has been increasingly recognized<sup>81,86,158-161</sup>, since the two subtypes have shown to have different histopathological, immunological and neurobiological features<sup>55, 60, 75, 162-168</sup>.

DMSO is a standard treatment of BPS/IC, one of few to stand the test of time. The issue of side-effects has only casually been addressed in previous reports on intravesical instillation therapy with DMSO. In Paper I we could report that side-effects after a single 6-week instillation series were common but fairly mild, except from one sepsis episode. It is usual for patients with Type 3C and nonulcer BPS/IC to diverge in response to different therapies<sup>141, 145, 153, 169, 170</sup>. Interestingly, a significant difference in side-effects during the first three installations compared to the following three instillations could be seen in patients with Type 3C BPS/IC but not in nonulcer BPS patients. An explanation could be that since patients with Type 3C BPS/IC often have severely damaged urothelium the solution reaches underlying nerves in very high concentrations. The mechanisms by which DMSO exerts a favourable effect in BPS/IC patients remain unclear but some of the beneficial effects of DMSO might be through modulation of sensory nerves with stimulation of bladder afferent pathways and nitric oxide (NO) release from afferent neurons<sup>171</sup>. In favour of this hypothesis is the finding that treatment with DMSO does not result in any histological improvement<sup>172</sup>. Somewhat in conflict with this hypothesis, though, is the fact that among the seven patients reporting symptom amelioration, either after a single 6-week instillation or during maintenance treatment at follow-up, no overrepresentation of patients with Type 3C BPS/IC could be seen. However, the number of patients included in the study was too small to draw conclusions about subtypes with a reasonable degree of certainty. When studying the functional capacity, frequency and visual analogue scale (VAS) at baseline and follow-up in the patients who had only received DMSO instillations or were on maintenance treatment, no convincing pattern concerning the objective data could be seen to support the subjective report by the patient on improvement. Speculatively, some of these patients represent examples of development of successful coping mechanisms. In other studies, overall relapse rate ranges from 35 to 40 per cent, with an average follow-up period of 1-2 years<sup>105, 173-176</sup>.

Intravesical application of medications establishes high concentrations at the target site with few systemic side effects. However, the need for intermittent catheterization, which is often painful in BPS patients, the cost and the potential risk of infection are drawbacks. There are reports of successful treatment with intravesical lidocaine<sup>177, 178</sup>, but an obvious disadvantage with this method is that very frequent instillations are needed. Frequent self-catheterization usually is so painful in this category of patients that this mode of treatment would be too difficult to accept. Like DMSO instillations, treatment with intravesical PPS seem to be possible with maintenance treatment as well. In one study including 10 patients receiving PPS and placebo respectively, at three months, four and two patients gained symptomatic relief. However, at 18 months, symptoms were relieved in eight patients while still receiving PPS instillations and in four without treatment<sup>114</sup>. However, since the initial effect is quite modest some problems with compliance might be expected. Instillations with BCG has been reported to be tolerated, just like DMSO, but unfortunately found to be inefficient as well as potentially harmful<sup>110, 113</sup>. DMSO is considered a standard treatment, possibly also first-line treatment, for patients with nonulcer BPS/IC and bearing that in mind, it is reassuring to find good safety and tolerability for this kind of treatment. Admittedly, a limitation of the study is that the adopted scoring system, used to evaluate side-effects, is not a validated one, but the strength is the originality, since side effects have not specifically been studied before.

In BPS/IC, a group of patients always remain in whom all forms of therapy fail and where the disease is severe enough to warrant a major operation. Oravisto<sup>4</sup> estimated that 1 of every 10 patients with interstitial cystitis has a severe form of the disease, an estimation later suggested by others<sup>179</sup>. Paper II is one of the hitherto largest studies, with longest follow-up, for patients with BPS/IC subjected to reconstructive surgery for refractory symptoms. The conclusions drawn from the study is that reconstructive surgery in patients with BPS/IC renders an eminent chance of symptom improvement in patients with end-stage Type 3C BPS/IC. To take into consideration, though, is the fact that, although BPS/IC is severely detrimental to quality of life, it has no direct mortality while major surgery includes a risk that is not negligible of morbidity and mortality. A decision on surgical reconstruction should therefore not be embarked upon without due consideration. Early intra- and postoperative complications were few. However, the complication rate in the group of nonulcer patients in our study was high, mainly due to nipple valve related problems. Several previous studies have shown that patients with BPS/IC or other benign functional or inflammatory disease have significantly worse outcomes after reconstructive surgery than patients with malignant disease, spinal cord injury or malformation<sup>180, 181</sup>.

Concerning the surgical approach to the bladder, there is nearly general agreement that at least the supratrigonal part of the bladder should be resected to avoid unfavourable outcomes. Additionally, some perform a subtrigonal resection as well<sup>182, 183</sup>. The advantage of a trigone-preserving procedure is that the ureteral orifices are left in situ, avoiding complications associated with ureteral reimplantation. Surgical failure to improve the symptoms of a patient with BPS/IC is thought to be due to inflammation in the trigone remnant<sup>184-186</sup>. Although this may be true, we do not routinely perform concomitant cystectomy. We believe this is an unusual complication in patients with Type 3C BPS/IC, affecting only two patients in the study, both with excellent outcome after TURB of the lesion and cystectomy, respectively. In contrast, eight patients with nonulcer BPS unsuccessfully underwent supplementary secondary simplex cystectomy in an attempt to overcome persistent suprapubic pain.

There are far more extensive approaches to deal with postoperative persisting pain, maybe most radically shown by Baskin et al<sup>187</sup>, performing hysterectomy, bilateral oophorectomy, presacral neurectomy and total cystectomy with ileal loop urinary diversion in a 19-year-old woman, with resistant pain. Other results can be more difficult to understand in terms of complications, with reports on 40 per cent experiencing mild degree of dyspareunia after cystectomy including resection of the urethra proximal to the pubourethral ligaments, but surprisingly without disturbance of sexual life<sup>188</sup>.

It is often stated, and quite universally accepted, that surgical therapy of BPS/IC never should be considered as first-line therapy and the importance of excluding possible mimicking conditions is emphasised. However, the importance of undertaking subtyping of the patients has not been equally accepted and not performed as consistently. Therefore, some of the previous results reported from reconstructive surgery on BPS/IC patients may be misguidedly discouraging. In the present series 82 per cent of the patients with Type 3C BPS/IC reported complete symptom resolution after the initial surgery and 94 per cent after supplementary surgery. The remaining 6 per cent were represented by late failures due to comorbidity such as cerebrovascular disease. These results are in accordance with earlier studies on caecocystoplasty for patients with Type 3C BPS/IC<sup>179, 189-191</sup>.

Unfortunately, only 8 per cent of the patients with nonulcer BPS experienced symptom resolution after major reconstructive surgery, increasing to 23% if a supplementary supravescical diversion procedure was performed. This is at variance with a report on 100 per cent successful outcome, after bladder substitution by ileal neobladder, in 35 patients diagnosed with intractable

BPS/IC but with no Hunner`s lesion on cystoscopy<sup>188</sup>. Whitmore et al<sup>192</sup> reported 80 per cent (12/15) success rate, with success defined as subjective improvement with intact reconstruction, but not mentioning subclassification. As a step in patient evaluation before cystoplasty, cystoscopy is often advocated, but primarily to exclude carcinoma in situ in patients with irritative bladder symptoms believed to be caused by interstitial cystitis<sup>193</sup>. Some argue that patients with improvement after surgery are more likely to have had a small bladder capacity under anaesthesia and a bloody effluent after hydrodistension preoperatively, and that the presence of glomerulations or ulcers is less predictive<sup>194</sup>. However, if only patients with Type 3C BPS/IC had been considered for reconstructive surgery, most likely the possibility for a good outcome had been optimized. Inadequate diagnostics accounts for the great part of conflicting results reported in the literature.

Our study compared results of different types of surgical procedures, performed for two different groups of patients, and attributing the different surgical outcome solely to the two groups of patients differing in their BPS/IC subtypes. Presentation of consistent pre/postoperative data, including pain scores, would of course have given the study a more robust design instead of just stating ‘Residual pain’, ‘Residual frequency’ or ‘Good’, but unfortunately this information quite often was missing in this study covering a quarter of a century. My opinion, though, is that due to the fact that BPS/IC is a benign disorder and reconstructive surgery is a major operation, a statistically significant decrease in VAS from e.g. VAS 10 to VAS 6 might still be of questionable relevance to the patient. Thus, the somewhat simplistic grading of improvement used may capture the entire outcome as good as, or maybe even better, than such a scale.

No finding of malignant transformation was noted in the patients subjected to ileocystoplasty. As for diversionary procedures, the potential risk of developing carcinoma in the defunctionalized bladder is frequently discussed, but only five cases were found after a comprehensive review of the literature by Garvin et al<sup>195</sup>. Quite in accordance with previous reports<sup>152, 153, 196</sup>, a significant number of patients (13/25) required clean intermittent self-catheterization at various stages during follow-up.

Today the urothelium is no longer looked upon as just an inert barrier but rather as a very active component of the bladder wall, that exhibits specialized sensory and signalling properties. Some of the symptoms experienced by patients with BPS/IC may be caused by vasoactive and inflammatory mediators secreted by mast cells. Tryptase, which is increased in the urine of

BPS/IC, causes microvascular leakage and stimulation of protease-activated receptors (PARs), resulting in inflammation and submucosal neuronal hyperexcitability<sup>197, 198</sup>. Another mast cell mediator with vasodilatory properties is vascular endothelial growth factor (VEGF), which is overexpressed in bladders, and may add to the hypervascularity and glomerulations characteristic of BPS/IC<sup>199</sup>. In paper III mast cell density in the lamina propria was assessed for possible correlation with duration of symptom amelioration after TURB. Our hypothesis was that, since mast cells by tradition have been thought to reflect intensity and grade of disease in patients with Type 3C BPS/IC, patients with a high mast cell density would respond more favourably to TURB.

Simmons<sup>200</sup> was the first to report that the number of mast cells in bladder tissue was increased in BPS/IC patients. Subsequently, it was reported that the increase in the number of mast cells in the bladder muscularis had diagnostic significance<sup>68, 71, 201, 202</sup>. However, it became clear that the number of mast cells varied depending on differences in staining methods. Some reports<sup>69, 203</sup> indicate that prolonged toluidine blue staining tends to cause an increase in the number of detected mast cells in lamina propria and detrusor muscle and this tendency is particularly apparent in Type 3C BPS/IC. Other reports indicate that the number of mast cells is increased in the lamina propria and detrusor in both Type 3C BPS/IC and nonulcer BPS/IC<sup>71</sup>. Meanwhile, some report that no significant difference is observed in the number of mast cells between nonulcer BPS/IC and control tissue<sup>164</sup>. Tryptase immunocytochemistry is the most accurate technique for histological examination of human mast cells, identifying a unique protease present in both types of human mast cells. When this technique was used a 6- to 10-fold increase in mast cells in classic IC and a 2-fold increase in patients with nonulcer IC, compared with controls, were seen<sup>75</sup>.

In the literature, the significance of the association between the clinical presentation of BPS/IC and increased numbers of mast cells is conflicting. In a previous study by Holm-Bentzen et al<sup>183</sup> no variation in severity of symptoms ( pain, dysuria, frequency and nocturia) could be seen in patients with or without detrusor mastocytosis, defined as 28 mast cells per mm<sup>2</sup>. However, patients with mastocytosis had hematuria more often and had a significantly reduced bladder capacity, indicating that it concerned patients with Type 3C BPS/IC. Lynes et al reported on lack of correlation between mast cell density and severity of clinical symptoms, but symptoms may be as severe in the two main types of BPS/IC. However, mast cell density did correlate with degree of submucosal inflammation<sup>70</sup>. Furthermore, neither mast cell density, nor the histological state

of the trigone have been found to be reliable predictors of outcome after supratrigonal cystectomy<sup>152</sup>. The only significant correlation between the clinical symptoms and pathological findings reported to date has been that of nocturia and an increased number of tryptase-positive urothelial mast cells<sup>73</sup>. Rudick et al<sup>76</sup> induced a neurogenic cystitis associated with lamina propria mast cell accumulation by infecting mice with pseudorabies virus (PRV). They reported that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and tumor necrosis factor, TNF, respectively. Pelvic pain developed normally in TNF- and TNF receptor-deficient mice, while bladder pathophysiology was abrogated. Conversely, genetic or pharmacologic disruption of histamine receptor, H1R or H2R, attenuated pelvic pain without altering pathophysiology. Their results suggest that mast cells contribute to both pain and bladder inflammation and pathophysiology through the divergent actions of histamine and TNF, respectively.

Outcomes after TURB in Paper III, with median durations of symptom remission of 4, 2 and 6.5 months, were far less convincing than in previously reported series<sup>18, 145, 146</sup>. This may be due to a sample size bias. However, in the hitherto largest series on patients with Hunner's lesions treated with TURB<sup>18</sup> four groups emerged: long-term good responders, short-term good responders, patients with slow (>2 years) progression to end stage disease with contracted bladder and patients with rapid (<2 years) progression to end-stage disease. In the present series 42 per cent of the patients would be allocated to the latter two groups, compared with 21 per cent of the patients in the study by Pecker et al<sup>18</sup> and, speculatively, this may explain the difference in outcome.

It has been suggested that mast cells counts  $>20$  cells/mm<sup>2</sup> should be defined as mastocytosis<sup>88</sup> and that this definition in bladder muscle have an 88 per cent diagnostic specificity and a 95 per cent diagnostic sensitivity for IC<sup>202</sup>. We reported on a median mast cell density in the lamina propria at the first, second and third TURB of 90, 78 and 68/mm<sup>2</sup>, respectively. No statistically significant correlation between mast cell density in the lamina propria and duration of symptom amelioration could be seen after the first, second or third TURB, and this was also true when correlating duration of symptom remission with mast cell density in other tissue compartments. The positive correlation between a high mast cell number in the urothelium at the third TURB and the risk of developing end-stage disease was surprising, since it has previously been suggested that patients with end stage disease display very few inflammatory signs on histopathological examination<sup>153</sup>. In summary, our hypothesis that mast cell density could be a predictor of clinical

outcome of TURB, was discarded. Our results suggest that inflammation caused by mast cells may not be directly associated with the grade of symptoms, as has earlier been thought, but mast cells are still an important diagnostic parameter.

In patients diagnosed with BPS/IC, presenting with incapacitating urinary frequency and nocturia, detrusor fibrosis can be seen in bladder biopsy specimens. This is a finding significantly associated with failure of standard urological therapy, resulting in a more intense treatment<sup>204</sup>. As mentioned before, patients with Type 3C BPS/IC seem to develop fibrosis in different extent and with varying time<sup>18</sup>. To date, not much research about bladder detrusor fibrosis has been undertaken and the cellular mechanisms of inflammation in BPS/IC and the processes leading to detrusor fibrosis are not yet understood. Speculatively, myofibroblasts might have a role in the evolution towards bladder contracture. The development of bladder contracture is no doubt an intrinsic event as a result of chronic inflammation. Whether repeated TURB may enhance the process leading to bladder contracture is an open question. In the short term, increase of bladder capacity has been registered<sup>123</sup>, paralleled by successful outcome after TURB, possibly due to the removal of intramural nerve endings engaged by the inflammatory process<sup>18</sup>. Since patients treated with TURB often need repeated resections, the possibility that treatment might enhance the process towards end-stage disease can not be excluded. In Paper IV an attempt to explore these hypotheses was made. The density of  $\alpha$ -SMA positive and  $\alpha$ -SMA negative fibroblast-like cells in patients recently diagnosed with Type 3C BPS/IC and the changes of density of these cells with repeated TURB were examined. No statistically significant increase or decrease in  $\alpha$ -SMA positive and  $\alpha$ -SMA negative fibroblast-like cells could be seen when comparing density of both types of cells with increased number of TURB, suggesting that myofibroblast activation might be one factor of importance in the development towards bladder contracture, independent of external influence like TURB.

Chronic inflammation has been related to end-organ failure due to fibrosis in a variety of organs<sup>205-208</sup>. In some inflammatory diseases, fibrosis is related to YKL-40. YKL-40 is a 40kDa heparin-, chitin- and collagen-binding, phylogenetically highly conserved glycoprotein<sup>209</sup>, promoting growth of fibroblast cell lines through activation of MAP kinase and PI3K signalling pathways propagating mitogenic signals<sup>210</sup>. Excessive production of YKL-40, through binding to and modulating collagen formation, may cause extracellular matrix accumulation with tissue fibrosis<sup>211</sup>. Recent studies have shown a correlation between the mammalian glycoprotein YKL-



40 and fibrosis in diseases such as liver fibrosis<sup>212-214</sup>, rheumatoid arthritis<sup>215-217</sup>, atherosclerosis<sup>218, 219</sup>, asthma<sup>220</sup>, and chronic obstructive lung disease<sup>221</sup>. In a study by Richter et al<sup>222</sup> detrusor fibrosis was significantly associated with numbers of YKL-40-positive cells and mast cells. A significant inverse correlation was seen between bladder capacity and number of YKL-40-positive cells and mast cells. However, no significant correlation between clinico-pathological parameters (nocturia, mucosal bleeding and treatment intensity) and detected cell numbers or concentrations of YKL-40 in serum and urine were seen.

A previous study has reported mast cell involvement, showing that mast cell chymase seems to stimulate collagen synthesis by fibroblasts in neurogenic bladder fibrosis<sup>223</sup>. Also, a tryptase present in large amounts in MC<sub>TC</sub> is fibroblast growth factor, promoting proliferation of fibroblasts and fibrosis. The involvement of tryptase in progression to atrophic bladder is also proposed in view of the inverse relationship between the number of MC<sub>TC</sub> in the muscularis and the bladder capacity as an indication of the degree of IC progress. Furthermore, it has been claimed that the chymase present in MC<sub>TC</sub> produces stem cell proliferation factors in the soluble form from the mucosa of stroma cells adjacent to mast cells and accumulates in mast cells in certain regions, promoting production, proliferation and differentiation of mast cells<sup>224, 225</sup>. However, as mentioned before, contradictory results have been reported in the numerous studies on the value of mast cell counts in biopsies of patients with BPS/IC. For example, some studies have reported a significant increase in detrusor mast cell counts compared to controls<sup>68,71, 202, 204, 226</sup>, while another has not<sup>164</sup>.

The  $\alpha$ -SMA positive fibroblast-like cells were counted in tissue covered by urothelium in the subepithelial compartment, above the lamina muscularis mucosa, avoiding the most ulcerated areas. The reason for this was to avoid any activated myofibroblast in ulcers, most probably being present as a normal component during the healing process. In that way cells generally related to the disease process should be more reliably identified. Still, since there is currently no specific cellular marker and considerable variation in reported findings, confirmation of the presence of this cell type requires a detailed survey of multiple features, particularly morphology, phenotype and ultrastructure<sup>227</sup>. Examination in this series was done only with light microscopic techniques; we have therefore chosen to call the cells  $\alpha$ -SMA positive and  $\alpha$ -SMA negative fibroblast-like cells. Combination of light and electron microscopic techniques to ascertain the cellular phenotype would more likely have ascertained the results of this study, but is arduous and should be a step in future research on the subject.

The upper limit for anaesthetic bladder capacity in Paper IV of 250 ml is arbitrary and it has to be noted that there is no generally accepted definition of end-stage Type 3C BPS/IC. At this stage the patients often primarily complain of intolerable urinary frequency while there is little pain. Using the suggested dividing line there was an interesting finding. In the group of eight patients, apparently at an earlier stage of the disease, a statistically significant overweight of  $\alpha$ -SMA positive fibroblast-like cells at the third TURB was found. This may lead to the assumption that patients with a substantial time of illness are the only ones to present significant myofibroblast overweight while no such findings seemed to be associated with earlier TURB episodes or established bladder contracture.

The present pilot study thus suggests that myofibroblast activation might be one factor of importance in the development towards bladder contracture, independent of external influence like TURB. This is a first attempt to take the role of myofibroblastic activity in BPS/IC, complicated by bladder contracture, into consideration. Despite the limited size of the material, the lack of controls and the need for more sophisticated histological techniques, like electron microscopy, we think that the results of this pilot study are of sufficient interest to warrant more extensive studies.

## **CONCLUSIONS**

Intravesical instillation with DMSO appears to be associated with a reasonably degree of discomfort, especially considering the potential benefit of the treatment in both subtypes of BPS/IC (Paper I). For patients with Type 3C BPS/IC, TURB seems to be a more efficacious treatment option. However, mast cell density does not appear to correlate with duration of symptom amelioration after complete transurethral resection of Hunner`s lesions, neither in the lamina propria nor in the urothelium or the detrusor (Paper III).

TURB does not seem to result in enhanced progress towards end-stage disease. The findings of an overweight of  $\alpha$ -SMA positive fibroblast-like cells in patients with signs of active disease, expressed by repeated TURB`s, might represent a time dependent factor of myofibroblast activation eventually resulting in a contracted bladder (Paper IV).

When conventional therapies no longer offer any symptom amelioration, but the patient present with bladder contracture and/or intolerable symptoms, reconstructive surgery can be an appropriate last resort, but only in patients with Type 3C BPS/IC. The most important determinant in the decision to embark upon major reconstructive surgery is the assessment of subtype and stage of the disease (Paper II).

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