

Chapter 4

Bladder Pain Syndrome/Interstitial Cystitis: A Large but Heterogeneous Field in Functional Urology

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Introduction and Definitions

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a distressing, chronic bladder disorder comprising symptoms of pain, pressure or discomfort perceived to be related to the bladder which is diagnosed primarily in women and of unknown aetiology, the diagnosis to be set after exclusion of many possible different confusable diseases. This debilitating condition was first identified in the nineteenth century, but it was not until 100 years later that an official definition, constructed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), became accepted. However, this definition has been debated because around 60 % of patients who were clinically diagnosed with interstitial cystitis (IC) were excluded when applying the NIDDK criteria. A further fundamental problem is that treatment requirements differ importantly between BPS/IC phenotypes. So far, the majority of available studies did not take important distinctions into account, limiting the utility of clinical research in BPS.

Due to increasing problems caused by international confusion as to definitions, there has been much activity during the last decade trying to harmonise terminology and the understanding of BPS/IC on the whole. The European Society for the Study of IC (ESSIC) has proposed a definition of “pelvic pain, pressure or discomfort perceived to be related to the urinary bladder”. The American Urological Association (AUA) guidelines for BPS/IC management used “an unpleasant sensation (pain,

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pressure, discomfort) perceived to be related to the bladder". The European Association of Urology (EAU) guidelines on chronic pelvic pain stated that BPS/IC should be diagnosed on the basis of symptoms of pain associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time urinary frequency. The international Continence Society (ICS) defined painful bladder syndrome/interstitial cystitis as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology. ICS reserves the diagnosis of IC to patients with "typical cystoscopic and histological features".

Epidemiology

Although BPS/IC mostly affects women, it can occur in people of any age, sex or race. Due to the controversies regarding both the definition and the diagnosis of BPS/IC, epidemiological studies have been in many aspects limited, based mainly on symptoms, and the symptoms have been interpreted and evaluated in various ways. Consequently, available studies are difficult to compare, and the reported prevalence ranges widely across different studies, definitions and populations. The Bladder Pain Syndrome Committee of the International Consultation on Incontinence has recently estimated the prevalence of BPS/IC to be 300/100,000 women and 30–60/100,000 men. BPS/IC seems to be more frequent in first-degree relatives of patients with interstitial cystitis.

Aetiology

The aetiology of BPS/IC is still unknown. Different possible aetiologies have been proposed although most of them without evidence good enough to be accepted as a general explanation.

Infection

No study has been able to demonstrate a relation between BPS/IC and urinary infection, neither Gram-negative or Gram-positive microorganism nor increase of urinary IgA and IgG. However, some reports have suggested a possible relation with urinary tract infection in a minority of patients. Other investigators have found absence of bacterial and viral DNA in bladder biopsies of patients with BPS/IC, while a possible role of nanobacteria has been suggested as a possible aetiology. In an intriguing recent congress report, it was stated that biofilm-forming *Corynebacterium* sp., identified in biopsy material but not in urine cultures, may be

associated with the occurrence of BPS/IC and especially the Hunner type of disease. In any case at present, although still unlikely, it is not possible to rule out a relation between infection and development of this disorder.

Mast Cell Activation

Mast cells are thought to play a role in the aetiology of BPS/IC. These are multi-functional immune cells that release a number of inflammatory mediators such as histamine, leukotrienes, serotonin and cytokines, which might be responsible for symptoms and findings in BPS/IC such as pain, frequency, oedema, fibrosis and angiogenesis in the lamina propria. Mast cells count has been observed to be tenfold higher in the bladder of patients with classic IC. In non-Hunner BPS/IC patients, the mast cell count is normal or slightly increased.

Neuronal Mechanisms

Neurogenic inflammation might be the result of abnormal release of neuropeptides by activation of sensory and sympathetic nerves. Such abnormal release is thought to promote mast cell activation and alteration of central nervous system processing of afferent stimuli as suggested in several reports. Furthermore, an increase of tyrosine hydroxylase immunoreactivity in bladder tissue of BPS/IC patients, compared with controls, has been reported as a sign of general increase of sympathetic flow raising the possibility of a neurogenic aetiology and/or pathogenesis.

Bladder Autoimmune Response

An autoimmune aetiology has been suggested since a number of autoantibodies have been found in patients with BPS/IC. Recently, it has been observed that the classic type of BPS/IC (type 3C) is characterised by a local adaptive response with elevated urinary antibody concentrations suggesting that quantification of urinary immunoglobulin levels might be used for a noninvasive diagnosis of the 3C type of BPS/IC.

Defective Bladder Epithelium

Although today it is well known that the bladder urothelium has a rich functional and metabolic activity, it is also a barrier to prevent low and high molecular weight solutes in the urine from leaking into the bladder interstitium. A dense layer of

glycosaminoglycans covering the cell layer composes this barrier and the intercellular junctions which can be compromised, allowing substances in urine to penetrate resulting in symptoms like in BPS/IC, the concept of lower urinary tract dysfunctional epithelium. Several studies have shown a defective glycosaminoglycan layer in patients with BPS/IC due to leaky epithelium allowing the transit of solutes to the interstitium. When this happens, submucosal nerves might be accessible to noxious agents in the urine that might explain symptoms in these patients as observed with scanning electron microscopy. Furthermore, it has been observed that Tamm-Horsfall protein is qualitatively different in patients with BPS/IC compared to controls, suggesting that an alteration of this protein may also be involved.

Antiproliferative Factor (APF)

Antiproliferative factor is a small glycoprotein made specifically by bladder cells in patients with BPS/IC that induces changes in expression of certain epithelial cell proteins and profoundly inhibits cell growth. APF has been identified in 86 % of patients with BPS, 12 % of patients with cystitis and 8 % of controls. The measurement of urine antiproliferative activity may be a useful noninvasive means for diagnosis of BPS/IC. APF has been shown to inhibit heparin-binding epidermal growth factor-like growth hormone factor (HB-EGF) release from the urothelium. It has been reported that this inhibition can be reversed by bladder hydrodistension.

Pathology

Although histological findings may be consistent with the diagnosis on BPS/IC, there is no histology pathognomonic for the entire spectrum of disorders. There is currently consensus that the role of histopathology in the diagnosis of BPS/IC is primarily to exclude other possible diagnosis. Several entities including carcinoma in situ of the bladder, eosinophilic cystitis, tuberculosis cystitis and some other diseases with specific histological findings must be ruled out. In patients with the Hunner type of IC (type 3C according to the ESSIC terminology), a number of characteristic findings are found though, like vacuolisation and urothelial detachment, perineural cell infiltrates, lymphocyte and plasma cell infiltrates and involvement of deeper layers of the bladder wall as well as a special mast cell response, including two distinct mast cell populations and a migratory capacity of cells. When trying to relate such findings to the entire BPS population, they will turn out to be unreliable due to the great variation of phenotypes among BPS/IC patients. A matter of concern is the report of variation of findings even among biopsies taken from the same patient over time. In this context, an issue of practical importance is noteworthy, that is, that the cooperation with a devoted pathologist with experience in

this particular field is a prerequisite for reliable reports. There have been lack of correlation between histological and cystoscopic findings when it comes to glomerulations, bleeding, mucosal tears and bladder capacity; completely normal biopsies may be found in patients with BPS who do not have Hunner lesions. Investigation with electron microscopy also failed to identify pathognomonic data. At this stage, characteristic and uniform findings have been identified in the classic type of IC only.

Diagnosis

As an analysis of data from the Interstitial Cystitis Database (ICDB) indicated that >60 % of BPS/IC cases may be missed when the NIDDK criteria are strictly applied, so the current diagnostic approach has rather been based on symptoms and exclusion of those painful conditions that resemble the disorder but have a different identifiable cause. Suspicion can be supported by cystoscopic and biopsy findings, including inflammation, Hunner lesions, glomerulations or general oedema. Nevertheless, in many non-Hunner patients, neither histological findings nor glomerulations or other lesions are found in severely symptomatic patients who may show a completely normal cystoscopy and/or biopsy. New means of assessment/diagnosis are needed.

Medical History

A detailed medical history is of paramount importance. A very thorough questioning on the localisation of pain, its possible relation to bladder filling and an explicit description of pain generators should be obtained. There should be special attention to previous pelvic surgery, urinary tract infections, other urological diseases or sexually transmitted diseases, any autoimmune disease, any other chronic pain condition or disease (like irritable bowel syndrome, vulvar pain syndrome, etc.), previous pelvic radiation treatment and chemotherapy.

Symptoms of BPS/IC

BPS/IC symptoms are urgency, frequency and/or pain quite often associated with dyspareunia. Some patients have only pain, while others have pain, urgency and frequency in various combinations. The overactive bladder syndrome (OAB) and BPS/IC share urgency as a common symptom. It should be noted that in OAB patients, urgency is linked to a fear of incontinence while in BPS/IC urgency is related to fear of pain.

Symptoms questionnaires have been found helpful in obtaining a complete picture of the patient's symptoms. The O'Leary-Sant Interstitial Cystitis Symptoms Index (ICSI) and Interstitial Cystitis Problem Index have demonstrated an excellent ability to discriminate characteristics from patients and controls. The Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) is another useful questionnaire that gives equal attention to pelvic pain, urinary urgency/frequency and symptoms associated with sexual intercourse. The PUF questionnaire correlates well with the results of the intravesical potassium sensitivity test, which is positive in some 80 % of patients with BPS/IC. An alternative questionnaire is the University of Wisconsin Interstitial cystitis scale (UW-IC scale).

A frequency/volume chart is extremely useful to determine voided volume, frequency and urgency episodes as recommended by the International Consultation on Incontinence.

Physical Examination

Physical examination should include an assessment of the pelvic floor in order to rule out pelvic floor dysfunction (PFD), which might be caused by BPS/IC. This is carried out through bimanual examination in women and rectal examination in men. The strength of the pelvic floor and the capability to contract and relax the sphincter should be taken into account, as PFD is not uncommon in highly symptomatic BPS/IC patients. In some women with BPS/IC, a bimanual examination might trigger pain at the bladder base or urethra, while digital rectal examination in men might be painful often leading to the diagnosis of chronic prostatitis.

In the more complex case, a very thorough clinical assessment has to be performed: a detailed history, scrutinising previous medical information including imaging examinations, neurologic examination especially of the lumbosacral plexus, when needed assisted by electrophysiologic examinations, testing of mechanosensitivity of various relevant areas and a detailed assessment of the musculoskeletal system. Thus, sometimes a very detailed examination is required before treatment can be contemplated.

Cystoscopy and Hydrodistention

Cystoscopy under anaesthesia is mandatory for the complete investigation of BPS/IC patients to identify lesions, with special attention to the presence or absence of Hunner lesions; adequate distention is required to identify such lesions with sufficient certainty. Plain cystoscopy is still a useful first step to examine the bladder and urethral mucosa and urethral calibre, to identify suspect lesions and to determine the degree of local tenderness of the bladder and/or urethra. Tenderness or increased external and internal genitalia sensations and/or tenderness of the various components of the pelvic floor (including trigger points) are also noted. A BPS/IC patient

can tolerate filling with only a limited volume in their unanaesthetised bladder, irrespective of the true bladder capacity during anaesthesia. Confusable diseases are excluded. Submucosal petechial bleedings, so-called glomerulations, seen after decompression of the previously distended bladder, have until recently been regarded as one of the endoscopic hallmarks of the disease. Current data is however casting severe doubt on the diagnostic usefulness of this finding.

The typical Hunner lesion is a circumscribed, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. It is not a true ulcer but rather a very vulnerable, inflamed area. On further bladder distension, this site ruptures (Fig. 4.1), with petechial haemorrhage from the lesion and the mucosal margins in a waterfall manner and with a central vulnus provoked by bladder wall stretch. The denomination Hunner ulcer is therefore incorrect, Hunner lesion to be the preferred term. A quite characteristic finding at the second filling of the bladder in a patient with this classic type of IC lesion is a varying degree of oedema, sometimes with peripheral extension. Diagnostic hydrodistention should be performed in a standard manner at a pressure of 80 cm H₂O above the level of the patient's bladder. Irrigating fluid is allowed to run into the bladder until it stops spontaneously at capacity, as observed when checking the dripping chamber of the fluid reservoir. This volume is then held for 2–3 min with any leakage around the cystoscope sheath controlled by urethral compression. The volume and the degree of bleeding into the bladder fluid are noted when evacuating the bladder. The bladder is refilled to approximately 20–50 % of capacity and again inspected for lesions and haemorrhages, which will not be conspicuous until the bladder is filled for a second time. The anaesthetic bladder capacity is a parameter of importance, since a reduced capacity together with other characteristics is a further indication of classic IC as being a destructive inflammation that can result in bladder contracture at end stage.

Over the years, controversy has developed as to the prevalence and even the actual existence of the Hunner lesion and some urologists maintain that they are rare, or do not exist, and the fact that they rarely detect them confirms this false impression. The distribution varies from 5 to 50 % of cases with BPS in various populations, centres and series. Detection is certainly a matter of attention and training though, and a rigorous routine increases detection. Supplementary techniques might be helpful to increase detection rate, like the narrow band imaging method.

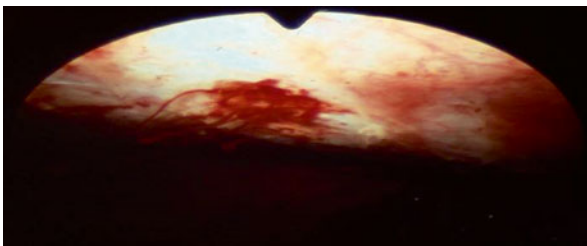


Fig. 4.1 Classic interstitial cystitis with Hunner lesion (bladder pain syndrome 3C), distension during anaesthesia provoking the lesion to split with petechial bleeding in a waterfall manner from the lesion site and the mucosal margins

It is important that these bladder lesions are identified as soon as possible since treatment options and responses differ considerably between the classic Hunner type of IC and other phenotypes.

Treatment

How to Select an Efficacious Treatment?

There are obvious dilemmas when trying to make a wise decision on therapy in BPS. A great variety of solutions have been tried, essentially on a trial-and-error basis. Many methods have been discarded; a few have stood the test of time. Correct classification and phenotyping of the heterogenic group of conditions that may result in pelvic pain is crucial for a good outcome of treatment, while in reality methods to reliably identify phenotypes are insufficient. The significance of this problem is very important but still not generally acknowledged. This is in contrast to a strive in urologic oncology to improve phenotyping and identify critical characteristics to optimize treatments. The fact is that, although the more inclusive attitude of later years has drawn a desirable attention to the entire spectrum of disorders resulting in bladder pain, the wish to include all of them into simple and handy entities has resulted in much scientific and clinical confusion. Ten years ago, a scientific association was founded, with one of its objectives to draw attention to the diagnostic and therapeutic problems in BPS/IC, denominated the European Society for the Study of Interstitial Cystitis (ESSIC), nowadays the International Association for the Study of Bladder Pain Syndrome. They suggested a standard on how to examine and classify patients with bladder pain, addressed the problem of so-called confusable diseases (Tables 4.1 and 4.2), stressed the importance of phenotyping and updated the terminology.

From a therapeutic standpoint, one entity stands out as especially important to identify. The so-called classic IC (Hunner disease, ESSIC type 3C) is a specific and well-defined entity and fulfils the requirements of the original denomination “interstitial cystitis”: There are histological signs of a marked inflammation in the bladder submucosa and musculature (the bladder interstitium) together with typical cystoscopic features. Evidence is accumulating on unique and outstanding features of this entity, with great implications on treatment.

Conservative Treatment

In the pelvic area, abnormal activity in the pelvic floor musculature with possible involvement of joints, ligaments, fasciae and viscera may cause adverse interactions. Therapeutic approaches include *breath work*, *biofeedback techniques* and *soft tissue manipulations* to aid in muscle relaxation of the pelvic floor. Especially important seems the identification of trigger points, frequently found in, e.g. the pubococcygeus, piriformis, external oblique, rectus abdominis, hip adductors and

Table 4.1 Confusable diseases for bladder pain syndrome

Carcinoma and carcinoma <i>in situ</i>
Infection with
Common intestinal bacteria
<i>Mycobacterium tuberculosis</i>
<i>Chlamydia trachomatis</i>
<i>Ureaplasma urealyticum</i>
<i>Mycoplasma hominis</i>
<i>Mycoplasma genitalium</i>
<i>Corynebacterium urealyticum</i>
Candida species
<i>Herpes simplex</i>
Human papilloma virus
Radiation
Chemotherapy including immunotherapy with cyclophosphamide
Anti-inflammatory therapy with tiaprofenic acid
Bladder neck obstruction and neurogenic outlet obstruction
Bladder stone
Lower ureteric stone
Urethral diverticulum
Endometriosis
Vaginal candidiasis
Cervical, uterine and ovarian cancer
Incomplete bladder emptying (retention)
Overactive bladder
Prostate cancer
Benign prostatic obstruction
Chronic bacterial prostatitis
Chronic nonbacterial prostatitis
Pudendal nerve entrapment
Pelvic floor muscle related pain

van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol.* 2008;53(1):60–7

Table 4.2 Cystoscopy with hydrodistension

	Not done	Normal	Glomerulations ^a	Hunner’s lesion ^b
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive ^c	XC	1C	2C	3C

Adapted from van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol.* 2008;53(1):60–7

^aCystoscopy: glomerulations grade 2–3

^bWith or without glomerulations

^cHistology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

gluteus medius muscles. A number of soft tissue manipulative but also invasive techniques are available to release symptoms related to soft tissue pathology in BPS/IC, but presently, this is an underused asset in the treatment armamentarium of this disease complex.

A recent example is a report on myofascial treatments, a multicentre trial in the US, involving numerous prestigious authors. Eleven clinical centres were included in a randomised study of 10 scheduled treatments compared to global therapeutic massage. A total of 81 women were randomised to the two treatment groups. They had similar symptoms at baseline. Subjects had demonstrable pelvic floor tenderness on physical examination and no more than 3 years' symptom duration. The primary outcome was the proportion of responders who were improved in overall symptoms compared to baseline on a 7-point global response assessment scale. Secondary outcomes included ratings for pain, urgency and frequency, the O'Leary-Sant IC Symptom and Problem Index and reports of adverse events. The response rate was 59 % in the myofascial physical therapy group vs 26 % in the global therapeutic massage group, a difference found to be significant. Pain, urgency and frequency ratings, and O'Leary-Sant IC Symptom and Problem Index decreased in both groups during follow-up, not significantly different between the groups though. Pain was the most common adverse event, occurring at similar rates in both groups. No serious adverse events were reported.

Per Oral Drugs

Pentosan polysulphate sodium (PPS), a highly sulphated mucopolysaccharide, is the only oral therapy approved by the US Food and Drug Administration, recommended in the AUA guidelines. It also has a high degree of recommendation according to the EAU guidelines, level of evidence 1a; grade of recommendation A. PPS has efficacy in a subset of 50 % of patients, by time dropping to 30 % of those initially treated. As a rule, it will take up to 6 months before benefit is experienced. The usual dosage is 150–300 mg daily, divided in two or three doses. Treatment responses are rather duration dependent than dose dependent. The safety and efficacy of oral pentosan polysulphate sodium (PPS), hydroxyzine and the combination of the two were evaluated in a pilot randomised clinical trial. A nonsignificant trend was seen in the PPS treatment groups as compared to no PPS. The low global response rates for PPS (and hydroxyzine) suggested that neither provided benefit for the majority of patients with BPS/IC. However, a serious limitation of the study was low numbers of subjects for follow-up. With reference to phenotyping, it can be noted that in an early, open study, patients with the classic Hunner type of disease seemed to be better responders than non-Hunner patients.

Systemic cortisone has also a long tradition; anti-inflammatory treatment using cortisone has been used, although not as a standard option, in BPS/IC for

more than four decades. Efficacy has been demonstrated even more recently in the classic Hunner type of disease, but since the side effects of chronic steroid treatment can be very serious, it is difficult to justify systemic, long-term use. For this reason, the EAU guidelines do not recommend systemic cortisone in BPS/IC.

Amitriptyline, a tricyclic antidepressant, has a number of properties like blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and noradrenalin, and blockade of histamine H1 receptors. This drug is standard in chronic pain treatment and can be used alone or in combination with other treatments. It is used in doses starting at 10 mg daily that are slowly increased over several weeks to up to 50–75 mg daily as tolerated. It tends to diminish pain, increase bladder capacity, block the actions of histamine, act as a mild antimuscarinic, and aid sleep. It has a high degree of recommendation according to the EAU guidelines, level of evidence 1a, and grade of recommendation A.

Hydroxyzine The mast cells are regarded to have pivotal role in BPS/IC, and activation might induce neurogenic inflammation resulting in chronic bladder pain and voiding dysfunction. Hydroxyzine is a histamine H1 receptor blocker inhibiting neuronal activation of mast cells. Hydroxyzine hydrochloride (Atarax) has been on trial in doses of 25 mg increasing to 75 mg/day, if tolerated. Initial results were promising, but a prospective RCT of hydroxyzine/PPS compared to placebo failed to demonstrate statistically significant effects for the active drugs. It still has a high degree of recommendation according to the EAU guidelines, level of evidence 1a, and grade of recommendation A.

Various *immunosuppressants* have been on trial. The most recent and promising one is *cyclosporine A*. In a RCT, comparing 1.5 mg/kg cyclosporine to 3 × 100 mg PPS for 6 months, the former drug was superior. There were more adverse events like gingival pain, paraesthesia, muscle pain, etc. in the cyclosporine arm though. Careful follow-up on blood pressure and kidney function is mandatory. As would be suspected, Cyclosporine A had a high success rate for patients with Hunner lesions, also in those where more conservative options and endoscopic treatment had failed, while the success rate was low for patients without Hunner lesions. Adverse events were common and led to discontinuation of cyclosporine A for some patients. According to the EAU guidelines, the level of evidence is 1b and grade of recommendation B.

Intravesical Treatment

Intravesical treatment has been widely used (and overused). This kind of treatment refers to the direct introduction of medication into the bladder and is considered as second-line treatment for patients who have failed conservative and oral therapies. According to a Cochrane report, the overall evidence for treating BPS/IC using

intravesical preparations is limited. In that analysis, the quality of trial reports was found to be mixed. Randomised controlled trials were found to be needed with a study design to incorporate relevant and standardised outcomes.

The most commonly used regimens include:

DMSO

Dimethyl sulfoxide (DMSO), a standard treatment with the longest history in IC, has been used for decades. It is a by-product of the paper pulp industry, an organic solvent, and has various properties: analgesic, anti-inflammatory, collagenolytic and muscle relaxant properties. It is also a scavenger of the intracellular OH radical. It is administered weekly or biweekly, sometimes combined in intravesical cocktails with lidocaine, heparin and sodium bicarbonate. DMSO is the only intravesical therapy approved by the US Food and Drug Administration for BPS/IC, recommended in the AUA guidelines. DMSO has a high rating in the EAU guidelines, too, level of evidence 1b, grade of recommendation A. Although DMSO has been a standard treatment through so many years, details of mechanism of action are not yet resolved, but there is still an ongoing interest from basic scientists to explain the action of this compound. DMSO has been used in all presentations of BPS. In a study comparing the two main phenotypes of BPS/IC, side effects were similar in patients with classic compared to non-ulcer disease. For classic IC, there was a significant difference when comparing side effects experienced during the first three instillations and the three subsequent instillations, however. After DMSO instillations, a positive treatment effect lasting 16–72 months was reported.

GAG Replacement

In the abundance of theories regarding pathogenesis, one of the most popular ones is the “leaky urothelium”, i.e. that a defect in the bladder glucosamine glycan layer (GAG) allows noxious substances of the urine to penetrate and affect the sensory innervation. Replenishment of the GAG would then restore mucosal integrity and reduce or cure symptoms. Treatment can be administered orally or intravesically. A variety of mucopolysaccharide products (heparin, pentosan polysulphate sodium, chondroitin sulphate, hyaluronan) have been used intravesically with the objective to get a more direct and prompt effect, with less systemic side effects, however involving the significant disadvantage of repeated urethral catheterisation.

Heparin has been attributed to long-term symptomatic improvement in more than 50 % of patients, and the current American Urological Association (AUA) recommendations list this as one of three options for BPS/IC instillation therapy, namely, dimethyl sulfoxide, heparin and lidocaine. In contrast, the EAU guidelines give heparin treatment a level of evidence 3 and a grade of recommendation C due to limited data on effectiveness.

Pentosan polysulphate Placebo-controlled studies indicated long-term significant effect of this compound. Pentosan polysulphate has a high rating in the EAU guidelines with a level of evidence 1b and grade of recommendation A.

Hyaluronic acid Early studies were promising. Morales et al. (*J Urol.* 1996;156(1):45–8) used 40 mg of HA intravesically on a weekly basis for 4 weeks, then monthly. Response to therapy was evaluated by symptom score, voiding diaries and visual analogue scales.

An initial positive response was maintained until 5 months and then a moderate decrease in the effects on symptoms. There was no significant toxicity, so the response was found to be gratifying. The author's made the point that many therapies that were initially considered promising failed the test of controlled studies. Such studies have been scant and results have to be interpreted with this fact in mind. Hyaluronic acid has a moderate degree of recommendation according to the EAU guidelines, level of evidence 2b, and grade of recommendation B.

Chondroitin sulphate has been advocated for use in BPS/IC. In a Canadian meta-analysis on three studies, a total of 213 patients were included in the pooled analysis. The chance of being an ICSI responder was similarly 54 % higher in the chondroitin sulphate group compared to a vehicle group. The small decrease in total ICSI score and urinary frequency between the two groups was less impressive and not statistically significant. Chondroitin sulphate and hyaluronic acid share level of evidence 2b and grade of recommendation B in the EAU guidelines.

Lidocaine

Local anaesthesia Sporadic early reports on the use of intravesical lidocaine in BPS/IC indicate a potential role of such a regimen. Alkalisiation of lidocaine before instillation is a means to improve pharmacokinetics, and in a placebo-controlled, multicentre study, actively treated patients had a significant, sustained symptom relief for up to 1 month. This modality has a high rating in the AUA as well as EAU guidelines (level 1b, grade of recommendation A). An important limitation is the need to use repeated urethral catheterisation, difficult to tolerate for many patients with BPS/IC. Other ways of administration is underway.

Vanilloids

Vanilloids disrupt sensory neurons, a conceptually attractive approach to control symptoms in BPS/IC. Capsaicin and resiniferatoxin (RTX) have been on trial, but a significant adverse event was pain on instillation, and although some preliminary reports were promising, this mode of treatment has not gained wide acceptance and is not recommended in the EAU guidelines. There might be room for vanilloids with improved drug formulas and modified treatment protocols.

Electrical Stimulation/Neuromodulation

Transcutaneous electrical nerve stimulation (TENS) The first trial of electrical stimulation in IC was presented in 1980: Fourteen women were treated either with long-term intravaginal or suprapubic transcutaneous nerve stimulation. Clinical and urodynamic evaluations were done after 6 months to 2 years. Improvement was not immediate but required a considerable period of continuous, daily use of electrical stimulation. The results were favourable although TENS was found to be more tolerable for long-term treatment in the target population. Since the methods were found to be effective and simple, cheap and non-destructive, electrical stimulation was recommended for all patients with chronic interstitial cystitis, and the favourable result of TENS was corroborated in a larger, open study. The response rate was much better in patients with the classic Hunner type of disease compared to non-Hunner subjects. The rationale behind the use of surface electrical nerve stimulation is to relieve pain by stimulation of myelinated afferents, thus activating segmental inhibitory circuits. In the last few years, tibial nerve stimulation has gained a wide acceptance, mainly for the treatment of overactive bladders. Quite recently, a systematic review was performed and four RCTs and six prospective observational cohort studies were identified. There is strong evidence for the efficacy of PTNS versus a sham treatment and a similar analysis for the treatment of CPP and BPS turned out favourably, too, although studies are scant on these indications. When treatment can be administered by the patient herself, surface stimulation techniques are cheap and with very few harmful effects.

Another off-label therapy is *sacral root stimulation*, often referred to as *neuromodulation* (mostly used for frequency and urgency syndromes), either by means of the sacral nerve approach but also pudendal nerve stimulation, and both with favourable preliminary results for patients with lower urinary tract dysfunction. This therapy has been suggested to be useful in the treatment of chronic pelvic pain, too. In an analysis of current literature, 12 relevant articles were identified. Of these articles, 10 mainly addressed the efficacy in patients with BPS/IC. Of the 10 articles, seven reported treatment outcome after implantation. The duration of follow-up ranged between 5 and 87 months. The mean reduction in pain scores was reported between 40 and 72 %. Two articles included patients with miscellaneous urogenital pain syndromes. The success rates after implantation ranged from 60 to 77 % with follow-up ranging between 19 and 36 months. So, at the present stage, there is not sufficient evidence to determine the role of sacral root stimulation in the treatment of chronic pelvic pain, and larger prospective trials with long-term evaluation are required to determine the ultimate efficacy of this treatment, statements in agreement with the moderate degree of recommendation according to the EAU guidelines, level of evidence 3 and grade of recommendation B. Alternative modalities like pudendal nerve positioning of the electrode are so far less explored in BPS/IC.

Botulinum Toxin

Botulinum toxin (BTX) injections, into the detrusor or the trigone, are used extensively in frequency, urgency and urge incontinence syndromes with varying aetiology. BTX has an anti-nociceptive effect; a decrease in daytime frequency, nocturia and pain and an increase in functional bladder volume have been demonstrated in BPS/IC. The results reported in the literature are conflicting though. Experimental observations suggest that BTX significantly attenuates bladder afferent nerve firing and inhibits ATP release from the urothelium, resulting in attenuation of the bladder afferent nerves involved in micturition and bladder sensation; BTX may exert its clinical effects on urinary urgency and other bladder symptoms through this effect on afferent nerves so an influence on symptoms in BPS might be quite plausible. A recent, interesting study aimed to determine whether intratrigoanal Onabotulinum toxin A (OnabotA) injection produces a different symptomatic outcome and duration of effect in subjects with Hunner lesions vs non-Hunner BPS/IC patients and in addition to compare the urinary levels of neurotrophins in response to BTX. Ten Hunner and 14 non-Hunner BPS/IC patients were included in this study. OnabotA (100 U) was injected in 10 trigonal sites, each receiving 10 U in 1 mL of saline. Outcome measures included pain visual analogue scales (0–10), a 3-day voiding chart, O’Leary-Sant Score (OSS) and quality of life (QoL) from International Prostate Symptoms Score assessed before treatment, 1 month after injection and every 3 months afterwards. Treatment duration was determined as the time when patients requested repeated injections. The Hunner-type patients had a mean age of 40 ± 12 years vs 47 ± 13 years in the non-Hunner group (ns). Other parameters were identical in the two groups although patients with the Hunner type had a longer duration of symptoms (28.8 ± 11 vs 19.2 ± 8 months, $P = .018$). Both groups responded equally, with significant improvements in pain intensity, frequency, nocturia, OSS, QoL and urinary neurotrophins. The effect lasted for 9 ± 2.8 (Hunner) and 10.5 ± 2 (non-Hunner) months. So, in this cohort, Hunner lesion patients and non-Hunner patients had similar symptoms at baseline and comparable clinical response to intratrigoanal OnabotA. The authors suggested that pain may not be directly and specifically related to the Hunner lesions (Pinto et al. *Urology*. 2014;83(5):1030–4), in contrast to reports that ablation of lesions leads to symptoms into remission. At this stage, BTX has a modest degree of recommendation: level of evidence 3 and grade of recommendation B, according to the EAU guidelines.

Cortisone Submucosally

Another modality is sub-lesional injection of cortisone, occasionally being reported to be efficacious in the Hunner type of BPS/IC. One study reported on thirty patients with Hunner lesions who underwent endoscopic submucosal injection of

triamcinolone; 21 of 30 patients (70 %) were very much improved. No perioperative complications were noted, and the submucosal injections of triamcinolone were well tolerated.

Surgery

Ablation of circumscribed Hunner areas of chronic bladder inflammation is the mainstay current treatment of BPS type 3C. Transurethral resection techniques have been advocated since many years. TURB yielded quite favourable results, also long term, and implies complete resection of all lesions, including the peripheral oedema zone and the underlying superficial detrusor muscle, using a minimum of coagulation. Some 10 years ago, the long-term outcome in 103 patients with classic Hunner disease and their response to complete TURB of visible lesions were retrospectively evaluated. In that series, a satisfactory symptomatic effect in 9 of 10 patients with classic BPS/IC could be seen. TUR has been suggested to result in symptom improvement by the removal of intramural nerve endings engaged by the inflammatory process. Similar results have been reported following neodymium YAG laser treatment. Because of technical simplicity, fulguration of lesions is currently the most popular technique. Surgical destruction of lesions is applicable in the genuinely inflammatory Hunner type of disease (ESSIC type 3C) only. The excellent symptomatic effect in the majority of patients makes TURB or fulguration a first-line treatment, with few comparable alternatives. Since there are no RCTs (having been considered unethical when it comes to this kind of treatment), the degree of recommendation is still not high: level of evidence 3 and grade of recommendation B, according to the EAU guidelines.

Major surgery for bladder pain syndrome is contemplated in patients with severe symptoms who have failed standard attempts at treatment and when the disease course suggests that spontaneous remission is not to be expected. There are serious limitations to major surgery though. Patients with a small bladder capacity under anaesthesia are less likely to respond to conservative attempts at therapy but have been found to be the best candidates for bladder reconstruction. In fact, patients with end-stage Hunner's disease and severe bladder contracture have the most favourable results with major surgery. At this stage of the disease process, there is little pain but intolerable urinary frequency. On this indication, subtotal cystectomy and ileocystoplasty have yielded excellent results, while the results of major surgery, irrespective of method, are little encouraging in other presentations of BPS/IC. Favourable results in the Hunner type of disease have been reported repeatedly. Experiences differ from centre to centre though. One study reported on a long-term follow-up of ileal conduit operations in 20 patients, with or without cystectomy. Nineteen patients were alive at the time of the study and 15 returned the questionnaires. The quality of life in both the cystectomy and the non-cystectomy groups was comparable with that in the general population. Seven patients in the non-cystectomy group were free of specific BPS/IC symptoms. The remaining five

patients had minimal symptoms. There was no difference between the cystectomy group and the non-cystectomy group with regard to the proportion of patients who were symptom-free.

In non-Hunner BPS patients with debilitating symptoms not responding to more conservative treatment attempts, the decision is difficult, but if one conceptualises bladder pain syndrome as composed of two main components, one of pain and the other of frequency, it becomes somewhat easier for the patient and physician to rationalise the decision. Conduit urinary diversion can be relied upon to resolve the frequency symptoms, and if the patient would consider this alone sufficient, there is reason to seriously contemplate this option although pain may persist; diversion, or cystectomy with diversion, or even more extensive surgery, cannot guarantee a pain-free result, and it is critical for the patient to seriously take this fact into account before the decision to embark to this irreversible step. There are no RCTs; the level of evidence is 3 but the grade of recommendation is A, according to the EAU guidelines. They emphasise that great experience with BPS surgery is a determining factor for the result.

Complementary

Acupuncture In a debilitating condition with severe therapy resistance and very long duration, complementary and alternative therapies are bound to be tested as an addition to the regular therapeutic armamentarium. Such methods include dietary modification, bladder training, stress reduction and sex therapy. Dietary modification involves reduction of bladder irritants, fluid regulation and a bowel regimen. These lifestyle modifications are frequently used although therapeutic benefit has not been scientifically proved. In daily practice, however, multimodal, nonconventional management may add efficacy to the treatment of BPS/IC. Many patients report on beneficial effects of acupuncture. At this stage, limited scientific reports on traditional, electrical or laser posterior tibial nerve acupuncture stimulation have been negative; however, acupuncture is not recommended by the EAU guidelines.

Hyperbaric oxygen has been tested in small trials, with repeated sessions of inhalation of 100 % and found helpful in a small subgroup of BPS/IC patients. This treatment is limited by high costs, time-consuming care and restricted availability. One randomised study proposed the combination of hyperbaric oxygen and DMSO to prolong a symptomatic response.

The Multidisciplinary Approach

A systematic approach to the treatment of chronic pelvic pain, like the one taken in the EAU guidelines work should include all relevant aspects of the disease process. In some instances, referral to a multidisciplinary pain centre is the appropriate early

step in conjunction with ongoing treatment of BPS. The reason is that in chronic pain, it is believed that changes occur within the CNS throughout the whole neuraxis and that central changes may develop and explain some of the psychological changes that subsequently modifies pain mechanisms. Core muscles may become hyperalgesic with multiple trigger points or fibromyalgia. Other organs may also become sensitised like the bowel with irritable bowel symptoms. There have been many ideas to explain such associations, like neuronal sensitisation in spinal segments of common projection, or that the disease progresses from an organ-centred condition to a regional and finally a systemic pain syndrome. A maladaptive coping strategy such as a catastrophising personality is associated with greater pain, increased symptoms and poorer quality of life. Thus, many aspects and other components than bladder pain itself must be identified and deserve close attention. Involvement of various experts may be needed: pain specialists and the pain nurse, physiotherapists, psychologists and sometimes psychiatrists. When standard, organ-centred trials of treatment fail, early involvement of the multidisciplinary team is vital. If consultation is delayed, hypothetically there is a risk that CNS patterns of pain processing will be permanently changed, resulting in a chronic pain condition very difficult to treat.

Tips and Tricks/Dos and Don'ts

It has to be accepted that the systematic and complete assessment of a patient with CPP/BPS is demanding. Remember that a correct initial judgment may be decisive for the long-term outcome.

First step: Exclude confusable diseases (Table 4.1).

Second step: Never miss a Hunner lesion disease! To reveal all lesions, distension during anaesthesia is recommended. If present, local ablation of all lesions is the therapy of choice.

Third step: If organ-specific affections that could explain symptoms (like Hunner disease) can be excluded, a thorough and comprehensive whole body assessment is required (Quaghebeur, Wyndaele. *Scand J Urol*. 2015;49(2):81–9).

Fourth step: Use a systematic treatment algorithm, starting with less harmful therapies.

Fifth step: If no treatable localised condition is identified, an as early as possible referral to the multidisciplinary team should be made, to avoid that CNS pattern of pain processing will be permanently changed, resulting in a difficult to treat chronic pain condition.

Recommended Reading

1. Chaitow L, Lovegrove Jones RE. Chronic pelvic pain and dysfunction. Practical physical medicine. Churchill Livingstone: Elsevier; 2012. ISBN 9780702035326.
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