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Review – Voiding Dysfunction

Treatment of Bladder Pain Syndrome/Interstitial Cystitis 2008: Can We Make Evidence-Based Decisions?

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Abstract

Context: Opinions on how to best treat bladder pain/interstitial cystitis are ambiguous.

Objective: To review previous and recent literature on this subject to assess the current state of evidence.

Evidence acquisition: With important previous papers reviewed for the 2003 European Association of Urology guidelines as background, the PubMed database was searched and articles published in 2003–2007 were reviewed and relevant ones were selected for detailed study.

Evidence synthesis: A large number of studies describing a variety of quite dissimilar therapeutic principles were retrieved. The various methods and level of evidence are summarised in tables. Only pentosan polysulfate sodium (oral and intravesical), amitriptyline, hydroxyzine, cyclosporin A, intravesical dimethyl sulfoxide, transurethral resection of visible Hunner lesions, and major reconstructive surgery reached a high degree of recommendation. However, a number of pitfalls hamper evaluation of the available information; a crucial one is that our understanding of basic mechanisms causing bladder pain is fragmentary. So far, we are faced with a large variety of hypotheses although it is difficult to identify the most relevant ones. In this respect, we are not much helped by the recent literature because many studies have poor descriptions of patients or are of a pilot character, with no follow-up by larger trials. Controlled studies are rather scarce. On the other hand, some good-quality studies following up positive pilot trials end up with negative results.

Conclusion: Perhaps the most significant problem concerns inclusion and exclusion criteria in bladder pain syndrome/interstitial cystitis studies. At this stage, it is not too easy to communicate the wide available expert knowledge to the general audience. More sophisticated standards, capable of being generally used, have to come.

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1. Introduction

The concept of interstitial cystitis (IC) has been transformed over the years. The term was coined by Skene [1] in 1887, describing a chronic inflammatory lesion of the bladder wall. Guy Hunner, another great pioneer, about one century ago gave his name to a symptom complex of chronic bladder inflammation associated with a peculiar cystoscopic feature, the so-called Hunner ulcer [2]. The lesion was subsequently called the “submucous ulcer,” but the terminology of Skene [1] was readopted in 1930 by Bumpus, who considered this term to be more appropriate due to the general involvement of the bladder wall [3]. In 1949, when John Hand [4] presented a large series of patients with IC with varying endoscopic and histopathologic presentations, he realised that his material on IC did not comprise just one single entity. This fact was later emphasised by Messing and Stamey [5] and Fall et al [6].

The definition of IC has become wider and more varying. In an attempt to get a standard to be used in scientific studies, at a workshop in 1987, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK, Bethesda, MD, USA) defined a number of criteria mainly based on exclusions [7]. Subsequently, these criteria have been used in the clinical setting, although many regard them as too restrictive for clinical use. Today, IC represents a symptom complex with varying contents.

The diagnostic shift is reflected in dramatically increasing prevalence figures. The first systematic study by Oravisto indicated that IC affected approximately 10 of 100,000 in the population in Helsinki, Finland [8]. Thirty years after the Oravisto study, Leppilahti et al [9], also in Finland, presented quite a different picture. Their estimate was that the prevalence of clinically confirmed IC in women was 230/100,000 and that of possible/probable IC was 530/100,000. Their conclusion was that this pain syndrome is substantially more common than previously thought, a contention shared by many around the world, an example of which is the very recent report by Temml et al [10]. In a review, Burkman claimed that 20% of women may be affected [11] and one of the highest figures ever was presented in another US study identifying probable IC in 30.6% of a young female population [12]. Bearing this dramatic change in mind, it is important to realise that we have moved far away from the understanding of IC of Hunner and Bumpus. We are actually dealing with a heterogeneous spectrum of disorders, still poorly defined, and different experts have varying perceptions as to what IC is about. In IC, as it is comprehended by a majority of clinicians today,

bladder inflammation is a dominating feature only in a minor subset of patients. To embrace all patients suffering with bladder pain, the terms painful bladder syndrome (PBS) [13] or bladder pain syndrome (BPS) [14,15] have been suggested as more adequate, assuming that IC represents a genuine chronic inflammation of the bladder wall while PBS or BPS refers to pain perceived in the bladder region. In the literature, however, this concept has still not come through. Unfortunately, because definitions seem to be rather loose and vary so markedly among different centres and in different parts of the world, the question is relevant: Is evidence-based treatment possible?

2. Evidence acquisition

The unrestricted, fully exploded Medical Subject Heading (MeSH) “interstitial cystitis” (including all related terms as “painful bladder syndrome,” or different terms such as “chronic interstitial cystitides,” etc.) was used to thoroughly search the PubMed database (<http://www.ncbi.nlm.nih.gov/PubMed/>) of the US National Library of Medicine of the National Institutes of Health; 858 hits were retrieved. After exclusion of publications on animals and scientifically uncommon languages (other than English, French, German, Italian, Japanese, Spanish, Swedish) and by limiting the publications to the time period January 2003 to October 2007, 362 publications resulted (296 with abstracts). Abstracts and titles of the 362 hits were reviewed, focusing on (but not limited to) clinical trials, randomised controlled trials, meta-analyses, scientific guidelines, and core clinical journals. A total of 155 papers thus selected where retrieved as full paper prints by the European Association of Urology (EAU) office and thoroughly studied and evaluated.

The literature update thus achieved was added to a preexisting database of 314 publications, covering the time period before 2003 (generated for the 2003 EAU guidelines) that was established according to the same protocol.

The 70 most relevant citations from the combined data sets are referenced in this review.

Rating of the level of evidence and grade of recommendation was performed according to the Oxford Scale and is presented in Table 1.

3. Evidence synthesis

This area has seen great activity in recent decades and activity is still high. Many articles have been

Table 1 – Level of evidence and grade of recommendation

Level	Type of evidence
1a	Meta-analysis of randomised trials
1b	At least one randomised trial
2a	One well-designed controlled study without randomisation
2b	One other type of well-designed quasi-experimental study
3	Non-experimental study (comparative study, correlation study, case reports)
4	Expert committee, expert opinion
Grade	Nature of recommendation based on
A	Clinical studies of good quality and consistency including at least one randomised trial
B	Well-conducted clinical studies without randomised trials
C	Absence of directly applicable clinical studies of good quality

directed to treatment. Due to the limited knowledge of aetiology and pathogenesis, various principles have been presented, in the majority as evidence based on a trial-and-error principle. Herein, we will give some examples of current interest.

3.1. Medical treatment of BPS/IC

3.1.1. Pentosan polysulfate sodium

Pentosan polysulfate sodium (PPS; ELMIRON[®]) has been evaluated in double-blind, placebo-controlled studies. PPS is one of several polysaccharides used to decrease urothelial permeability by substituting for a defect in the glycosaminoglycan layer. Subjective improvement of pain, urgency, and frequency but not nocturia was reported in patients taking the drug compared to placebo [16]. In an open multicentre study, Fritjofsson et al demonstrated that PPS had a more favourable effect in classic than in nonulcer IC [17]. The normal dose is 150–200 mg twice daily between meals. However, absorption is incomplete. Therefore, Nickel et al [18] conducted a randomised, double-blind study comparing higher dosages; 300 mg PPS compared to 600 and 900 mg. The study was performed in 380 patients and the mean symptom scores improved significantly for all dosages. The response to treatment was not dose dependent but rather related to the duration of treatment; at 32 wk about half of all patients were responding. Adverse events were mild and resolved without intervention. These favourable results with PPS are at variance with a prospective, randomised, placebo-controlled multicentre study testing PPS and hydroxyzine against placebo [19]. The study failed to demonstrate a statistically significant outcome for either drug, although PPS approached statistical significance ($p = 0.064$).

3.1.2. Amitriptyline

The tricyclic antidepressant amitriptyline has been reported to alleviate symptoms in patients with BPS/IC. The drug is thought to act via mechanisms such as blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and norepinephrine, and blockade of the histamine H₁ receptor. It is also an anxiolytic. Several reports have indicated amelioration after oral treatment with amitriptyline [14]. Van Ophoven et al [20] conducted a prospective, randomised, placebo-controlled, double-blind study to examine amitriptyline in 48 patients with IC. Patients were treated for 4 mo and allowed to escalate drug dosage in 25-mg increments in 1-wk intervals (maximum dosage of 100 mg). Mean symptom score, pain, and urgency intensity improved significantly in the amitriptyline group. Frequency and functional bladder capacity improved but were not statistically significant.

In a subsequent prospective, open-label study [21] a 20-mo long-term administration was examined among 94 patients. The response rate was 64% with an overall mean dose of 55 mg. Patient overall satisfaction was excellent/good in 46%. Improvement in IC symptoms was statistically significant. The therapeutic response was uniformly observed in patients fulfilling NIDDK criteria and in those with clinical diagnosis of IC. Anticholinergic side-effects (mouth dryness and weight gain) were common and are a drawback.

3.1.3. Hydroxyzine

Mast cells are considered to play a pivotal role in IC. Among the substances released by mast cells is histamine. Histamine receptor antagonists have been used to block the H₁-receptor subtype as well as the H₂-receptor subtype, with variable results.

Hydroxyzine is a histamine H₁-receptor antagonist that can block neuronal activation of mast cells by inhibition of serotonin secretion from thalamic mast cells and neurons. Usually, hydroxyzine hydrochloride (Atarax) is used, starting with 25 mg at bedtime, increasing the dose to 50 mg/d or even 75 mg, if tolerated. In the first series using this drug, >90% of patients responded with an improvement of the whole range of IC symptoms and, interestingly, an improvement in associated symptoms such as migraine, irritable bowel syndrome, and allergies was also noted [22]. However, a prospective, randomised, placebo-controlled seven-centre study of hydroxyzine or PPS compared with placebo failed to show a statistically significant effect [19]. In this study 121 patients were recruited although power calculation demanded 136 patients. This underscores

the difficulties in recruiting patients for well-designed studies and could be one reason the study failed to demonstrate a statistically significant outcome for either drug compared with placebo. Combination therapy showed the highest response rate of 40% compared with a placebo response rate of 13%.

3.1.4. Immunosuppressants

Early attempts included azathioprine, cyclosporine, and methotrexate [14].

Cyclosporin A (CyA) was investigated in more recent studies by Sairanen et al [23,24]. In 23 patients with IC, daily voiding, maximal bladder capacity, and voided volume improved significantly during 1 yr of treatment. The effect was maintained throughout a 5-yr follow-up. Twenty of 23 patients reported remission of bladder pain. However, when treatment was discontinued, symptoms recurred within months. In a recent randomised study [24] CyA was compared to PPS. Sixty-four patients were randomised to receive 1.5 mg/kg CyA twice daily or low-dose PPS for 6 mo. CyA was superior to PPS in all clinical outcome parameters. The clinical global response rates were 75% (CyA) and 19% (PPS). However, more and significant adverse events occurred in the CyA arm.

3.2. Intravesical treatment

Intravesical application of medications allows for high concentrations at the target site with few systemic side-effects. The need for intermittent catheterisation, which can be painful in patients with BPS/IC, the costs, and the risk of infection are drawbacks. Various intravesical treatments have been proposed and investigated for BPS/IC.

3.2.1. Dimethyl sulfoxide

One of the most long-lived agents used in BPS/IC, dimethyl sulfoxide (DMSO) is a chemical solvent and water-soluble liquid that penetrates cell membranes and is claimed to have analgesic, anti-inflammatory, collagenolytic, and muscle relaxant effects. It has been tested empirically and found to alleviate PBS and is a standard treatment. In a controlled, crossover trial [25], 33 patients with IC received instillations of a 50% DMSO solution and placebo. Subjective improvement was noted in 53% of patients receiving DMSO versus 18% receiving placebo and objective improvement in 93% and 35%, respectively. Other uncontrolled trials with DMSO have reported response rates of 50–70% for a period of 1–2 mo [26]. Rössberger et al [27] evaluated the discomfort and long-term effect of DMSO

instillations in 28 patients. Side-effects were not more common or pronounced in patients with classic compared to nonulcer disease. After DMSO instillations, a residual treatment effect lasting 16–72 mo could be seen.

3.2.2. *Bacillus Calmette-Guérin*

Immunomodulatory properties of the tuberculosis vaccine bacillus Calmette-Guérin (BCG) are used for intravesical treatment of superficial bladder carcinoma. In 1997, a small prospective, double-blind pilot study on BCG demonstrated response rates of 60% for BCG versus 27% for placebo in 30 patients [28]. In a subsequent 24–33-mo follow-up report, eight of the nine responders reported favourably and BCG did not worsen symptoms in non-responders [29]. However, these results are at variance with two controlled trials.

In a first prospective, double-blind crossover trial of BCG and DMSO [30], BCG treatment failed to demonstrate any benefit. A second randomised placebo-controlled double-blind trial on 260 patients with refractory IC [31] reported global response rates of 12% for placebo and 21% for BCG ($p = 0.062$). Small improvements were observed for all secondary outcomes (voiding diary, pain, urgency, symptom indexes, and adverse events), some more so with BCG, but these differences were of borderline statistical significance. In a subsequent analysis [32], 156 non-responders from both groups of this randomised trial were offered treatment with open-label BCG. The low response rate (18%) for BCG in this series further argues against this treatment for BPS/IC.

3.2.3. PPS

The bioavailability of PPS is poor after oral administration, hence, the intravesical application. A double-blind placebo-controlled study [33] was performed in 20 patients, of whom 10 received intravesical PPS (300 mg in 50 ml 0.9% saline) twice a week for 3 mo and 10 received placebo. At 3 mo, four patients in the PPS group and two patients in the placebo group gained significant symptomatic relief.

3.2.4. Hyaluronic acid

Hyaluronic acid, or more correctly hyaluronan, is a natural glycosaminoglycan. Morales [34] treated 25 patients and reported a response rate of 56% at week 4 and 71% at week 7. After week 24, effectiveness decreased, but there was no significant toxicity. Nordling and Kallestrup [35] reported a 3-yr follow-up to a 3-mo, prospective, nonrandomised study evaluating the effect of intravesical hyaluronan on IC symptoms. Of 20 patients, 11 chose to continue

treatment, and modest beneficial long-term effects were noted in about two thirds of patients.

3.2.5. Chondroitin sulfate

Intravesical chondroitin sulfate, another glycosaminoglycan, yielded beneficial effects in two non-randomised, uncontrolled, open-label pilot studies:

Steinhoff [36] treated 18 patients with 40 ml instilled intravesically once a week for 4 wk and then once a month for 12 mo. Thirteen of 18 patients were followed for the entire 13-mo study. Twelve of these patients responded to treatment within 3–12 wk, on average. Six of 13 (46.2%) showed a good response, 2 of 13 (15.4%) had a fair response, 4 of 13 (30.8%) had a partial response, and 1 of 13 (7.7%) showed no response.

In a second trial [37], 24 refractory patients with BPS/IC were treated with high-dose (2.0%) chondroitin sulfate instillations twice weekly for 2 wk, then weekly with 0.2% solution for 4 wk, and monthly thereafter for 1 yr. The average symptom improvement reported in 20 patients completing the trial was 73.1% (range: 50–95%). The time to optimum response was 4–6 mo. Eight patients needed the more concentrated 2.0% solution to maintain results.

3.2.6. Vanilloids

Vanilloids modulate the activity of sensory neurones. Resiniferatoxin (RTX) is an ultra-potent analogue of the chilli pepper extract capsaicin, causing less pain on instillation and is therefore easier to use. In a small randomised, placebo-controlled trial on 18 patients with hypersensitive bladder disorder and pain [38], RTX significantly reduced mean frequency, nocturia, and pain scores by approximately 50%. Apostolidis et al found that RTX significantly improved several sensory-related parameters as well as King's Health Questionnaire scores [39]. These results are in contrast with those of Payne et al [40] who performed a randomised, double-blind, placebo-controlled study in 163 patients with BPS/IC, randomly assigned to receive a single intravesical dose of 50 ml of either RTX (0.01 μ M, 0.05 μ M, 0.10 μ M) or placebo. RTX resulted in a dose-dependent increase in instillation pain and was otherwise well tolerated. However, it did not improve overall symptoms, pain, urgency, frequency, nocturia, or average void volume during 12 wk of follow-up.

More favourable results were reported from a prospective study on multiple intravesical instillations of RTX [41]. Among 12 patients, the overall satisfactory rate was 58.3%. International Prostate Symptom Score (IPSS), 5-Point Pain Scale, and

Quality-of-Life Index were significantly decreased. There was no significant improvement in functional bladder capacity or urodynamic parameters.

3.3. Interventional treatments

3.3.1. Bladder distention

The most traditional treatment of IC is hydrodistention. A frequently cited report by Bumpus [3] claims imprecisely that hydrodistention achieved symptom improvement in 100 patients over several months. In 1957, an uncontrolled retrospective study was presented by Franksson [42] who treated 33 patients with repeated, up to 10-fold distentions. Twelve patients improved for up to 4 wk, in 14 patients for up to 6 mo, and in 7 up to 1 yr. British studies from the 1970s reported contradictory results. Dunn [43] claimed to have achieved complete absence of symptoms in 16 of 25 patients during a mean follow-up of 14 mo using the Helmstein method [44]. Bladder ruptures occurred in two cases. These results disagree with those of Badenoch [45] who failed to notice any improvement in 44 of 56 patients after hydrodistention. Twenty years later, McCahy [46] rejected balloon hydrodistention because of inefficacy and a complication rate of 20%. In recent literature there are reports of bladder necrosis following hydrodistention [47]; however, this complication is extremely rare.

According to a study by Erickson et al [48] the median symptom score for newly diagnosed patients decreased after distention, but only a minority of patients had at least 30% symptom improvement. Bladder distention altered urine antiproliferative factor and heparin-binding epidermal growth factor levels toward normal, but the mechanism of symptom relief remains unknown. In a retrospective review on 185 patients who underwent hydrodistention [49], there were no statistically significant differences in objective findings after distention (anaesthetic capacity, glomerulations) or therapeutic benefits when patients were categorised according to presenting symptoms.

Although hydrodistention of the bladder is a common treatment, scientific justification is scarce. It represents a diagnostic tool but has a limited therapeutic role.

3.3.2. Botulinum toxin A

The increasing use of intravesical botulinum toxin A (BTX-A) injections in neurogenic/overactive bladder disorders has also challenged its use in BPS/IC.

Smith [50] reported that BTX may have an antinociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improve-

ments. Thirteen patients with bladder pain received injections with 100 to 200 U into 20 to 30 sites submucosally. Overall, nine (69%) patients noted subjective improvement. Interstitial Cystitis Symptom Index (ICSI) scores improved by 70% ($p < 0.05$). Daytime frequency, nocturia, and pain by visual analogue scale (VAS) registrations decreased by 44%, 45%, and 79%, respectively ($p < 0.01$). The first desire to void and maximal cystometric capacity increased by 58% and 57%, respectively ($p < 0.01$). In a pilot study, Giannantoni et al [51] found that 12 patients (85.7%) reported subjective improvement at the 1 and 3 mo follow-up. The mean VAS score was significantly reduced at 1 and 3 mo after treatment ($p < 0.05$ for both). By modulating afferent C-fibre activity within the bladder walls, BTX-A significantly improved urodynamic parameters and reduced bladder pain and urinary frequency.

These results are in contrast with those of Kuo et al [52] who studied 10 patients. In five patients, 100 U BTX was injected sub-urothelially into 20 sites, and an additional 100 U was injected into the trigone in the other five patients. In this study none of the patients was symptom free and only a limited improvement in bladder capacity and pain scores was achieved in two patients.

3.3.3. Hyperbaric oxygen

Van Ophoven et al [53] conducted a prospective pilot study on hyperbaric oxygen (HBO) therapy in six patients. They underwent 30 sessions of 100% HBO inhalation and were followed up over 15 mo. Four patients rated the therapeutic result as excellent/good, two showed only short-term amelioration.

In a subsequent double-blind, sham-controlled study [54], 3 of 14 patients on HBO and no control patients were identified as responders ($p < 0.05$). At 12 mo three patients (21.4%) still reported treatment response. HBO therapy resulted in a decrease of baseline urgency and pain ($p < 0.05$). ICSI scores decreased from 26 to 20 points in patients on HBO, whereas sham treatment did not result in any improvement.

HBO seems to be safe and feasible, with moderate effects on a small subgroup of patients with BPS/IC. High costs, limited availability of treatment sites, and the time-consuming treatment are obvious drawbacks.

3.4. Surgical treatment

3.4.1. Conservative surgery: transurethral resection and coagulation

Endourologic ablation of bladder tissue aims to eliminate visible lesions, in particular Hunner

lesions. Greenberg et al [55] reported data on 77 patients with Hunner lesions treated over a 40-yr period; 42 were managed conservatively, 7 underwent fulguration, and 28 were treated by transurethral resection (TUR) in a nonrandomised fashion. Fulguration improved symptoms in five of seven patients. All patients experienced symptom recurrence in < 1 yr and efficacy was not superior to nonsurgical treatment. In another series of 30 patients with classic IC [56], complete TUR of all visible lesions resulted in initial disappearance of pain in all and a decrease in frequency in 21 patients. A relapse was noted in one third of patients after 2–20 months, whereas the remaining two thirds were still free of pain after 2–42 mo. The same centre recently reported the largest series of patients with classic IC treated with complete TUR of all visible Hunner lesions [57]. A total of 259 TURs were performed in 103 patients; 92 experienced amelioration and symptom relief lasted > 3 yr in 40% after three or fewer TUR procedures. The majority of the remaining patients responded well to subsequent TUR.

Transurethral application of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is suggested as a more easily performed alternative to TUR for endoscopic treatment in patients with IC. Shanberg et al [58] initially treated five patients with refractory IC, of whom four demonstrated cessation of pain and frequency within several days. Follow-up at 3–15 mo revealed no relapse except mild recurrent voiding symptoms. This series was extended to 76 patients treated at two institutions [59]. Although 21 of 27 patients with Hunner lesions noted symptom improvement, 12 experienced relapse within 18 mo. In the group without Hunner lesions, only 20 of 49 patients improved, of whom 10 required further therapy within 1 yr. Recently, Rofeim et al [60] investigated 24 patients with refractory classic IC undergoing ablative Nd:YAG laser ablation of Hunner lesions. All patients had symptom improvement within days without complications. At 23 mo, mean pain and urgency scores, nocturia, and voiding intervals were significantly improved. However, relapse in 11 patients required up to four additional treatments.

These techniques may provide long-term alleviation of symptoms, but do not cure the disease. Endourologic ablation is not applicable to nonulcer BPS/IC. Controlled studies are still lacking.

3.4.2. Major surgery: supratrigonal/subtrigonal cystectomy or urinary diversion

When all conservative efforts fail, surgical removal of the diseased bladder represents an ultimate

option [61,62]. Three major techniques of bladder resection are common: supratrigonal (ie, trigone-sparing) cystectomy, subtrigonal cystectomy, or radical cystectomy including excision of the urethra. All techniques require some kind of substitution mostly performed with bowel segments.

As early as 1967, Turner-Warwick reported that mere bladder augmentation without removal of the diseased tissue would not seem appropriate [63]. Reports telling that unresected IC bladders will cease to cause symptoms when excluded from filling of urine are scarce.

Supratrigonal cystectomy followed by enterocystoplasty represents the most favoured continence-preserving technique. Various intestinal segments have been used for trigonal augmentation including ileum, ileocecum, right colon, and sigma. The therapeutic success of supratrigonal cystectomy has been reported in numerous small studies. In 1966, von Garrelts reported excellent results in 8 of 13 patients with a follow-up of 12–72 mo [64]. Nielsen reported data on a series of eight patients undergoing supratrigonal cystectomy with ileocecostoplasty. Although symptoms resolved in two patients, treatment failure in another six patients necessitated secondary cystectomy and conduit formation [65]. Linn [66] followed six patients with IC after supratrigonal cystectomy with an ileocecal augmentation for a period of 30 mo and reported that all were symptom free and voided spontaneously.

In 2002, van Ophoven [67] reported the long-term results of trigone-preserving cystectomy with orthotopic substitution enteroplasty for 18 patients, using ileocecal ($n = 10$) or ileal ($n = 8$) segments. At 5 yr,

14 patients were completely pain free, 12 voided spontaneously, and 15 reported complete resolution of dysuria. Ileocecal segments showed superior results because in the group augmented with ileum three patients required self-catheterisation and one a suprapubic catheter. Overall, surgery achieved significant improvement of frequency, functional bladder capacity, and symptom scores with only two treatment failures.

Patient selection is a crucial issue. Nielsen [65] noted that responders and non-responders following orthotopic substitution differed in mean preoperative bladder capacity (200 ml vs. 525 ml, respectively). This observation was supported by Peeker et al [68], who found that patients with bladder contracture (end-stage classic IC) had excellent results following ileocystoplasty, whereas nonulcer cases were not helped by the procedure. This notion is further emphasised in a recent report from the same institution. Rössberger retrospectively analysed 47 patients with BPS/IC, all fulfilling the NIDDK criteria, who underwent reconstructive surgery with various techniques between 1978 and 2003 [69]. Interestingly, the initial surgical procedures resulted in complete symptom resolution in 28 of the 34 patients with the classic Hunner type of disease and a further four following various additional procedures, whereas only 3 of the 13 patients with nonulcer disease experienced symptom resolution, a Bricker conduit being the only successful procedure in this category of patients.

There is agreement that reconstructive surgery for refractory BPS/IC is an appropriate last resort only for well-selected patients with refractory end-stage disease although there is no consensus on the

Table 2 – Peroral medical treatment of BPS/IC

	Type of evidence	Nature of recommendation	Comment
Analgesics	2b	C	Indications limited to cases awaiting further treatment
Corticosteroids	3	C	Corticoids not recommended as long-term treatment
Hydroxyzine	1b	A	Standard treatment but limited efficacy in RCTs
Cimetidine	1b	B	Insufficient data
Amitriptyline	1b	A	Standard treatment
Pentosan polysulfate sodium	1a	A	Standard treatment
			Data contradictory
Antibiotics	1b	C	Limited role in the treatment of BPS/IC
Prostaglandins	3	C	Insufficient data on BPS/IC, adverse effects
L-Arginine	1b	C	Effect in BPS/IC uncertain
Cyclosporin A	1b	A	RCT: superior to PPS but more adverse effects
Duloxetine	2b	C	No effect, tolerability poor
Oxybutynin/tolterodine	3	C	Limited indication in BPS/IC
Gabapentin	3	C	Preliminary data so far
Suplatast tosylate	3	C	Preliminary data so far
Quercetin	3	C	Preliminary data so far

BPS/IC = bladder pain syndrome/interstitial cystitis; RCT = randomised controlled trial; PPS pentosan polysulfate sodium.

Table 3 – Intravesical, interventional, alternative, and surgical treatment of interstitial cystitis

	Type of evidence	Nature of recommendation	Comment
Intravesical anaesthetics	3	C	
Intravesical PPS	1b	A	
Intravesical heparin	3	C	
Intravesical hyaluronic acid (Cystistat [®])	2b	B	
Intravesical chondroitin sulfate (Uracyst [®])	2b	B	
Intravesical DMSO	1b	A	
Intravesical bacillus Calmette-Guérin	1b	Not recommended	
Intravesical Clorpactin	3	Not recommended	Obsolete
Intravesical vanilloids	1b	C	Data contradictory
Bladder distention	3	C	
Electromotive drug administration	3	B	
Transurethral resection coagulation and laser	na	A/B	Hunner lesions only
Nerve blockades/epidural pain pumps	3	C	For crisis intervention, effect on pain only
Sacral neuromodulation	3	B	Not recommended beyond clinical trials
Bladder training	3	B	Patients without pain
Manual and physical therapy	3	B	
Diet	3	C	
Acupuncture	3	C	Data contradictory
Hypnosis		No data	
Psychological therapy	3	B	
Reconstructive surgical treatment	na	A	Largely varying data Ultima ratio, experienced surgeons

PPS = pentosan polysulfate sodium; DMSO = dimethyl sulfoxide; na = type of evidence not applicable because randomised controlled trials are unethical in such surgical procedures.

meaning of those terms. At this stage, there are reasons to emphasise that contemplation of major reconstructive surgery should be preceded by a thorough preoperative evaluation, with emphasis on assessment to determine the relevant disease location and subtype.

Summaries of the treatment options for BPS/IC, adopted from the EAU Guidelines on Chronic Pelvic Pain [14], also including options not discussed in this communication to illustrate the variety of trials, with rating of the level of evidence and grade of recommendation, are given in Tables 2 and 3.

4. Conclusions

According to the tables, the best evidence-based oral treatment option is PPS, closely followed by amitriptyline, hydroxyzine, and CyA. It must be remembered that these compounds are not readily exchangeable because they have quite a varying spectrum of adverse effects as well as somewhat different indications. It appears that some methods are, in fact, to be regarded as outdated but also that some compounds have shown promising preliminary results although data at this stage are too incomplete to allow for a high degree of recommendation. Of all the intravesical agents tested, only PPS and DMSO appeared to have an adequate

evidence base. As for surgical treatment on patients with the classic subtype of IC, TUR of visible lesions and major reconstructive surgery reach a high degree of recommendation.

As would be evident from the examples presented, a large number of studies have been produced including a large variety of quite dissimilar therapeutic principles. This mirrors lack of knowledge; our understanding of basic mechanisms causing bladder pain is fragmentary and insufficient. So far, we are faced with a variety of hypotheses because it is difficult to identify the most relevant ones. What data need to be obtained? Treatment trials can help in sorting out potential target areas for focused basic research but many studies so far have a pilot character and have not been followed up by larger trials. Controlled studies are quite scarce. Some techniques even involve a methodology where a randomised control trial (RCT) principle is difficult to practice for ethical reasons. Unfortunately, many of the existing studies in the field have a low level of evidence. On the other hand, some studies with good evidence following up positive pilot trials end up with negative results.

There are a number of possible explanations for this dilemma. One of them is suggested in the large PPS/hydroxyzine study. In this study 121 patients were recruited although power calculation demanded 136 patients. The difficulties in recruiting

patients could be one reason a study fails to demonstrate a statistically significant outcome, that is, a type 2 error. In studies involving technical procedures, the precise application of the technique is essential and may make the difference. Greenberg [55] did not get an overwhelming long-term success with TUR of Hunner lesions, whereas Fall [56] and Peeker et al [57] found systematic, complete resection of lesions to be extremely rewarding. By the same token, Malloy and Shanberg [59] did not find an impressive long-term outcome of Nd:YAG laser treatment of Hunner lesions, whereas Rofeim et al [60] reported excellent results. Contradictory results with other techniques, such as BCG and BTX treatment, may be due to similar differences in recruitment or technique or both. Major surgery in BPS/IC is frequently reported, but results are difficult to compare because most series are small and based on inhomogeneous materials using various techniques.

Perhaps the most significant problem concerns inclusion and exclusion criteria in BPS/IC studies. The overwhelming majority of studies have a poor patient description, just stating that subjects were fulfilling the NIDDK criteria. If nothing more is said, this is not sufficient because those criteria are essentially based on exclusions with few reliable positive factors. In the years ahead, we must search for, identify, and use positive factors allowing a more accurate description (and relevant subcategories) of patients in clinical studies. This includes relevant and reliable instruments to assess and describe symptoms in more detail. Different experts have varying comprehension of diagnostic requirements. The lack of consensus on diagnostic requirements and the imperfect account of patient characteristics make it difficult to evaluate and compare various clinical trials. In studies that are published there might be evidence but evidence for what?

A commendable initiative to improve standardisation of procedures and definitions has been brought forward by the European Society for the Study of Interstitial Cystitis (ESSIC). This group has suggested that a schematic account of hydrodistention and biopsy findings be presented in all clinical studies and confusable diseases be identified, along with more scientifically appropriate terminology [15,70]. This is, no doubt, the way to go but there is still much work to do to find relevant and robust clinical parameters.

What are current recommendations worth considering the quality of current literature? Can the results presented be generalised? The large RTCs are valid for a general, unselected population of BPS/IC

although when focusing on selected subgroups the picture might change. Results may be diluted by incorporation of a variety of conditions under the same label, which includes the risk of disregarding a treatment that would be quite useful in a specific population. People in centres with a large practice on BPS/IC would know how to handle various problems but at this stage it is not too easy to communicate such expert knowledge to a general audience. More sophisticated standards, capable of being generally used, have to come.

In conclusion, a large number of treatments have been tried over a long period of time but only PPS (oral or intravesical), amitriptyline, hydroxyzine, CyA, intravesical DMSO, TUR of visible lesions, and major reconstructive surgery reach a high degree of recommendation.

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Study concept and design: Fall, Oberpenning, Peeker.

Acquisition of data: Oberpenning, Fall.

Analysis and interpretation of data: Fall, Oberpenning, Peeker.

Drafting of the manuscript: Fall, Oberpenning, Peeker.

Critical revision of the manuscript for important intellectual content: Fall, Oberpenning, Peeker.

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Editorial Comment on: Treatment of Bladder Pain Syndrome/Interstitial Cystitis 2008: Can We Make Evidence-Based Decisions?

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According to the standardisation of terminology in lower urinary tract function, painful bladder syndrome (PBS) is defined as a 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. The same standardisation suggested that the term PBS should replace the common definition of interstitial cystitis, which is a specific diagnosis and requires confirmation by typical cystoscopic and histological features [1]. Most of the issues regarding this disease are currently controversial, including definition, prevalence, aetiology, pathophysiology, and treatments.

Fall et al provided a comprehensive nonsystematic review of the available evidence in the field of medical and surgical treatment of BPS, with major attention to the results of randomised controlled trials (RCTs). The authors concluded that the actual knowledge was “fragmentary and insufficient” and that some sort of evidence was available for the oral use of pentosan polysulfate sodium (PPS), amitriptyline, hydroxyzine, and

cyclosporin A as well as for the intravesical use of PBS and dimethyl sulfoxide [2].

In the era of evidence-based medicine, high-quality health care implies a practice that is consistent with the best available pieces of evidence [3]. Unfortunately, such a statement is very hard to apply to diseases such as PBS, where RCTs are difficult to perform because of the prevalence of the disease and the lack of clear, “positive” criteria for identifying and stratifying the patients. Consequently, some of the available RCTs are not good-quality trials, which strongly limits the level of the evidence.

The authors should be commended for their efforts to summarise the available studies on PBS but, most of all, for the provided suggestions for improving the quality of clinical research in the field, aiming at a better knowledge of this complex disease.

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Editorial Comment on: Treatment of Bladder Pain Syndrome/Interstitial Cystitis 2008: Can We Make Evidence-Based Decisions?

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The etiologic factors underlying the urinary tract disorders referred to as interstitial cystitis (IC) and/

or painful bladder syndrome (PBS) are not yet clearly understood. Experimental evidence indicates that a component in the cell coat of the vesical epithelium, a polysaccharide named glycosaminoglycan (GAG), regulates urothelial permeability and prevents noxious compounds in the urine from infiltrating into the bladder wall [1]. This function would be similar to the well known role GAG plays in renal physiology, where it imparts selectivity to filtration through the

glomerular basement membrane. Because GAG in the urothelial coating may be defective or even lost in IC/PBS patients, as shown recently [2], urinary compounds would infiltrate into the vesical wall and trigger inflammatory reactions and/or nerve stimulation that would ultimately account for most of the clinical manifestations of IC/PBS [1,2].

In line with its physiological role in the urothelium, GAG or physicochemically similar polymers, such as pentosanpolysulfate, have been used to repair the putatively defective coating. Often these polymers are administered singly, and they remain a mainstay in IC/PBS therapy, as well discussed by Fall, Oberpenning, and Peeker [3]. However, a GAG may also be used as an adjuvant to another polymer, such as pentosanpolysulfate, especially when the latter does not adequately improve symptoms [4].

The present review [3] is a useful critical appraisal of the many different therapies currently available for the treatment of IC/PBS, enabling the clinician to make more objective decisions. Of special interest is the inclusion of alternative treatments, a more comprehensive evaluation of surgical procedures, and the classification of the various treatments according to their level of evidence and recommendation. Although there are other recent reviews on this subject, these

usually focus on pharmacologic treatments and only a few evaluate in greater detail other available therapies, notably the surgical ones [5].

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Editorial Comment on: Treatment of Bladder Pain Syndrome/Interstitial Cystitis 2008: Can We Make Evidence Based Decisions?

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The urologic, gynaecologic, and medical literature of our time has become so huge on the definition, diagnosis, and treatment of interstitial cystitis/painful bladder syndrome (IC/PBS) that, honestly, no one, clinician or investigator, can read more than a small fraction of it [1]. Most of us rely heavily on synoptic manuscripts, such as review articles, looking for answers to important questions, with the hope of saving time in searching and sifting the literature for reliable guidance in daily practice for treatment of IC/PBS. The result is a wide range of treatments, which may not reach a high level of evidence and/or of recommendation

[2,3]. Fall and coworkers report on an extensive review about the treatment of this challenging syndrome [4]. They address an entire range of treatments—oral drugs, intravesical compounds, interventional treatments, and surgical strategies—and they reach the conclusion that, unfortunately, many of the existing studies “in the field” have a low level of evidence. They also report that studies with good evidence following up positive pilot trials, end up with negative results. The strength of this report is that Fall and colleagues do not hide the truth: A large number of treatments have been tried over a long period of time but only a few of them have reached a high degree of recommendation.

Most sections of this paper are naturally devoted to basic science and clinical research, the evidence-based medicine underpinning the research, and the efforts for better pharmacologic treatment. Still, when you face a patient with this complex syndrome, you should realise that his/her disease

may be influenced by several factors that have little to do with our “scientific approach.” In our classical approach, the emphasis is on the final outcome as it may be driven by randomised controlled trials, cost-effectiveness therapies, and professional tables of evidence and recommendation. This results-based philosophy—“If you cannot measure it, by common agreement, it does not matter”—was recently addressed by Horton in his editorial in *The Lancet* [5]. We agree with Horton’s statement that “numbers, powerful and important as they are, do not embody or explain everything of value.” This is particularly true for patients suffering from IC/PBS. It is most important that the physician does not forget the general principles of practice when approaching these patients. Remember, you have to invest extra time on the first office visit, as it is essential to develop rapport and trust. You must collect a detailed history, do an accurate physical examination, and plan a therapeutic strategy. You must not be afraid to involve nursing personnel, as they are extraordinarily helpful in the management of therapies, patient telephone/e-mail contact, patient counselling, and teaching. You have to be loyal to patients, since they need to understand that no specific cure exists, that often the goal of therapy is to minimise symptoms and improve quality of life, and that the treatment of associated comorbidities is fundamental. Finally, never forget to involve other specialists and indicate the presence of support

groups, as patients with IC/PBS often have the sense that they suffer alone: Discussing their problems with other afflicted patients may offer them a great benefit [6].

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