Committee 19

Bladder Pain Syndrome International Consultation on Incontinence

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INTRODUCTION

1. EVIDENCE ACQUISITION

The unrestricted, fully exploded Medical Subject Heading (MeSH) ''interstitial cystitis'' (including all related terms as ''painful bladder syndrome,'' ''bladder pain syndrome", or different terms such as ''chronic interstitial cystitis,'' etc.) were 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; 1795 hits were retrieved. After exclusion of uncommon languages (other than English, French, German, Italian, Japanese, Spanish, Swedish) and by limiting the publications to the time period January 2004 to May 2008, 512 publications resulted.

Abstracts if available and titles of the 512 hits were reviewed, focusing on (but not limited to) clinical trials, randomised controlled trials, meta-analyses, scientific guidelines, and core clinical journals. The literature update thus achieved was added to the pre-existing database, covering the time period before and during 2004 (generated for the 2004 ICI Incontinence guideline, published 2005) that was established according to the same protocol.

Rating of the level of evidence and grade of recommendation was performed according to the Oxford Scale.

The committee believes that the Oxford system for categorizing levels of evidence is primarily relevant only for the sections on treatment, which follow. While the committee's opinions will be expressed, where applicable, regarding evidence and conclusions for other areas, including diagnosis, aetiology, and pathophysiology, use of the Oxford system in this context is more open to interpretation.

2. DEFINITION

Bladder Pain Syndrome (BPS) is a clinical diagnosis that relies on symptoms of pain in the bladder and or pelvis and other urinary symptoms like urgency and frequency. Based on the evolving consensus that BPS probably is strongly related to other pain syndromes like Irritable Bowel Syndrome, Fibromyalgia and Chronic Fatigue Syndrome, the European Society for the Study of Bladder Pain Syndrome/ Interstitial Cystitis (ESSIC) recently published a comprehensive paper on definition and diagnosis of BPS [1].

BPS was defined as chronic (>6 months) pelvic pain, pressure, or discomfort *perceived to be* related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydro-distension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioural, emotional, and sexual symptoms should be addressed.

This definition has been broadly accepted although actual wording differs somewhat [2]. Because omitting the name "Interstitial Cystitis" might cause serious problems in different health systems by affecting reimbursement, the possibility of patients gaining disability benefits, and so forth, the name Bladder Pain Syndrome/ Interstitial Cystitis (BPS/IC) could be used in parallel with BPS for the time being. ***In this chapter the term Bladder Pain Syndrome largely replaces the older Interstitial Cystitis term, but the two are essentially interchangeable as there is no accepted definition that clearly delineates the interstitial cystitis syndrome from bladder pain syndrome. The Consultation believes the latter term more appropriately describes the disorder.***

Historically, definitions of IC have moved from a severe inflammatory bladder disease to a condition described primarily by symptoms (**table 1**) [2].

The International Continence Society [9] (ICS) used the term Painful Bladder Syndrome (PBS) defined 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 reserved the diagnosis Interstitial Cystitis (IC) to patients with "typical cystoscopic and histological features", without further specifying these. It has however been shown, that only a fraction of patients believed by experts to have BPS fulfil this definition [10].

The condition will therefore in the remainder of this chapter be referred to as BPS. As the terminology is in flux, some of the older literature may be discussed using the original terminology in the interests of clarity. Logically "interstitial cystitis" should include some form of demonstrable inflammation in the bladder wall, while "bladder pain syndrome" should include pain in the region of the bladder. The diagnosis of BPS is based on exclusion of other diseases in the bladder, urethra, and other pelvic organs including the musculoskeletal system. As with other diseases without clear objective diagnostic criteria or pathophysiological explanation, countless theories have been put forward without adding much to the delineation or understanding of the disease.

In practice, patients with symptoms of BPS are screened to exclude other relevant diagnoses or confusable diseases [1], and a focused evaluation is performed at the discretion of the physician or centre. This evaluation might include cystoscopy under local or general anaesthesia, bladder distension with registration of bladder capacity and/or the presence of glomerulations and Hunner's lesion. Bladder wall biopsies might be obtained and evaluated for inflammation, ulcer, fibrosis, mast cells etc. The evaluation might also include urodynamics with registration of bladder capacity, compliance and bladder stability [11]. One view of the relationship of BPS with OAB is graphically depicted in **Figure 1** [12]. The 14% incidence of urodynamic detrusor overactivity in the BPS [13] patients is probably close to what one might expect in the general population if studied urodynamically [14].

In the end, these investigations might prove to be normal and the patients are identified as having BPS as a diagnosis of exclusion. The relevance of urodynamic, cystoscopic and histological findings is further obscured, because the methodology by which these results is obtained is rarely comparable and it is therefore recommended to use the standardisations described by ESSIC [1].

Table 1. Historical definitions of interstitial cystitis

- 1887 Skene [3] : An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes.
- 1915 Hunner [4]: A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).
- 1951 Bourque [5] : Patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate at all moments of the dav and of the night suffering pains *every* time they *void.*
- 1978 Messing and Stamey [6]: Nonspecific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat *relieved* by voiding when associated with glomerulations upon bladder distention under anesthesia.
- 1990 Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and, glomerulations or Hunner's ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 *voids* per day, 1 *void* per night, and cystometric bladder capacity less than 350cc [7].
- 1997 NIDDK Interstitial Cystitis Database Entry Criteria: Unexplained urgency **or** frequency (7 or more *voids* per day), **OR** pelvic pain of at least 6 months duration in the absence of other definable etiologies [8].

I. NOMENCLATURE/ HISTORY/ TAXONOMY

1. HISTORICAL NOTES

Recent historical reviews confirm that interstitial cystitis was recognized as a pathologic entity during the 19th century [15,16]. In his textbook Practical Observations on Strangulated Hernia and Some Diseases of the Urinary Organs, Joseph Parrish, a Philadelphia surgeon, described 3 problematic cases of recurrent, severe lower urinary tract symptoms in which he made repeated attempts to locate a bladder stone, which was the most common source for these symptoms in early 19th century America [17]. As Teichman et al have convincingly argued, these patients displayed all of the clinical hallmarks of IC including chronic frequency, urgency, dysuria and pelvic pain in the absence of demonstrable pathology [18]. Although he used the term repeatedly in his manuscript, Parrish did not elaborate upon the clinical definition of "tic doloureux," likely because contemporaneous physicians would have been familiar with the concept. However, Parrish attributed the term Tic doloreux to his mentor, Dr. Phillip Syng Physick, who had applied it to patients with severe lower urinary tract symptoms with no discernible etiology, with the most common etiology during the 19th century being bladder stones.

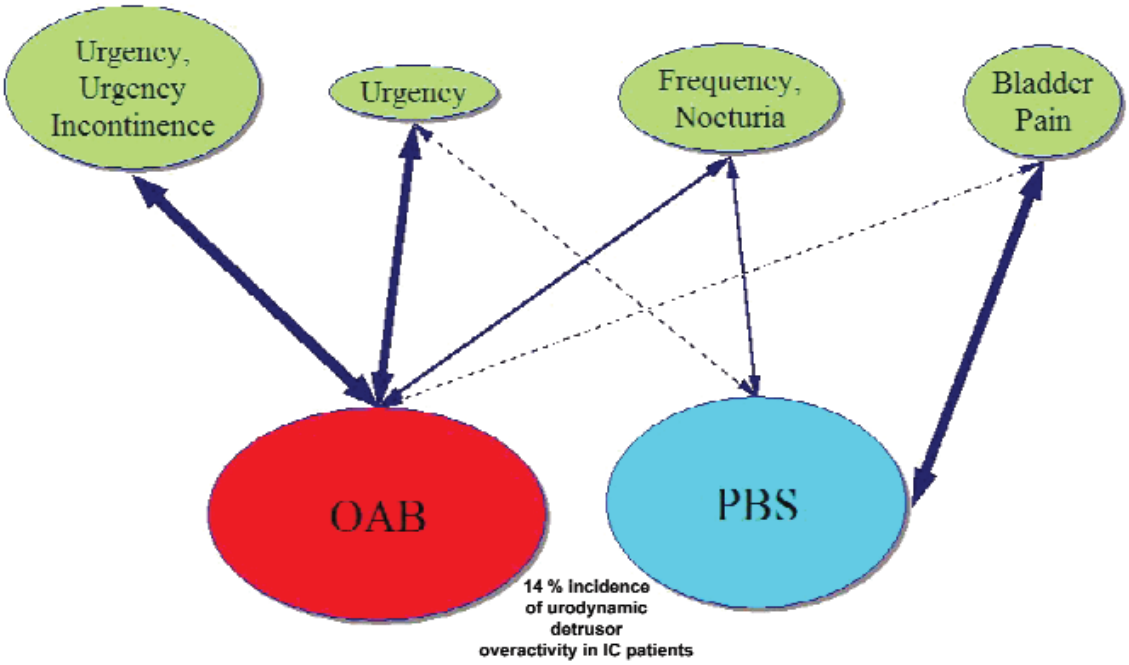

Figure 1 : Overactive Bladder (OAB) and its relationship to Painful Bladder Syndrome (PBS). Abrams, P., Hanno, P., and Wein, A.: Overactive bladder and painful bladder syndrome: there need not be confusion. Neurourol Urodyn, 24: 149, 2005.

A review of archival material from the Philadelphia College of Physicians indicates that by 1808 Physick had developed a concept of bladder inflammation, a "bladder ulcer," that produced lower urinary tract symptoms in the absence of bladder stone [15]. Tic douloureux at its time represented a neurological irritation, most often associated with the trigeminal nerve but applicable to other sensory distributions as well, which produced pain and discomfort in the absence of injury or other specific physical findings. In applying the concept of tic douloureux to bladder sensation Parrish was ascribing the paroxysmal lower urinary tract symptoms occurring in patients to an idiopathic process affecting the nerves of the bladder. This sophisticated concept continues to be a prominent component of modern theories of BPS pathogenesis. Furthermore, Tic douloureux allowed him to formulate a diagnosis for those patients who chronically manifested the symptoms caused by a stone (severe frequency, urgency, dysuria and pelvic pain) but had no stone that could be detected. That is, he considered a neuropathic etiology in the absence of any other tangible causes of bladder pain. Clearly, this experience strongly resonates with the contemporary diagnosis of BPS.

50 years after Parrish's first publication on the condition, Skene used the term interstitial cystitis to describe an inflammation that has "destroyed the mucous membrane partly or wholly and extended to the muscular parietes" [3]. Early in the 20th century, at a New England Section meeting of the American Urological Association, Guy Hunner reported on 8 women with a history of suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years [4,19]. He drew attention to the disease, and the red, bleeding areas he described on the bladder wall came to have the pseudonym "Hunner's ulcer". As Walsh observed, this has proven to be unfortunate [20]. In the early part of the 20th century, the very best cystoscopes available gave a poorly defined and ill-lit view of the fundus of the bladder. It is not surprising that when Hunner saw red and bleeding areas high on the bladder wall, he thought they were ulcers. For the next 60 years, urologists would look for ulcers and fail to make the diagnosis in their absence. The disease was thought to be a focal, rather than a pancystitis.

Hand authored the first comprehensive review about the disease, reporting 223 cases [21]. Many of his epidemiologic findings have held up to this day. His description of the clinical findings bears repeating. "I have frequently observed that what appeared to be a normal mucosa before and during the first bladder distention showed typical interstitial cystitis on subsequent distension". He notes, "small, discrete, submucosal hemorrhages, showing variations in form…dot-like bleeding points…little or no restriction to bladder capacity." He portrays three grades of disease, with grade 3 matching the small-capacity, scarred bladder described by Hunner. Sixty-nine percent of patients were grade 1 and only 13% were grade 3. Walsh later coined the term "glomerulations" to describe the petechial haemorrhages that Hand had described [20]. But it was not until Messing and Stamey discussed the "early diagnosis" of IC that attention turned from looking for an ulcer to make the diagnosis to the concepts that 1) symptoms and glomerulations at the time of bladder distention under

anesthesia were the disease hallmarks, and 2) the diagnosis was primarily one of exclusion [6,20].However, this description was not suitable for defining this disease in a manner that would help physicians make the diagnosis and set up research protocols.

The National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK) held a major meeting in 1987 with researchers and clinicians from around the world [22]. This ultimately resulted in the **1990 Revised NIDDK Criteria**: Pain associated with the bladder or urinary urgency, **and**, glomerulations or Hunner's ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc [7]

In order to validate the criteria, which were designed not for clinical diagnosis, but rather to ensure that patients enrolled in research trials could be agreed upon to have the disease, a database with broad entry criteria was created. The **1997 NIDDK Interstitial Cystitis Database Entry Criteria**: unexplained urgency **or** frequency (7 or more voids per day), **OR** pelvic pain of at least 6 months duration in the absence of other definable etiologies [23]. Urgency was not defined in the protocol. Participants were given a 10 point scale, and those who scored 2 or higher on self report satisfied the urgency criteria. The protocol was written in 1992, a time when the definition of "urgency" was not a particularly controversial topic. When a comparison of the NIDDK revised criteria with the database entry criteria was performed, it was apparent that up to 60% of patients clinically believed to have interstitial cystitis by experienced clinicians were being missed when the NIDDK research criteria were used as a definition of the disease [24]. The last decade has been an active one from an international standpoint in terms of wrestling with the issues of diagnosis and definition [25-27].

2. NOMENCLATURE AND TAXONOMICAL CONSIDERATIONS

There is currently no agreement how this complex syndrome should be referred to. The literature over the last 170 years has seen numerous changes in description and nomenclature of the disease. The syndrome has variously been referred to as tic doloureux of the bladder, interstitial cystitis, cystitis parenchymatosa, Hunner's ulcer, panmural ulcerative cystitis, urethral syndrome, and painful bladder syndrome [3,5,16,18,19,28,29]. The term ''interstitial cystitis,'' which Skene is credited with coining and Hunner for bringing it in to common usage, is a misnomer; in many cases not only is there no interstitial inflammation, but also, histopathologically, there may be no inflammation at all [30-33].

By literally focussing exclusively on the urinary bladder, the term interstitial cystitis furthermore does not do justice to the condition from both the physician's and the patient's perspective. The textual exclusiveness ignores the high co-morbidity with various pelvic, extra-pelvic and non-urological symptoms [34] that frequently precede the onset of the bladder condition [35].

With the formal definition of the term ''painful bladder syndrome'' by the ICS in 2002, the terminology discussion became an intense international focal point [9].

- In Kyoto at the ICICJ in March 2003, it was agreed that the term ''interstitial cystitis'' should be expanded to ''interstitial cystitis/chronic pelvic pain syndrome'' when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/ pathology [36].
- The European Society for the Study of Interstitial Cystitis (ESSIC) held its first meeting in Copenhagen soon after Kyoto. Nomenclature was discussed, but no decision was reached, as the meeting concentrated on how to evaluate patients for diagnosis [11].
- At the 2003 meeting of the NIDDK titled, "Research Insights into Interstitial Cystitis,'' it was concluded that ''interstitial cystitis'' will inexorably be replaced as a sole name for this syndrome. It will be a gradual process over several years. At the meeting it was referred to as ''interstitial cystitis/painful bladder syndrome'' in keeping with International Continence Society nomenclature [37].
- At the 2004 inaugural meeting of the Multinational Interstitial Cystitis Association in Rome, it was concluded that the syndrome should be referred to as ''painful bladder syndrome/interstitial cystitis'' or ''PBS/IC'' to indicate an intellectual and taxonomical hierarchy within the acronym [37].
- The International Consultation on Incontinence in 2004, cosponsored by the ICS and Societe Internationale d'Urologie in association with the World Health Organization, included the syndrome as a part of its consultation. The chapter in the report was titled, ''painful bladder syndrome (including interstitial cystitis),'' suggesting that the IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter, co-authored by nine committee members and five consultants from four continents, it was referred to as PBS/ IC (one inclusive entity) [38].
- In June 2006 Abrams and colleagues published an editorial focussing on the nomenclature problem [39]. They noted that: "It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. Unfortunately, the latter is not the case for many of the pain

syndromes suffered by patients seen at most pain, gynecological, and urological clinics. For the most part these "diagnoses" describe syndromes that do not have recognized standard definitions, yet infer knowledge of a pathophysiologic cause for the symptoms. Unfortunately the terminology used to describe the condition may promote erroneous thinking about treatment on the part of physicians, surgeons and patients. These organ based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous." The editorial went on to note that a single pathologic descriptive term (interstitial cystitis) for a spectrum of symptom combinations ill serves patients.

The umbrella term "painful bladder syndrome" was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS. It would fall within the rubric of chronic pelvic pain syndrome. Sufferers would be identified according to the primary organ that appears to be affected on clinical grounds. Pain not associated with an individual organ would be described in terms of the symptoms.

One can see in this the beginnings of a new paradigm that might be expected to change the emphasis of both clinical and basic science research, and that removes the automatic presumption that the end-organ in the name of the disease should necessarily be the sole or primary target of such research.

- At the major biannual IC research conference in the fall of 2006, held by the National Institute of Diabetes, Digestive, and Kidney Disorders (Frontiers in Painful Bladder Syndrome/Interstitial Cystitis), the ESSIC group was given a block of time with which to present their thoughts and conclusions. Because PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, and because IC is open to different interpretations, ESSIC suggested that Painful Bladder Syndrome be redesignated as Bladder Pain Syndrome (BPS), followed by a type designation. BPS is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistention findings (1, 2, or 3, indicating increasing grade of severity) and the second to biopsy (A, B, and C, indicating increasing grade of severity of biopsy findings) (**Table 2**). Although neither cystoscopy with hydrodistention nor bladder biopsy was prescribed as an essential part of the evaluation, by categorizing patients as to whether either procedure was done, and if so, the results, it is possible to follow patients with similar findings and study each identified cohort to compare natural history, prognosis, and response to therapy [40].

As Baranowski et.al. conceived it in early 2008, BPS is thus defined as a pain syndrome with a collection of symptoms, the most important of which is pain perceived to be in the bladder [41]. IC is distinguished

Table 2.

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

[1] cystoscopy: glomerulations grade II-III
[2] with or without glomerulations
[3] histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

van de Merwe, J. P., Nordling, J., Bouchelouche, P., Bouchelouche, K., Cervigni, M., Daha, L. K. et al.: Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol, 53: 60, 2008

as an end-organ, visceral-neural pain syndrome, whereas BPS can be considered a pain syndrome that involves the end-organ (bladder) and neuro-visceral (myopathic) mechanisms. In IC, one expects end-organ primary pathology. This is not necessarily the case in the broader BPS.

A didactically very demonstrative way to conceptualize the dawning shift in conception of the condition is with the drawing of a target (**Figure 2**). There may be many causes of chronic pelvic pain. When an aetiology cannot be determined, it is characterized as pelvic pain syndrome. To the extent that it can be distinguished as urologic, gynecologic, dermatologic, and the like, it is further categorized by organ system. A urologic pain syndrome can sometimes be further differentiated on the site of perceived pain. Bladder, prostate, testicular, and epididymal pain syndromes follow. Finally, types of BPS can be further defined as IC, or simply categorized by ESSIC criteria. Patient groups have expressed their concerns with regard to any nomenclature change that potentially drops the term ‘‘interstitial cystitis’’ because the U.S. Social Security Administration and private insurances recognize IC but not the term BPS, and benefits potentially could be adversely affected. Whether the term “interstitial cystitis”, as difficult as it is to define and as potentially misleading as it is with regard to aetiology and end-organ involvement, should be maintained, is a subject of ongoing controversy.

II. EPIDEMIOLOGY

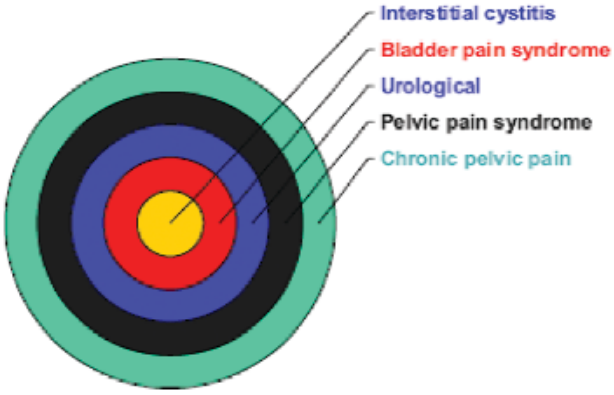

Figure 2: Conceptual Diagram of Pelvic Pain

It has been estimated that the prevalence of chronic pain due to benign causes in the population is at least 10% [42]. Numerous case series have, until recently, formed the basis of epidemiologic information regarding BPS. Farkas and associates [43] discussed IC in adolescent girls. Hanash and Pool [44] reviewed their experience with IC in men. Geist and Antolak [45] reviewed and added to reports of disease occurring in childhood. A childhood presentation is extremely rare and must be differentiated from the much more common and benign-behaving *extraordinary urinary frequency syndrome of childhood*, a self-limited condition of unknown etiology [46,47]. Nevertheless, there is a small cohort of children with chronic symptoms of bladder pain, urinary frequency, and sensory urgency in the absence of infection who have been evaluated with urodynamics, cystoscopy, and bladder distention and have findings consistent with the diagnosis of BPS. In Close and colleagues’ review of 20 such children [48], the median age of onset was younger than 5 years, and the vast majority of patients had long-term remissions with bladder distention.

A study conducted at the Scripps Research Institute [49] included 374 patients at Scripps as well as some members of the Interstitial Cystitis Association, the large patient support organization. A more recent, but similar study in England [50] concurred with the Scripps findings of urgency, frequency, and pain in the vast majority of these patients, devastating effects on quality of life, and often unsuccessful attempts at therapy with a variety of treatments. Although such reviews provide some information, they would seem to be necessarily biased by virtue of their design.

Epidemiology studies of BPS are hampered by many problems [51]. The lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology make much of the literature difficult to interpret. Overlapping patterns of lower urinary tract symptoms and pelvic pain are common and present challenges for clinical practice and research [52]. This is most apparent when one looks at the variation in incidence reports in the United States and around the world. These range from 1.2 per 100,000 population and 4.5 per 100,000 females in Japan [53], to a questionnaire based study that suggests a figure in American women of 20,000 per 100,000 [54]. Certainly, bladder pain symptoms are more common than suggested by coded physician diagnoses [55].

Several population-based studies have been reported in the literature, and these studies tend to support the reviews of selected patients or from individual clinics and the comprehensive follow-up case-control study by Koziol [56]. The first population-based study [57] included “almost all the patients with interstitial cystitis in the city of Helsinki”. This superb, brief report from Finland surveyed all diagnosed cases in a population approaching 1 million. The prevalence of the disease in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. The annual incidence of new female cases was 1.2 per 100,000. Severe cases accounted for about 10% of the total. Ten per cent of cases were in men. The disease onset was generally subacute rather than insidious, and full development of the classic symptom complex occurred over a relatively short

time. IC does not progress continuously, but usually reaches its final stage rapidly (within 5 years in the Koziol study [49]) and then continues without significant change in symptomatology. Subsequent major deterioration was found by Oravisto to be unusual. The duration of symptoms before diagnosis was 3-5 years in the Finnish study. Analogous figures in a classic American paper a quarter of a century earlier were 7-12 years [21].

Another early population study, this in the United States, first demonstrated the potential extent of what had been considered a very rare disease [58]. The following population groups were surveyed: 1) random survey of 127 board-certified urologists 2) 64 IC patients selected by the surveyed urologists and divided among the last patient with IC seen, and the last patient with IC diagnosed 3)904 female patients belonging to the Interstitial Cystitis Association 4) random phone survey of 119 persons from the US population. This 1987 study reached the following conclusions:

1. 43,500 to 90,000 diagnosed cases of IC in the USA (twice the Finnish prevalence)
2. Up to a five-fold increase in IC prevalence if all patients with painful bladder and sterile urine had been given the diagnosis, yielding up to half million possible cases in the USA
3. Median age of onset 40 years
4. Late deterioration in symptoms unusual
5. 50% temporary spontaneous remission rate, mean duration 8 months
6. 10 times higher incidence of childhood bladder problems in IC patients vs controls
7. 2 times the incidence of a history of urinary tract infection vs. controls
8. Lower quality of life than dialysis patients
9. Costs including lost economic production in 1987 of $427 million

Other population studies followed. Jones et al [59] obtained their data from self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey. The survey estimated that 0.5% of the population, or >1,000,000 people in the United States reported having a diagnosis of IC. There was no verification of this self-report by medical records. Bade et al [60] used a physician questionnaire-based survey in the Netherlands yielding an overall prevalence of 8-16 per 100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells. This prevalence in females compares to 4.5 per 100,00 in Japan [53]. The Nurses Health Study I and II [61] showed a prevalence of IC between 52 and 67 per 100,000 in the USA, twice the prevalence in the Held study [58] and three-fold greater than the Netherlands [60]. It improved on previous studies by using a large sample derived from a general population and careful ascertainment of the diagnosis. If the 6.4% confirmation rate of their study were applied to the Jones et al National Health Interview Survey data, the prevalence estimates of the two studies would be nearly identical. Ibrahim and colleagues [62] studied prevalence among community-dwelling women in Michigan, comparing survey responses from 215 established BPS cases with 823 age-matched controls of 3.7% to 4.4%., a figure that corresponds with other symptom-based assessments around the world [63-65].

1. POPULATION BASED STUDIES AND THE NEED FOR A BETTER QUESTIONNAIRE: (Figure 3)

Increasingly epidemiological studies of BPS are being conducted on large populations. This is the best way to evaluate risk factors, as well as obtain more accurate measures of disease prevalence. However, in population based studies, disease assessment is done by symptom-based questionnaires. Warren, et al [66] combined a mail-in survey with randomly selected telephone surveys to determine the prevalence of BPS amongst first degree relatives in comparison to that of the general population. They concluded that adult female first degree relatives of patients with BPS may have a prevalence of BPS 17 times that found in the general population. This suggests but does not prove a genetic susceptibility to BPS. The O'Leary Sant (OLS) and the Pelvic Pain and Urgency/Frequency (PUF) questionnaires were compared by Rosenberg and Hazard [67] in the same general practice population of 1218 patients. The prevalence of BPS with the OLS was determined to be 0.57%, with the PUF the prevalence was determined to be 12.6%. This indicated the need for a more accurate screening tool/questionnaire to be used with population based studies. When Nickel, et al [68] utilized the OLS in outpatient urology practice populations of 65 urologists, the prevalence of IC was determined to be 2.8%. This is strikingly similar to studies using the OLS in Finland, Austria, and Taiwan [63-65]. Again this demonstrates the need for a more refined symptom based questionnaire which can be used by epidemiologists and non-urolgogists to get an accurate determination of prevalence in population studies.

Leppilahti, et al [64,69] studied a general population of women, in Finland, using the OLS. These urologists estimated the prevalence of BPS in the general Population of Finland to be 6.8%. However, when a sample of those women was examined by one of the urologists, the more accurate prevalence approached that reported by Nickel, et al: 3.0%. This demonstrates the variability of the OLS questionnaire, and how the

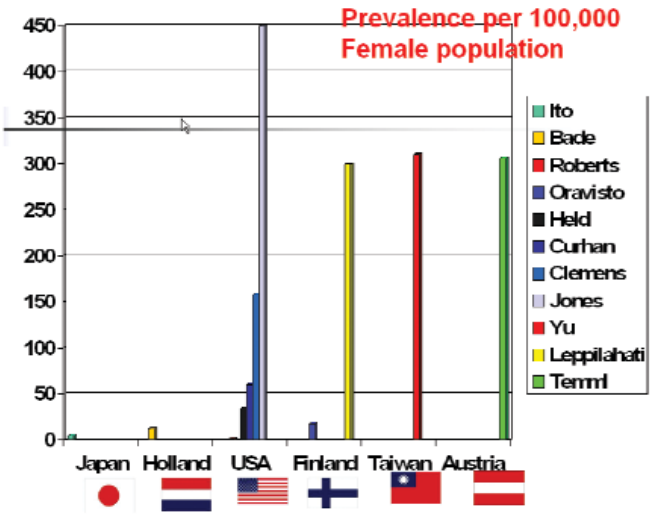

Figure 3 : Prevalence studies of bladder pain syndrome. Refer to text.

estimates can differ when confirmed by clinical examination.

The need for a more general symptom based questionnaire specific for epidemiological studies was again demonstrated by Clemens et.al [70]. They administered the OLS questionnaire to 5000 women and men that a clinician had determined not to have IC. Their results demonstrated that the OLS questionnaire, when utilized as a screening tool in a general population estimated IC to be 30 to 50 fold higher in women than the prevalence of a coded physician diagnosis. These findings suggest that the current population based studies conducted using either the OLS or PUF questionnaires tend to report a much higher prevalence of BPS than confirmed by physical exam. This increasingly becomes a problem as population based studies are conducted by epidemiologists and findings are not confirmed by clinical examination. It indicates the pressing need for development of a validated symptom based questionnaire with documented sensitivity and specificity to identify not only prevalence, but also risk factors and associated disorders.

An estimation of the prevalence at this time, recognizing that a consistent definition of the condition has not been used in epidemiologic studies, appears to be about 300 per 100,000 women, and a male prevalence of 10% to 20% of the female estimate. **Level of Evidence: 1 Grade of Recommendation: A**

2. OTHER CONSIDERATIONS

The Interstitial Cystitis Database Cohort (ICDB) of patients has been carefully studied, and the findings seem to bear out those of other epidemiologic surveys [71]. Patterns of change in symptoms with time suggest regression to the mean and an intervention effect associated with the increased follow-up and care of cohort participants. Although all symptoms fluctuated, there was no evidence of significant long-term change in overall disease severity. The data suggest that BPS is a chronic disease and no current treatments have a significant impact on symptoms over time in the majority of patients. Quality of life studies suggest that BPS patients are 6 times more likely than individuals in the general population to cut down on work time owing to health problems, but only half as likely to do so as patients with arthritis [72]. There is an associated high incidence of comorbidity including depression, chronic pain, and anxiety and overall mental health [38,38,73,74]. There seems to be no effect on pregnancy outcomes [75].

Most studies show a female to male preponderance of 5:1 or greater [38,76]. In the absence of a validated marker, it is often difficult to distinguish BPS from the chronic pelvic pain syndrome (nonbacterial prostatitis, prostatodynia) that affects males [77], and the percentage of men with BPS may actually be higher [78-80]. Men tend to be diagnosed at an older age and have a higher percentage of Hunner's lesion in the case series reported [80,81].

3. ASSOCIATED / OVERLAPPING DISORDERS

Until recently bladder pain syndrome was investigated by urologists and urological scientists focusing predominantly on the bladder. This can be attributed at least in part to the fact that the NIDDK Diagnostic Criteria, and other BPS definitions focused almost entirely on the bladder symptomatology. In 1994, a biostatistician at the Scripps Research Institute [56] reported that there was a significant association of IC with irritable bowel syndrome, as well as sinusitis, allergies and other inflammatory and autoimmune disorders. In the following year Dan Clauw, a rheumatologist, [82] published a novel unifying hypothesis which linked many chronic pain disorders such as BPS, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and others, to a common central pathogenesis and pathophysiology. Dr. Clauw concluded that "a multidisciplinary approach which examines a number of symptoms and systems concurrently is likely to be much more effective than examining one aspect at a single point in time". In 1997, Clauw, et al [83] reported on the symptom overlap between two cohorts of patients, one with fibromyalgia and one with IC. In the same year an analysis of a survey by Alagiri, et al [84] of over 6,700 persons who had a physician diagnosis of Interstitial Cystitis reported that individuals with BPS were 100 times more likely to have inflammatory bowel disease, and that allergies, irritable bowel syndrome, sensitive skin, and fibromyalgia also have an increased association with IC. The investigators concluded that" IC, which at present has neither a specific nor a curative treatment, has an increased association with certain chronic disease and pain syndromes, and raises the question of whether these dysfunction syndromes should be investigated for a common

biochemical defect". Unfortunately over a decade has passed and these concluding statements remain relevant, and the investigation of associated symptoms has not been a significant focus of investigation by BPS treating physicians.

Erickson, et al [85] reconfirmed the data reported by Clauw, et al 4 years earlier, in which BPS and fibromyalgia cohorts were compared. The Erickson group concluded that BPS patients had significant occurrence of symptoms of aches in joints, abdominal cramps, headache, other pelvic discomfort, etc. They concluded that the pathophysiology that affects BPS symptoms may affect other organ systems besides the bladder. An analysis of a co-twin control study in Seattle, Washington assessed the association of numerous chronic pain disorders including BPS, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, etc. and concluded that there was a high rate of association between these disorders [86,87]. It went on to suggest that treating physicians should examine affected patients for comorbid clinical conditions. They concluded that this multisystem assessment will help in determining a temporal relationship between the disorders as well as develop strategies for early intervention.

Peeker, et al [88] sub-classified BPS into classic (with ulcer) and non-ulcer and then evaluated for concurrent systemic and autoimmune disorders. Their findings supported the co-occurrence of associated disorders but did not see any significant differences between findings in the two categories of BPS patients. Weissman, et al [89] reported from a case-control and family history study the association of panic disorder with confirmed BPS and suggested there might be a subset of BPS patients with a genetic linkage to a possible syndrome associated with panic disorder, thyroid disorder and other disorders of autonomic or neuromuscular control.

There are very few studies reported by urologists using a patient sample. The study reported by Erickson, et al [85] is, perhaps, the most complete patient centered investigation reported by a urologist. Clemens, et al [90] reported a medical record survey at Kaiser Permanente Northwest in Portland, Oregon. They confirmed that BPS is associated with multiple other unexplained physical symptoms. They also confirmed previous findings of Peters, et al [91] that BPS is also associated with a history of child abuse.

Recent literature strongly suggests that these associated symptoms must be assessed in both BPS patients as well as patients with related disorders.. Brand, et al [92] have published "The Fibromyalgia Bladder Index" which is a validated fibromyalgia-specific instrument that captures information about the sensory bladder symptoms in a patient with fibromyalgia. Aaron and Buchwald [93] developed a series of multidisciplinary screening questions which address the more common associated /overlapping conditions. This is an excellent start to a complex problem.

The study of the associated symptoms and disorders must be continued and expanded utilizing cohorts of BPS diagnosed patients. A screening questionnaire must be developed by a multidisciplinary team of clinical specialists so that IC and its co-morbidities can be more effectively evaluated and treated by urologists, gynecologists, rheumatologists, general practice physicians and other clinical providers.

III. AETIOLOGY

The aetiology of BPS is still an enigma. Hypotheses abound with sparse evidence to support them. Studies on all aspects of BPS are hampered significantly because there is no general consensus on how to define and classify this condition.

1. INFLAMMATION

Inflammation is a non-disputable feature only in the classic or ulcerative form of BPS. Histological examination of bladder lesions has revealed pan-cystitis and perineural inflammatory infiltrates of lymphocytes and plasma cells [94,95]. **Level of Evidence:1 Grade of Recommendation: A**

2. MAST CELL ACTIVATION

Mast cells are thought to have a role in the etiology and/or pathogenesis of BPS. They are multifunctional immune cells that contain highly potent inflammatory mediators such as histamine, leukotrienes, serotonins, and cytokines [96]. These cells are the repositories of many potent inflammatory factors. Many of the symptoms and findings in ulcerative BPS such as pain, frequency, oedema, fibrosis, and the production of new vessels in the lamina propria, could possibly be ascribed to the release of mast cell-derived factors. Hence, the mast cell-IgE system and its interaction with other inflammatory cells and the nervous system[97] seems to be of importance when it comes to pathogenesis.

There is a ten-fold increase in mast cell count in bladder tissue from patients with ulcerative BPS as compared to controls. In non-ulcer BPS, however, the mast cell count is normal or only slightly increased [96,98,99].

Other mechanisms have also been put forward. Bouchelouche [100] compared the urinary excretion of leukotrienes E4 and eosinophil protein X in patients in IC and noted detrusor mastocytosis and increased urinary leukotrienes E4 and eosinophil protein X. **Level of Evidence: 1 Grade of Recommendation: A**

3. UROTHELIAL DYSFUNCTION/GAG-LAYER DEFECTS

A defect in the glycosaminoglycan (GAG) layer has been proposed by Parsons and co-workers [101]. With such a defect the sub-mucosal nerve filaments might become accessible to noxious substances in the urine and this might explain bladder pain and urinary frequency. In ulcerative BPS there is granulation tissue indicating a reparative process following repeated disruption of the mucosa [102]. Widened tight junctions and increased permeability have been demonstrated by scanning electron microscopy and other techniques [103,104].

A more recent study by Parsons et al [105] has shown that Tamm-Horsfall protein is quantitatively different in BPS patients as compared to controls. Tamm-Horsfall protein is synthesized in the kidney and excreted into the urine. It has been suggested to have a role in immune defense and in preventing damage to the urothelial cells by injurious urinary constituents. **Level of Evidence: 2 Grade of Recommendation: B**

4. INHIBITION OF UROTHELIAL BLADDER CELL PROLIFERATION

One explanation of the bladder epithelial dysfunction might be the fact that the cells produce an inhibitor of heparin-binding epidermal growth factor-like production in BPS [106]. It was shown that explanted urothelial cells from BPS patients differ from controls not only as to production of epithelial growth factors but also in the rate of proliferation and the production of an antiproliferative factor (APF). Keay and co-workers [107] studied gene expression patterns in normal bladder urothelial cells treated with APF and with mock APF as compared to patterns expressed by BPS urothelial cells. The results indicate that the mechanism of APF inhibition of urothelial cells may involve both down-regulation of genes that stimulate cell proliferation along with up-regulation of genes that inhibit cell growth. The same group of researchers has indicated that APF seems to be specifically elevated in the urine of patients with BPS but not in persons with no or other conditions. These findings might open up new avenues for identification and development of urine markers for BPS [108]. **Level of Evidence:2 Grade of Recommendation: B**

5. AUTOIMMUNE MECHANISMS

There are numerous reports on autoantibodies in patients with BPS [109-112]. The precise identity of these of autoantibodies has yet to be determined. Some of the common clinical and histopathological characteristics present in BPS patients show certain similarities with other known autoimmune disturbances. Studies on autoantibodies in BPS have shown that these mainly consist of antinuclear antibodies [111] and these findings are in turn similar to the autoantibody profiles in some systemic diseases like Sjögren syndrome, which is known to be of autoimmune origin [88,113,114]. Only a portion of BPS patients have auto-antibodies. It has been proposed that the presence of auto-antibodies in these patients could be a reflection of disease severity [115].

Vascular immunopathology with immune deposits in the bladder wall was found by Mattila [116]. Further studies also suggest activation of complement [117]. By means of immunophenotyping and flow cytometric analyses of the bladder mucosa and peripheral blood, differences between ulcerative and non-ulcer BPS patients have been demonstrated. In the former group intense T-cell infiltrates and B-cell nodules were seen, compared to far less T-cell infiltrates in non-ulcer BPS [118]. Involvement of the immune system is one feature found in some individuals with BPS, but findings are conflicting and have not been helpful in explaining the aetiology. The lack of thorough descriptions of patients in many published studies has made classification and comparison between series impossible. **Level of Evidence: 2 Grade of Recommendation: C**

6. INFECTION

No microorganism has ever been revealed as the cause of BPS. Lynnes and coworkers did not find any evidence of recent or remote Gram negative or Gram positive infections in patients with BPS, nor did they find increased urinary IgA and IgG elevation [119]. This makes infection by an untested organism unlikely.

Warren et al [120] in a case control study of women with recent onset of BPS symptoms, reported that documented evidence of UTI at symptom onset was found in only a minority of patients. Polymerase chain reaction techniques to amplify bacterial 16S rRNA genes that would be present if there were bacteria in bladder tissue or urine in BPS patients despite negative cultures have been without success [121]. Contrary to what was demonstrated for chronic gastritis, there is no evidence for helicobacter in BPS patients [122] The possibility of a microbial contribution to the etiology of BPS remains an open question. **Level of Evidence: 1 Grade of Recommendation: A**

7. NEUROBIOLOGY/PELVIC CROSS-TALK

Several authors have described autonomic nerve changes [123-125], but the findings are far from uniform. An increase of sympathetic innervation and activation of purinergic neurotransmission has been reported. The S-100 family of proteins appear in Schwann cells of the peripheral nervous system [126,127]. Decreased levels of S-100 protein in the non-ulcer group as compared to controls has been found [128], which is consistent with a decreased nerve content in patients with non-ulcer BPS, a finding conflicting with the results of Hohenfellner [124] who used polyclonal antihuman protein gene product 9.5 antibody and found the overall nerve content increased

in BPS patients as compared to controls. However, their study did not include subtyping of the disease into ulcerative and non-ulcer type. A distinctive utrastructural appearance of specimens from patients with non-ulcer BPS prompted Elbadawi and Light to propose neurogenic inflammation as a trigger to a cascade of events taking place in this disease [129]. In this context it should be noted that afferent nerves release transmitters like substance P which could activate immune cells, or vasoactive intestinal polypeptide. These events may constitute a link to the immune cell system and promote a decrease of lymphocyte proliferation.

A prominent increase of tyrosine hydroxylase immunoreactivity in bladder tissue of BPS patients, as compared to controls, has been described [130]. This can presumably be interpreted as a sign of generally increased sympathetic outflow. This lends support to the notion of a neurogenic aetiology and or pathogenesis.

Malykhina and others [131-135] have demonstrated in innovative animal studies that there is a bidirectional neural cross-sensitization of the colon and lower urinary tract. Acute colitis sensitized lumbosacral spinal neurons receiving input from the urinary bladder result in spinal neuronal hyperexcitabiity that may be involved in central cross-organ sensitization of visceral nociception between the colon and urinary bladder. This provides information which not only supports a neurogenic etiology but also may account for the substantial overlap of BPS with other chronic pelvic pain disorders, especially the inflammatory bowel disorders [84]. Rudick and Colleagues have shown in a murine model organ cross talk in pelvic pain and modulation of pain responses by visceral inputs distinct from the inflamed site [136]. **Level of Evidence: 2 Grade of Recommendation: B**

8. NITRIC OXIDE METABOLISM

Regulation of urinary nitric oxide synthase activity has been proposed to be of importance for immunologic responses in BPS. The oral administration of L-arginine, the substrate for nitric oxide production [137] has been shown to increase nitric oxide related enzymes and metabolites in the urine of patients with BPS [138].

It has been reported that differences in NO evaporation between ulcerative and nonulcer BPS allows for subtyping of cases meeting the NIDDK criteria. This could negate the need for cystoscopy [139].**Level of Evidence: 2 Grade of Recommendation: C**

9. TOXIC AGENTS

There are a few publications which have suggested that toxic substances in the urine may cause injury to the bladder resulting in symptoms consistent with BPS. One published hypothesis is that heat labile, cationic urine components of low molecular weight may exert a cytotoxic effect [140]. Another group of investigators has suggested that defective constituent cytokine production may decrease mucosal defense to toxic agents [141]. **Level of Evidence: 3 Grade of Recommendation: D**

10. HYPOXIA

Decreased microvascular density has been reported to be a feature of bladders from some individuals with BPS [142] One group of investigators has reported that bladder perfusion decreased with bladder distension in some PBS patients compared to the opposite effect in control subjects [143] Despite these observations, the investigators have noted that bladder ischemia alone would not account for the symptoms associated with BPS. **Level of Evidence: 4 Grade of Recommendation: D**

11. THE ROLE OF GENETICS IN BPS

Warren et al [144] report findings from a small cohort of twins which demonstrated a greater concordance of BPS among monozygotic that among dizygotic twins. This finding suggested that there could be a genetic susceptibility to BPS. A later study by the same research group [66] suggested that adult female first-degree relatives of patients with BPS may have a prevalence of IC 17 times that found in the general population. This coupled with the previously reported twin data suggests, but does not prove, a genetic component adds to the susceptibility for BPS.

The report by Weissman et al [89] of the increased frequency of BPS in patients and their first degree relatives with panic disorder and other seemingly disparate disorders, has suggested that there is a familial syndrome consisting of BPS and other disorders of possible autonomic or neuromuscular dysfunction. More recent studies by the same group [145] from a case control study, suggested that this syndrome might include other anxiety disorders as well, and that families with and without this collection of symptoms were genetically distinguishable on chromosome 13. **Level of Evidence: 1 Grade of Recommendation: B**

CONCLUSIONS

There have been no significant conclusive advances made in understanding either the etiology or pathogenesis of BPS. It is now believed that the aetiology of BPS is more complex than has been previously envisioned [84,86,90,146-148]. The consideration of BPS as a part of a generalized somatic disorder should open new pathways to the study of BPS. Investigators should continue to explore central neurological mechanisms of pathogenesis, as well as genetic/familial, immunological and infectious etiologies of this puzzling, complex disorder.

An algorithm that attempts to illustrate an etiologic schema is presented below (**Figure 4**).

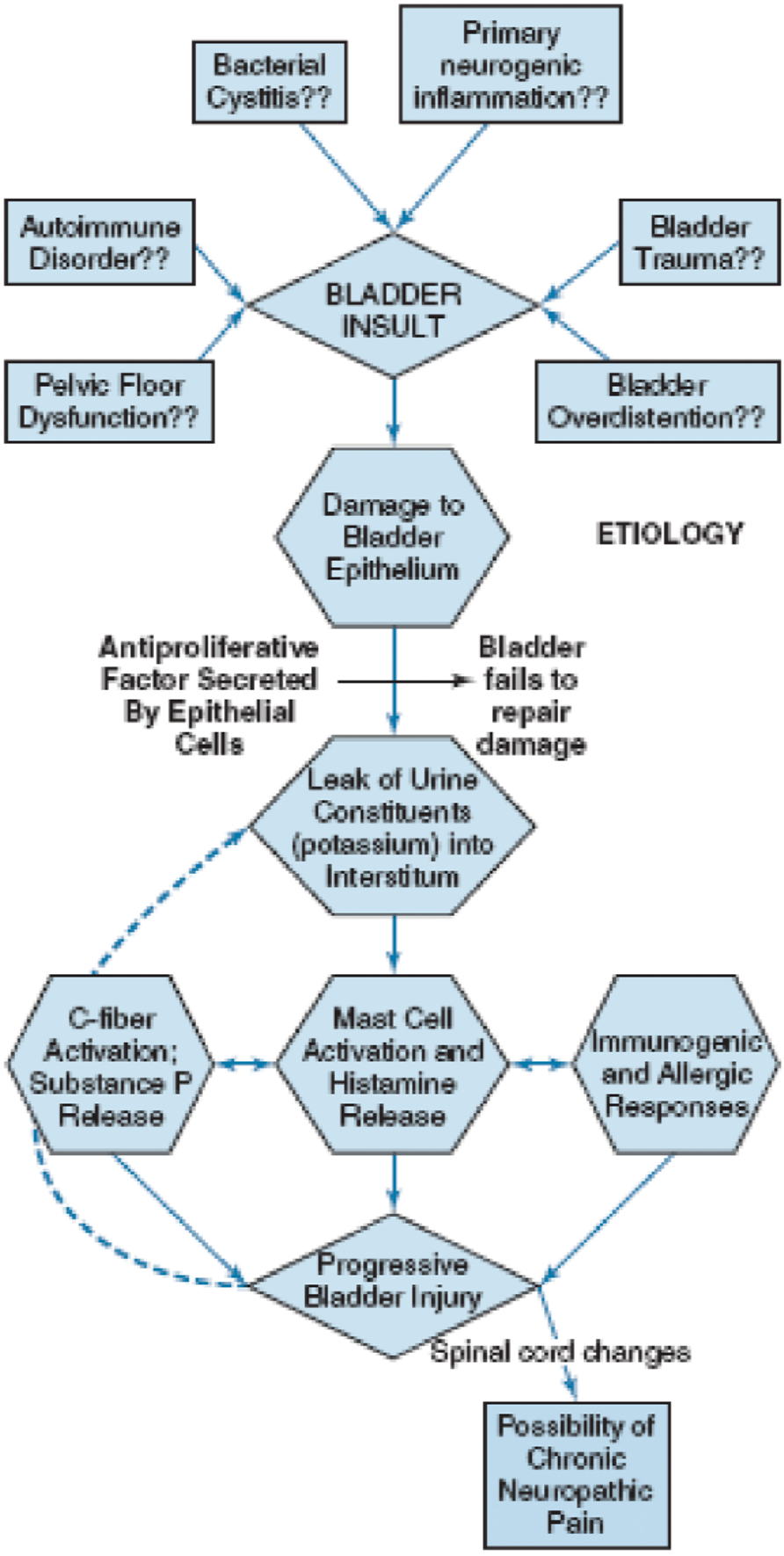

Figure 4 : Proposed Pathogenesis of Bladder Pain Syndrome

IV. PATHOLOGY

One can have pathology consistent with the diagnosis of BPS, but there is no histology pathognomonic of this syndrome. The role of histopathology in the diagnosis of BPS is primarily one of excluding other possible diagnoses. One must rule out carcinoma and carcinoma-in-situ, eosinophilic cystitis, tuberculous cystitis, as well as any other entities with a specific tissue diagnosis [102,149,150]. **Level of Evidence: 1 Grade of Recommendation: A**

While earlier reports described a chronic, edematous pancystitis with mast cell infiltration, submucosal ulcerations and involvement of the bladder wall and chronic lymphocytic infiltrate [151,152], these were cases culled from patients with severe disease and not representative of the majority of cases currently diagnosed. The pathologic findings in BPS are not consistent. There has been a great variation in the reported histologic appearance of biopsies from BPS patients, and even variation among biopsies taken from the same patients over time [22].

Lepinard and colleagues [153] reported a pancystitis affecting the 3 layers of bladder wall. In nonulcerative disease the vesical wall was never normal, epithelium being thinned and muscle being affected. Johansson and Fall [102] looked at 64 patients with ulcerative disease and 44 with nonulcerative IC. The former group had mucosal ulceration and hemorrhage, granulation tissue, intense inflammatory infiltrate, elevated mast cell counts and perineural infiltrates. The nonulcer group, despite the same severe symptoms, had a relatively unaltered mucosa with a sparse inflammatory response, the main feature being multiple, small, mucosal ruptures and suburothelial hemorrhages that were noted in a high proportion of patients. As these specimens were almost all taken immediately after hydrodistention, how much of the admittedly minimal findings in the nonulcer group were purely iatrogenic is a matter of speculation.

One can see completely normal biopsies in the nonulcerative BPS group [154]. Transition from nonulcerative to ulcerative BPS is a rare event [98], and pathologically the two types of IC may be completely separate entities. While mast cells are more commonly seen in the detrusor in ulcerative BPS[155], they are also common in patients with idiopathic bladder instability [156]. Mastocytosis in BPS is best documented by tryptase immunocytochemical staining [157]. Larsen and colleagues recommend taking biopsies from the detrusor of patients with suspected BPS and examining them with tryptase-stained 3 micron thick sections, with every seventh section used for quantification. They consider 27 mast cells/mm^2 indicative of masto-cytosis [158]. Despite attempts to develop a diagnostic algorithm based on the detrusor to mucosa mast cell ratio and nerve fiber proliferation [97], mast cell counts per se have no place in the differential diagnosis of this clinical syndrome.

Mast cells could be valuable in clinical phenotyping, but as yet that is unproven. Mast cells trigger inflammation that is associated with local pain, but the mechanisms mediating pain are unclear. In a murine model of neurogenic cystitis, Rudick and colleagues [159] demonstrated that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and tumor necrosis factor respectively. Therefore, pain is independent of pathology and inflammation, and histamine receptors may represent direct therapeutic targets for the pain of BPS and other chronic pain conditions.

Lynes and coworkers [32] concluded that biopsy specimens are often not helpful in confirming the diagnosis. Although BPS patients in his study had a higher incidence and degree of denuded epithelium, ulceration, and submucosal inflammation, none of these findings was pathognomonic. In addition, these "typical" findings occurred only in BPS patients with pyuria or small bladder capacity. Epithelial and basement membrane thickness, submucosal edema, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis were not significantly different in the BPS and control patients.

Attempts to definitively diagnose BPS by electron microscopy have also been unsuccessful. Collan's group [160], in the first such study, wrote that the similarity of the ultrastructure of epithelial cells in controls and IC patients makes it improbable that the disease process originates in the epithelium. Other investigators found no differences in the morphologic appearances of the glycocalyx and of urothelial cells in patients with IC when compared with controls [161]. Anderstrom and colleagues [104] saw no surface characteristics specific for IC, but believed that the mucin layer covering the urothelial cells seemed reduced in IC compared with controls, a fact disputed by Nickel in a very elegant paper [162]. Elbadawi and Light [129] observed ultrastructural changes sufficiently distinctive to be diagnostic in specimens submitted for pathologic confirmation of nonulcerative interstitial cystitis. Marked edema of various tissue elements and cells appeared to be a common denominator of many observed changes. The wide-ranging discussion of the etiology of IC in his paper is fascinating, but the pathological findings are potentially marred by the methodology, in that specimens were obtained after diagnostic hydrodistention [163].

So what is the place of pathologic examination of tissue in BPS? Attempts to classify the painful bladder by the pathoanatomical criteria described by Holm-Bentzen [164] are of questionable value. There is a

group of patients with what she describes as "nonobstructive detrusor myopathy" [165]. In her series, these patients with degenerative changes in the detrusor muscle often had residual urine, a history of urinary retention, and an absence of sensory urgency on cystometry with bladder capacities over 400cc. Most would not be clinically confused with BPS. A similar English series [166], however, included patients who met NIDDK research criteria and associated detrusor myopathy with diminished detrusor compliance and ultimate bladder contracture.

The Interstitial Cystitis Database (ICDB) study worked backwards from symptoms to pathology, and concluded that certain symptoms are predictive of specific pathologic findings [30,167]. Denson et. al. [33] analyzed forceps biopsies from 65 females and 4 males with BPS. Ten per cent of specimens showed vasodilatation or submucosal edema. Inflammation was absent in 30% of patients, and mild in another 41%. Cystoscopic changes did not correlate with degree of inflammation. Hanus and colleagues [168] studied 84 biopsies from 112 BPS patients and reported a linear relationship between the mean bladder capacity under anesthesia and severity of glomerulations. They did not find a correlation between severity of symptoms and histopathological changes observed by light or electron microscopy.

Rosamilia reviewed the pathology literature pertaining to BPS in 2 recent publications and presented her own data [31,38]. She compared forceps biopsies from 35 control and 34 PBS/IC patients, 6 with bladder capacities less than 400cc under anesthesia. Epithelial denudation, submucosal edema, congestion and ectasia and inflammatory infiltrate were increased in the BPS group. Submucosal hemorrhage did not differentiate the groups, but denuded epithelium was unique to the BPS group and more common in those with severe disease. The most remarkable finding in her study was that histological parameters were normal and indistinguishable from control subjects in 55% of BPS subjects. Method of biopsy can be important in interpreting findings, as transurethral resection biopsies tend to show mucosal ruptures, submucosal hemorrhage and mild inflammation [102], while histology is normal approximately half the time with cold-cup forceps biopsies [31,32,169].

Histopathology plays a supportive diagnostic role at best [170]. Major reconstructive procedures appear to have better outcomes in patients with pathology consistent with Hunner's lesions [171]. Inflammatory features can be seen in 24% to 76% of patients without a visible Hunner's lesion [172]. While recent studies suggest that a severely abnormal pathology may be associated with poor prognosis [173,174], this is not necessarily the case [175]. **At this point in time**, excluding other diseases that are pathologically identifiable is the primary utility of bladder biopsy in this group of patients.

V. DIAGNOSIS

Much work has been put into the attempt to define objective diagnostic criteria based on, among other factors, cystoscopy under local or general anesthesia, bladder distention with registration of bladder capacity and/or possible presence of glomerulations and Hunner's lesion, bladder wall biopsies evaluated for inflammation, ulcer, fibrosis, mast cells, etc. and urodynamics with registration of bladder capacity, compliance and bladder stability. Results have, however, been frustrating. It is more fruitful to establish a broad clinical diagnosis, mainly on the basis of symptoms and exclusion of other diseases, and then stratify patients by urodynamic, cystoscopic, histological, and other tests on the basis of the significance of these findings for results of treatment and prognosis of disease. Current efforts to phenotype the disorder by the presence or absence of associated syndromes and diseases may also prove useful in the same way.

What follows is based solely on expert opinion. ***Level of Evidence:4 Grade of Recommendation:C***

It is hoped that future Consultations will have the data to base such suggestions on more a more firm foundation.

1. HISTORY

A general thorough medical history should be taken. Special emphasis should be given to:

- Previous pelvic operations
- Previous UTI
- Bladder history/urological diseases
- Location of pelvic pain (referred pain) and relation to bladder filling/emptying.
- Characteristics of pain: onset, correlation with other events, description of pain
- Previous pelvic radiation treatment
- Autoimmune diseases
- Physical examination

A common physical examination should be performed including palpation of the lower abdomen for bladder fullness and tenderness:

- Standing: kyphosis, scars, hernia
- Supine: abduction/adduction of the hips, hyper-aesthetic areas

In **females** physical examination should include a vaginal examination with pain mapping of the vulvar region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor. Tenderness might be graded as mild, moderate or severe.

2. PAIN MAPPING

Inspection:

- Vulva
- exclusion of vulvar/vestibular diseases (vulvitis, dermatosis etc.)
- evaluation of introital area (endometriosis)
- tenderness of vestibular glands or vulvar skin (Touch Test: use wet cotton stick or finger tip)
- Vagina
- tenderness during insertion and opening of speculum
- cervical pathology
- vaginal fornices (endometriosis)
- Bimanual physical examination
- tenderness of urethra, trigone and bladder
- superficial/deep vaginal tenderness
- tenderness of pelvic floor muscles (levator, adductor)
- tenderness in adnexal areas

In **males** digital rectal examination (DRE) should be performed with pain mapping of the scrotal–anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and the scrotal content.

3. LABORATORY TESTING

- Urine dipstick (ABS, pH, leucocytes, nitrate), urine culture in all. If sterile pyuria culture for tuberculosis.
- Urine cytology in risk groups.
- Investigations for vaginal Ureaplasma and Chlamydia in females and prostatitis in men are optional.

4. SYMPTOM EVALUATION

- Voiding diary with volume intake and output for 3 days at initial evaluation. Patient sensation at voiding might be recorded (see chapter outcome assessment, Hanno).
- At follow-up only number of voidings during day and night time is necessary. Morning volume might be recorded as a help to monitor highest functional capacity.
- The O'Leary–Sant Symptom Score supplemented should be used as basic symptom score supplemented with the Quality of Life Score from the International Prostate Symptom Score (see chapter symptom scales, Hanno3).
- Pain should be recorded using a Visual Analogue Scale (VAS) for pain during the last 24 hours (to fit with the voiding diary). Separate scores for the average, mildest and worst pain should be obtained (see symptom scales)

5. URODYNAMICS

Level of Evidence:4 Grade of Recommendation:C

The NIDDK criteria excluded patients with detrusor overactivity at filling cystometry in order not to confuse the picture in clinical trials [22]. This does not however mean that detrusor overactivity can not coexist with bladder pain syndrome. In the interstitial cystitis database approximately 14% of BPS patients had overactive bladders [13]. Whether these patients respond better to antimuscarinics than BPS patients with stable bladders has never been systematically investigated. If so, a rationale for routinely employing urodynamics as a part of the evaluation would follow. In males, infravesical obstruction might be a differential diagnosis [176], and it is recommended to do flowmetry in all males and pressure-flow studies in men with a peak flow rate below 20ml/seconds.

There are no data to support the following recommendations:

In females, flowmetry, post void residual urine volume and pressure- flow study are optional. In males, a flowmetry should be done in all, and if maximum flow rate <20 ml/s a pressure-flow study and measure of residual urine volume should be done. It is recommended to perform filling cystometry with a filling rate of 50 ml/s (to comply with the revised Potassium Test - see below) to look for overactivity, volume at first desire to void and cystometric capacity.

6. POTASSIUM TESTING

Level of Evidence:1 Grade of Recommendation: -A (not recommended)

Parsons has championed an intravesical potassium chloride challenge, comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4 M potassium chloride solution. The test has proved controversial [177]. Pain and provocation of symptoms constitutes a positive test. Whether the results indicate abnormal epithelial permeability in the subgroup of positive patients, or hypersensitivity of the sensory nerves is unclear. Normal bladder epithelium can never be absolutely tight, and there is always some leak, however small [178]. The concentration of potassium used is 400meq per liter, far exceeding the physiologic urinary concentrations of 20-80meq/liter depending upon dietary intake [179]. Healthy controls can distinguish KCl from sodium chloride, though they don't experience severe pain [180]. The hope is that this test may stratify patients into those who will respond to certain treatments (perhaps those designed to fortify the glycosami-noglycan layer), but to date this information is lacking [181].

Used as a diagnostic test for interstitial cystitis, the potassium chloride test is not valid [182]. The gold standard in defining BPS for research purposes has been the NIDDK criteria. These criteria are recognized

to constitute a set of patients that virtually all researchers can agree have BPS, though they are far too restrictive to be used in clinical practice [24]. Thus, this group of patients should virtually all be positive if the KCl test is to have the sensitivity needed to aid in diagnosis. Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test [183]. In the group it should perform the best in, it is lacking in sensitivity. When we look at the specificity side of the equation, in the universe of asymptomatic persons, it performs relatively well and is rarely positive, although a recent study reported a 36% false positive rate in asymptomatic men [184]. It is in the patient population with confounding conditions for which we would want help in sorting out BPS from other disorders. Twenty-five percent of patients with overactive bladder test positive and virtually all patients with irritative symptoms from radiation cystitis and urinary tract infection test positive [183,185]. The results with chronic prostatitis / chronic pelvic pain syndrome in men are variable, but 50-84% of men have been reported to test positive [184,186,187]. In women with pelvic pain results are similar [188], and based on these findings, Parsons has expressed the view that BPS may affect over 20% of the female population of the United States [189]! Others have reported prevalence in unselected female textile workers in Turkey using similar methods at 32.8% [190]. Another way to interpret the findings would be that the KCl test is very nonspecific, missing a significant number of BPS patients and over-diagnosing much of the population.

Prospective and retrospective studies looking at the KCl test for diagnosis in patients presenting with symptoms of BPS have found no benefit of the test in comparison with standard techniques of diagnosis [182,191,192]. A recent modification of the test using 0.3 molar potassium chloride for potential differentiation between patients with IC and detrusor overactivity (DO) showed that the 0.3 M KCl reduces maximum cystometric capacity in BPS and DO, the effect being more pronounced in DO. Urothelial hyperpermeability was not specific to IC. Comparative cystometry using NS and 0.3 M KCl does not help to differentiate BPS from DO [193,194].

The development of a painless modification of the potassium chloride test [195] using cystometric capacity and a 0.2M solution may improve acceptability among patients. The so-called revised or Comparative Potassium Test has shown prognostic value in bladder irrigation studies, [196] but is considered optional by ESSIC. If performed it should be performed according to Daha et al. [195]: A Foley balloon catheter (14F) is inserted and the bladder drained. Instill into the bladder 500 ml saline (0.9%) at a rate of 50 ml/min via an infusion set until the maximum capacity is reached. Drain the bladder and measure the saline filling volume. Repeat the instillation and measurement with 500 ml 0.2 M potassium chloride at a rate of 50 ml/min (taking care that filling lines are emptied of all saline before KCl instillation), and calculate the filling volume difference. A difference in bladder capacity > 30% is considered positive. Besides reduction of bladder capacity with 0.2 M KCl there is a stronger feeling of urgency in IC patients compared to the saline filling, which is also clinically relevant.

7. CYSTOSCOPY

Level of Evidence:2 Grade of Recommendation:B

The classic cystoscopic picture of BPS as an “elusive” bladder ulcer with a corresponding cystoscopic appearance of patches of red mucosa exhibiting small vessels radiating to a central pale scar was described by Hunner in 1914 [4]. Since then, glomerulations, described as punctuate petechial hemorrhages and observed after hydrodistention, have become the primary cystoscopic feature of BPS [6]. But not all patients with symptoms of BPS have glomerulations, [24,33,197] and not all patients with glomerulations have symptoms of BPS [198-200]. Neither presence nor severity of glomerulations correlate with any of the primary symptoms of BPS, [30] although the presence of a Hunner’s lesion is significantly associated with bodily pain and urinary urgency [199]. The finding of a Hunner’s lesion or glomerulations has been somewhat subjective. Some researchers find a Hunner’s lesion in 50% of their BPS patients, while others rarely see one [201].

No study comparing individual perceptions and variations in reporting or classifying glomerulations has ever been reported. Bladder capacity during hydrodistention has not drawn much attention, although it is strongly associated with increased urgency [199].

Because considerable variation in the duration of distension, repetition of distension, the pressure used for distension, and the measurement of bladder capacity have been described [202], the ESSIC has suggested a standardized procedure for cystoscopy and hydrodistension [11]:

A rigid cystoscope is preferred to facilitate taking of adequate biopsies. Glycine or corresponding filling fluid should be used to allow for coagulation after biopsies. Infusion height should be approximately 80 cm above the Symphysis Pubis. A dripping chamber is used and the bladder is filled until fluid dribbling stops. If necessary, a digital block is applied around the urethra to prevent leakage. Pre-distension inspection includes observation for radiating vessels, coagulum or fibrine deposits, white spots, hyperaemia, oedema, cracks, scars or any other mucosal changes. Continuous inspection while filling the bladder is advised. When maximum capacity is reached, the distension is maintained for 3 minutes. The bladder is emptied and the colour of the fluid checked for the

degree of bleeding. The total volume drained is the measured maximum bladder capacity. During a second filling, the bladder is filled to approximately 1/3rd to 2/3rd of the bladder capacity to achieve optimal vision for inspection and biopsies. The bladder should not be filled to maximum capacity or distended again to avoid further provocation of changes with doubtful reproducibility.

a) Inspection

Describe lesions in anterior wall, posterior wall, lateral quadrants and fundus. At the fundus one should be alert for possible artefacts if there is blind introduction of the scope. Bladder mapping by drawing is mandatory. Photographs are recommended but optional.

b) Classification

Grade 0 = normal mucosa

Grade I = petechiae in at least two quadrants

Grade II = large submucosal bleeding (ecchymosis)

Grade III = diffuse global mucosal bleeding

Grade IV = mucosal disruption, with or without bleeding/oedema

c) How useful is hydrodistention?

Hydrodistension results fail to identify any statistically significant differences in post-distention objective findings (anesthetic capacity, glomerulations) or therapeutic benefits when patients are categorized according to presenting symptoms [203]. Cystoscopy with hydrodistention may provide little useful information above and beyond the history and physical examination findings. In one study, 56% of 84 patients reported symptom improvement, but the duration was short lived with a mean of 2 months [204].

Lamale and colleagues examined the relationships between symptoms and cystoscopic findings in 12 women newly diagnosed with BPS who had not previously received treatment. Pain symptoms had consistent positive correlations with the cystoscopic findings. An increase in pain with bladder filling was associated with inflammation ($P = 0.011$), ulceration, and smaller bladder capacity. Pain relief after voiding correlated with smaller bladder capacity ($P = 0.019$), hematuria, and total cystoscopic score. Pain intensity in the urethra was related to ulceration and hematuria, and pain in the lower abdomen was related to a smaller bladder capacity ($P = 0.047$), glomerulations, and a larger total cystoscopic score. Daytime frequency correlated negatively with most cystoscopic findings, and nocturnal frequency had a positive relationship with most cystoscopic findings and was significantly associated with a smaller bladder capacity ($P = 0.010$). Urgency showed no strong associations with any cystoscopic findings. The results of this study contradict those of previous studies that found no relationship between symptom reports and cystoscopic findings suggesting possible effects of treatment on pain perception and therapeutic influence on cystoscopic findings [205].

It is important to keep in mind that the cystoscopic appearance of the bladder wall after hydrodistention may not be constant over time, and the absence of initial findings of glomerulations or terminal hematuria does not preclude further development of these hallmarks of the disease on subsequent evaluation [206]. Rare cases of hydrodistension induced bladder necrosis have been described [207].

d) Morphology

Pathological changes in light microscopic and electron microscopic features in patients with BPS have been described including infiltration with inflammatory cells in all or specific parts of the bladder wall. Although these findings are important in our attempt to understand the disease and perhaps as an aid to stratification of patients, there are at this time no pathognomonic findings on biopsy in terms of diagnosis [30]. Expert opinion as per the ESSIC suggests the following procedures when biopsy is planned for BPS evaluation: [11]

1. Biopsies

During cystoscopy the bladder is distended to full capacity. After draining the bladder, bladder biopsies are taken at roughly half full bladder capacity: Biopsy procedures should be performed by using large forceps and include detrusor muscle; alternatively double punch biopsies or resections of lesions can be used.

2. Number of biopsies

At least 3 biopsies from the two lateral walls and bladder dome should be taken in addition to biopsies from visually abnormal areas. The biopsies are to be immediately fixed in neutral buffered 4% formalin.

3. Biopsy handling

Biopsies are treated conventionally. Six adjacent 3 mm sections are cut and placed with 3 specimens on each of two specimen slides. The first slide is stained with H&E, the next with a connective tissue stain suitable for the individual institute. Twenty-four 10 mm sections are then cut and every third section is mounted on a specimen slide for mast cell counting. The specimens are stained by Lederstain (naphto-lesterase) according to routine procedures. Finally, a 3mm section is obtained to ensure the presence of detrusor muscle in the specimens.

4. Mast cell counting

The use of a measuring grid (e.g. Leitz periplan 6F 10_N ocular containing a standardized grid) is necessary. Only mast cells containing nucleus are included. When counting the cells those covering or touching the bottom should be excluded whereas those covering the upper and left line are included. At least 3 biopsies must be the subject of mast cell counting and if possible one including a lesional area.

Biopsies for mast cell counting should contain detrusor muscle.

5. The pathology report

- Epithelium
  - Not present
  - Present
  - Dysplasia with grading
  - Abnormal but no dysplasia: description is mandatory.
- Propria
  - Normal
  - Inflammation: description with a grading
  - Other findings are described
- Detrusor muscle. Abnormal muscle cells: describe
- Intrafascicular fibrosis
  - Not present
  - Present
- Mast cell count: At least three biopsies should be included in the counting. Only the biopsy with the highest number of mast cells per mm2 should be reported

The enzymatic (naphtolesterase) staining is, for the time being, recommended since standardized values are available:

- less than 20 mast cells/mm^2:no detrusor mastocytosis;
- between 20 and 28 grey zone!
- more than 28 mast cells/mm^2: detrusor mastocytosis.

Larsen recommends examining the detrusor biopsies with tryptase-stained 3 micron thick sections, with every seventh section used for quantification; 27 mast cells/mm^2 is considered indicative of mastocytosis [158].

e) Biomarkers

The lack of universally accepted clinical diagnostic criteria for BPS affects all aspects of making progress in understanding this disease. Insights into risk factors, pathogenesis, trials for effective therapy, prognosis, and outcome criteria for treatment are all affected by this lack of diagnostic criteria. A major factor affecting the controversy over accepted clinical diagnostic criteria is that the current criteria are predominantly symptom specific. An objective biomarker would advance the establishment of reproducible diagnostic criteria for BPS and also aid in monitoring effects of treatment.

A biomarker for any disease needs to demonstrate high sensitivity and high specificity. In addition, the marker assay needs to be reproducible in many laboratories and should be suitable for use in a clinical diagnostic laboratory.

Many of the published studies on biomarkers for BPS have been on biomarkers isolated from urine. Erickson et.al has published excellent reviews of urine markers for BPS [08,209]. The most thoroughly investigated marker is antiproliferative factor (APF). This factor has been identified and characterized by Dr. Susan Keay and her colleagues at the University of Maryland [210,211]. Control subjects for this study included asymptomatic individuals, patients with bacterial cystitis, and patients with vulvovaginitis. APF is found in urine from the bladder and not from the renal pelvis [212-214]. Treatment of symptomatic BPS by either hydrodistention or neurostimulation normalized the APF levels concurrent with symptom relief [215]. It is not known if other forms of treatment will affect APF levels. Preliminary studies in 58 women with documented BPS demonstrated a sensitivity value of 91.4% and a specificity of 90.6% [216]. A later study with 219 symptomatic BPS patients and 325 controls with and without other urological disorders documented the sensitivity as 94% and the specificity at 95% [217]. APF has been isolated from urine and found to be a frizzled 8 protein-related sialoglycopeptide which interacts with the epithelial cell receptor CKAP4/p63 [210,218]. Keay et al have suggested that APF might inhibit cell proliferation by the down-regulation of genes that stimulate cell proliferation along with the upregulation of genes that inhibit cell growth [107]. Cell growth inhibition of human urothelial cells appears to be mediated by p53 [219] APF treatment caused significant increases in the paracellular permeability of normal bladder epithelial cell monolayers and the attenuation of tight junctions compared to mock APF, similar to changes seen in IC cells. APF treatment also decreased expression of the tight junction proteins zonula occludens-1 and occludin [220].

APF seems an ideal candidate for a biomarker for symptomatic BPS. There need to be additional studies to determine if it can serve as a BPS marker for patients in remission or for those who have not yet become symptomatic. As of 2008, the findings on symptomatic patients have yet to be replicated by laboratories around the world, and the biologic assay has not proven suitable for commercial development as it currently exists.

GP-51 is a glycoprotein present in both the transitional epithelium and urine of humans and other mammals. Moskowitz et. al have shown that bladder biopsies of BPS patients had decreased staining for GP-51 [221] The same laboratory also demonstrated that although GP-51 demonstrates a high specificity for BPS, it is not as sensitive as APF [222].

There have also been many published studies on heparin-binding epidermal growth factor-like growth factor (HB-EGF) [107,213,214,223,224]. HB-EGF is a growth factor found in normal urine. It has been shown that APF inhibits the production of HB-EGF. There have been no large population studies focusing solely on HB-EGF as a biomarker for BPS.

f) Confusable Diseases

Criteria for a diagnosis are needed only if the target disease may be confused with other diseases (confusable diseases) because of overlapping features [225]. For a diagnosis, the target disease has to be recognized in a pool of confusable diseases in one of two ways: by recognition of the specific combination of features of the target disease or by exclusion of confusable diseases. For the diagnosis of BPS both methods might be used because:

- Confusable diseases are more common than BPS, so recognition is mandatory because many can be treated.
- Failure to diagnose a confusable disease would automatically incorrectly yield a diagnosis of BPS.
- Patients may have a confusable disease plus BPS.

The diagnosis of BPS can thus made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS), the presence of a second diagnosis is possible. Symptoms and signs for use in diagnostic criteria do not need to be specific for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the specific feature and diagnostic criteria would not be necessary.

In evidence-based medicine, diagnoses are based on medical history, physical examination, and appropriate clinical investigations to eliminate diseases from a list of differential diagnoses (confusable diseases) and to confirm the final diagnosis. BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis. Cystoscopy with hydrodistention and biopsies might in this situation document positive signs of BPS thereby making a double diagnosis more probable. For therapeutic studies it makes sense to exclude patients who also have a confusable disease because symptoms and signs may be caused by BPS, the confusable disease, or by both. For prevalence studies of BPS, on the other hand, all cases with BPS should be included, also those with a confusable disease. This approach eliminates the need for separate diagnostic criteria for clinical practice and scientific studies. **Table 3** summarizes confusable diseases related to BPS and their mode of exclusion based upon the aforementioned diagnostic proposals and procedures [11,40].

Table 3. Differential Diagnosis of Bladder Pain Syndrome.

Confusable disease	Excluded or diagnosed by[a]
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with	
Common intestinal bacteria	Routine bacterial culture
Chlamydia trachomatis, *Ureaplasma urealyticum*	Special cultures
Mycoplasma hominis, *Mycoplasma genitalium*	
Corynebacterium urealyticum, Candida species	
Mycobacterium tuberculosis	Dipstick; if "sterile" pyuria culture for *M. tuberculosis*
Herpes simplex and human papilloma virus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder-neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or hematuria: upper urinary tract imaging such CT or IVP
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis
Pelvic floor muscle-related pain	Medical history, physical examination

CT = computed tomography; IVP = intravenous pyelogram; PSA = prostate-specific antigen.
[a] The diagnosis of a confusable disease does not necessarily exclude a diagnosis of BPS.

Nordling, J., Anjum, F. H., Bade, J. J., Bouchelouche, K., Bouchelouche, P., Cervigni, M. et al.: Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol, 45**:** 662, 2004.

VI. CLASSIFICATION

Interstitial cystitis was originally described as bladder disease with severe inflammation of the bladder wall described by Hunner as an ulcer [4]. The lesion is however not an ulcer but a vulnus (weakness) that can ulcerate on upon distention, and the name of the bladder lesion has consequently been changed to "Hunner's lesion " [1]. The finding of a Hunner's lesion could therefore originally be regarded as a diagnostic criterion for IC. Messing and Stamey introduced glomerulations as another typical finding for IC and this was included in the NIDDK criteria [7]. Magnus Fall proposed, that patients with Hunner's lesion (classic IC) and patients with glomerulations (non-ulcer type) represented two different subtypes [98] with different clinical pictures, different outcomes, and different responses to treatment [226] meaning that patients fulfilling the NIDDK criteria represents **at least** two different patient populations. Moreover up to 60% of patients clinically believed to have BPS by experienced clinicians do not fulfil the NIDDK criteria [24] and whether or not these patients are comparable to the patients fulfilling the NIDDK criteria is unknown. Finally Japanese urologists consider that "interstitial cystitis" should be preserved as a disease name for patients with urinary symptoms and cystoscopic findings of glomerulations or Hunner's lesion as outlined in the NIDDK criteria [227].

In an attempt to unite these different philosophies into a coherent schema, ESSIC proposed a classification of BPS based on findings during cystoscopy with hydrodistension and morphological findings in bladder biopsies [1]. (Table 2) The classification includes groups not having had cystoscopy with hydrodistension (group X) as well as groups not having had morphological investigation of bladder biopsies (group XX). By using this classification future research will be able to identify if findings of glomerulations and/or Hunner's lesion as well as morphological changes in bladder biopsies does have significant importance for disease prognosis and/or treatment outcome.

VII. CONSERVATIVE TREATMENT

1. BEHAVIORAL MODIFICATION

A PubMed search (performed in June, 2008) using the keywords, "interstitial cystitis" and "behavioral therapy" identified 6 articles. One English-language article focused on behavioral therapy [1] has been summarized with two additional articles [2,3]. **Level of evidence: 3 Grade of recommendation: C**

Despite a low level of evidence, behavioral therapy has become the cornerstone of treatment for patients with BPS. Some efficacy has been reported in the treatment of motivated patients with urinary frequency and urgency. No problematic side effects have been identified.

Behavioral therapy includes timed voiding (scheduled voiding time and interval), controlled fluid intake, pelvic floor muscle training and bladder training (gradually extending voiding interval).

Chaiken et al [228] reported that when they conducted behavioral therapy consisting of frequency-volume chart, timed voiding, controlled fluid intake and pelvic floor muscle training for the treatment of 24 female patients, 50% of the patients showed improvement in the number of urinations and bladder capacity. At the same time, they considered that as the data was collected from 12 weeks' intensive therapy conducted by skilled therapists for selected patients whose main symptom was urinary frequency, it should not be generalized.

Parsons and Koprowski [229] reported that when 21 patients with the main symptom of urinary frequency underwent bladder training using a frequency-volume chart, 15 patients showed improvement. In 15 patients, the mean voided volume after one month increased by 65cc, whereas a persistent sensation of bladder fullness remained unchanged.

2. PHYSICAL THERAPY

A PubMed search (performed in June, 2008) using the keywords, "interstitial cystitis" and "physical therapy" identified 60 articles. Three usable English-language articles [230-232] focused on physical therapy were examined with 4 additional articles [233-236]. **Level of evidence: 3 Grade of recommendation: C**

Some efficacy has been reported in the treatment of motivated patients with urinary frequency, urinary urgency and coital pain. No problematic side effects are reported.

Physical therapy for the pelvic floor is said to be effective for genitourinary and anorectal disorders [235]. Biofeedback and soft tissue massage may stimulate the relaxation of the pelvic floor muscles [233,234].

Lukban et al conducted a direct myofascial release treatment on 16 BPS patients with high-tone pelvic floor dysfunction and sacroiliac dysfunction. The treatment was effective for urinary frequency and suprapubic pain. Fifteen patients (94%) showed improvement in the O'Leary & Sant symptom score. Coital pain relief was observed in 15 of 16 patients, with 9 patients becoming able to resume sexual intercourse [231,236]. Transvaginal Theile massage was also reported to be effective for 9 of 10 patients of the same group [232] Mendelowitz showed a 69% success rate when treating 16 patients using electromyographic biofeedback [233]. However, it was suggested that a placebo effect may have occurred because the effect did not correlate with the improvement in patient's

awareness of the pelvic floor muscle movement and position before and after the therapy. Weiss [230] reported that 70% of 10 patients with IC showed symptomatic improvement, rating from “effective” to “remarkably effective”. ??

3. STRESS REDUCTION

A PubMed search (performed in June, 2008) using the keywords, “interstitial cystitis” and “mental health” identified 7 articles. Four articles [73,74,237,238] which are focused on interstitial cystitis have been summarized with 5 additional articles [49,239-242 here. **Level of evidence: 4 Grade of recommendation: C**

Stress reduction is believed to contribute to an overall improvement in quality of life. No problematic side effects are reported.

It is known that mental stress is one of the factors which aggravate the symptoms of BPS. Koziol et al [49] reported, in a survey of 374 patients, that more than half of the patients experienced intensified pain due to stress. Rothrock et al [241] reported that when comparing patients with BPS and healthy people, increased pain and urgency caused by stress were observed only in patients with BPS.

It is believed that exercise and bathing favorably influence the quality of life by reducing stress, [242] however, behavioral therapies may not provide sufficient effect [49]. It can be beneficial, when possible, to shorten working hours, choose a job with less stress or create a less stressful home environment. At the same time, involvement in patient education programs and patient support groups are considered to be beneficial [239,243].

World-wide patient support groups, including the Interstitial Cystitis Association (ICA) [240], http://www.ichelp.com/welcome.htm, are important sources of information for patients with IC. In Japan, there is an IC patient support group, “TOMONOKI” http://www.tomonoki.org/. Another good source of information is the International Painful Bladder Foundation http://www.painful-bladder.org/. Psychiatric support is important because IC patients often suffer depression, which may negatively impact upon the quality of life. Effective self-care strategies taught by psychiatric nurses are considered to be useful [73,74,238,244].

4. DIETARY MANIPULATION

A PubMed search (performed in June, 2008) using the keywords “interstitial cystitis” and “diet” identified 17 articles. Nine English-language articles [245-253] which are mostly focused on dietary manipulation have been summarized with additional 5 articles [49, 56, 242, 254, 255] here. **Level of evidence:4 Grade of recommendation :C**

No problematic side effects have been reported.. Acidic beverages, coffee, spicy food, and alcohol may aggravate the symptoms of most patients with BPS [49,56,242,247]. The symptoms of the majority of BPS patients can be improved by dietary manipulation [242,246,247,249,255]. On the other hand, Nguan et al [256] reported that there was no statistically significant difference in pain and other symptoms, when they evaluated the influence of the changes in urinary pH on the symptoms of 26 patients with BPS by instilling pH5.0 and pH7.5 saline solutions into the bladder.

Although dietary manipulation has no proven scientific basis, it was ranked in the top five frequently used treatments in a cohort study of the Interstitial Cystitis Data Base (ICDB) [251]. As the influence of diet is variable with regard to food, beverage, and patient, there is no reason for patients to be uniformly on a strict diet. It is advised that each patient experiment to find out the foods that tend to aggravate their symptoms and avoid them. The ICA home page, (http://www.ichelp.com/welcome.htm) introduces the foods often avoided by patients with IC.

VIII. ORAL THERAPY

Several categories of medication have been used in the management of patients with bladder pain syndrome including analgesics, antidepressants, antihistamines, immunosuppressants, and glycosaminoglcans. Many of these drugs are used empirically. Only a few of them have been studied in randomized controlled trials and none have a grade A recommendation (**Table 4**).

1. ANALGESICS

The long-term, appropriate use of pain medications is indispensible in the treatment of bladder pain syndrome. Many nonopioid analgesics including acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) and even antispasmodic agents [257] have a place in pain therapy. Patients with more severe symptoms can often be helped with medical pain management using medications commonly used for chronic neuropathic pain syndromes including antidepressants, anticonvulsants, and opioids.

Gabapentin, introduced as an anticonvulsant, has found efficacy in neuropathic pain disorders including diabetic neuropathy [258] and postherpetic neuralgia [259]. It demonstrates synergism with morphine in neuropathic pain [260]. Sasaki et al reported that 10 of 21 male and female patients with refractory genitourinary pain had subjective improvement of their pain following treatment with gabapentin [261].

Pregabalin has similar structure as gabapentin and also has been shown to reduce the pain of diabetic neuropathy [262]. Prebabalin was proved effective for treating pain associated with fibromyalgia [263].

Table 4. Some of the oral medications that have been used for treatment BPS: Oxford system recommendations

Drug	Level of Evidence	Grade of Recommendation
Amitriptyline; tricyclic antidepressants [274,276,318]	2	B
Analgesics	4	C
Antibiotic regimens [311,319,320]	4	D
Azathioprine [295]	4	D
Benzydamine [321,322]	3	D
Cholroquine derivatives [295]	4	D
Cimetidine [286,288,323]	3	C
Cyclosporine [290,291]	3	C
Doxycycline [324]	4	D
Duloxetine [325]	4	-C (Not effective)
Gapapentin [261]	4	C
Hydroxyzine [282, 285]	1	D
L-Arginine [308,309]	1	-A (Not effective)
Methotrexate [314]	4	D
Misoprostol [317]	4	D
Montellukast [315]	4	D
Nalmefene [326]	1	-A (Not effective)
Nifedipine [327]	4	D
Quercetin [310]	4	D
Sodium pentosanpolysulfate	1	D (conflicting RCT results)
Suplatast tosilate [294,328]	3	D
Vitamin E [329]	4	D

Pregabalin might be worthwhile to try for bladder pain syndrome, particularly for those with concurrent fibromyalgia, though studies are lacking.

Opioids are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analgesics have failed [264]. Chronic opioid therapy can be considered as a last resort in selected patients, who have disabling pain and often receive inadequate doses of short-acting pain medications, which put them on cycles of short-term relief, anxiety, and pain.

The major impediment to the proper use of opioids when they are prescribed for long-term nonmalignant pain is the fear of addiction. Some studies suggest the risk is low [265], but not zero [266]. Using opiates is a difficult decision that requires much thought and discussion between patient and urologist, and a pain specialist. They are best administered in a pain clinic setting, requiring frequent reassessment by both patient and physician [267].

In addition to narcotics, concurrent usage of nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, acetaminophen, and tricyclic antidepressants may provide better pain control [268]. The common side effects of opioids include sedation, nausea, mild confusion, and pruritis. These are generally transient and easily managed. Respiratory depression is extremely rare if they are used as prescribed. Constipation is common and a mild laxative is generally necessary. The long-acting narcotic formulations that result in steady levels of drug over many hours are preferable.

2. ANTIDEPRESSANTS

a) Amitriptyline

Amitriptyline is a tricyclic antidepressant with the

property of blocking H1-histaminergic receptors [269]. It stabilizes mast cells and inhibits mediator stimulated vascular leakage. It inhibits synaptic reuptake of serotonin and norepinephrine, thus inhibiting painful nociception from the bladder at the level of the central nervous system. Its nighttime sedation can be therapeutic in the BPS population and its purported beta-adrenergic receptor stimulation in the bladder may facilitate urine storage [270].

Using a dose titration of up to 75mg taken before bed, Hanno and Wein reported success in about half of 20 patients who could tolerate the medication. Twenty percent of the initial 25 patients dropped out because of fatigue, weight-gain, or dry mouth. In a follow-up report [271], 18 of 28 patients who could tolerate the drug had major relief of symptoms within 3 to 6 weeks of onset of therapy with a mean follow-up of 14.4 months. However, about one-third of patients initially placed on the drug could not continue on it because of side effects. Kirkemo et. al [272] treated 30 patients and 90% had subjective improvement in 8 weeks. Pranikoff and Constantino [273] reported improvement in 16 of 22 patients with urinary frequency and pain who did not have a diagnosis of interstitial cystitis, noting that 5 of the 22 could not tolerate the drug.

van Ophoven et al performed the only reported prospective, double-blind, placebo-controlled study of amitriptyline. Fifty patients were randomized to placebo or a titrated dose of amitriptyline up to 100mg daily. Forty-two percent of amitriptyline patients had greater than 30% decrease in O'Leary/Sant symptom and problem scores at 4 months compared to 13% in the placebo group [274]. They subsequently reported a long-term follow-up of amitriptyline for patients who can tolerate the side effects and continued the medication. With a mean follow-up of 19 months, 64% of 94 patients had response [275].

b) Doxepin, desipramine, duloxetine

Other tricyclic antidepressants that have been used for bladder pain syndrome are doxepin and desipramine. Wammack et al used the combination of doxepin and piroxicam, a cox-2 inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms [276]. One study reported satisfactory outcome with desipramine [277]. Duloxetine, a serotonin-norepinephrine reuptake inhibitor has also been tried but without therapeutic effects [278].

3. ANTIHISTAMINES

Simmons first proposed use of antihistamines in 1955 [279]. His findings of mast cells in the wall of a normal bladder and the edema and increased vascularity seen in the IC bladder suggested that histamine may be responsible for the development of interstitial cystitis. He reported on 6 patients who had some improvement with pyribenzamine for limited periods [280].

a) Hydroxyzine

Hydroxyzine is the most widely used antihistamine for bladder pain syndrome. Its ability as an H-1 receptor antagonist, to inhibit bladder mast cell activation, along with its anticholinergic and anxiolytic properties and good safety profile, have made it a reasonable candidate for use as a therapeutic agent for bladder pain syndrome [281]. In 1933, Theoharides first reported significant benefits of hydroxyzine in reducing pain and urinary symptoms [282]. His two subsequent reports of uncontrolled series further suggested the therapeutic effects of hydroxyzine [283 284]. However, in an NIDDK randomized controlled trial, the global response rate for hydroxyzine was only 31% compared to a 20% response to those not treated with hydroxyzine. When looked at by itself the response was 23% vs. 13% on placebo. None of the results in this under-powered trial reached statistical significance [285].

a) Cimetidine

Cimetidine, a H2 histamine receptor antagonist, has been explored for treatment of bladder pain syndrome. In a pilot study [286], 9 patients were treated with a dose of 300mg orally twice daily for one month. At follo-wup 26 to 42 months later, 4 patients had complete relief of urinary symptoms and suprapubic pain. Lewi [287] reported 31 patients given 200mg three times daily with mean followup of 6.6 months. Seventy-one per cent experienced varying degrees of symptomatic relief, 45% were pain free, and 26% went into remission of all symptoms. In a later report [288] of 69 patients treated over a 4 year period, 67% of patients had complete relief of all symptoms.

A small, prospective, placebo-controlled RCT studied 36 patients who either received oral cimetidine or placebo [289]. Median suprapubic pain and frequency scores improved significantly, but the publication does not state exactly how many patients in each group improved.

4. IMMUNOSUPPRESSANT

a) Cyclosporine

Cyclosporine, a widely used immunosuppressive drug in organ transplantation, was the subject of a novel bladder pain syndrome trial [290]. Eleven patients received cyclosporine for 3-6 months at an initial dose of 2.5-5 mg/kg daily and a maintenance dose of 1.5 to 3mg/kg daily. Micturition frequency decreased, and mean and maximum voided volumes increased significantly. Bladder pain decreased or disappeared in 10 patients. After cessation of treatment, symptoms recurred in the majority of patients.

In a longer-term follow-up study, 20 of 23 refractory IC patients on cyclosporine therapy followed for a mean of 60.8 months became free of bladder pain. Bladder capacity more than doubled. Eleven patients

subsequently stopped therapy, and in 9, symptoms recurred within months, but responded to reinitiating cyclosporine [291]. Sairanen et al further found that cyclosporine A was far superior to sodium pentosan-polysulfate in all clinical outcome parameters measured at 6 months [292]. Patients who responded to cyclosporine A had a significant reduction of urinary levels of epidermal growth factor (EGF) [293].

b) Suplatast Tosilate

Suplatast Tosilate (IPD-1151T) is an immunoregulator that selectively suppresses IgE production and eosinophilia via suppression of helper T cells that produce IL-4 and 5. It is used in Japan to treat allergic disorders including asthma, atopic dermatitis, and rhinitis. Ueda et al reported a small study in 14 women with interstitial cystitis [294]. Treatment for one year resulted in a significantly increased bladder capacity and decreased urinary urgency, frequency, and lower abdominal pain in 10 women. Concomitant changes occurred in blood and urine markers suggesting an immune system response. Larger, multicenter, randomized controlled trials in the United States and Japan are planned.

c) Azathioprine and Cholroquine derivatives

In a single report in 1976, Oravisto et al used azathioprine or chloroquine derivatives for BPS patients not responding to other treatments [295]. About 50% patients responded.

5. SODIUM PENTOSANPOLYSULFATE

Sodium pentosanpolysulfate (PPS), a synthetic sulfated polysaccharide, is available in an oral formulation, 3-6% of which is excreted into the urine and theoretically may replenished the damaged glycosaminoglycan (GAG) layer overlying transitional epithelium of the urinary bladder of BPS patients. An intact urothelial GAG layer has been proposed to be essential to keep the urothelium impermeable to urinary components. A defective bladder GAG layer is hypothesized to be one important cause for BPS [296].

PPS's mechanism of action has been attributed not only to correction of a putative defect in the GAG layer, but also its ability to inhibit histamine release from mast cells, [297] and a possible effect mediated by nonspecific binding of the molecule with the inflammatory stimulants of urothelial activation, an action that would occur in the urine rather than at the mucosal membrane [298].

PPS is the most intensively studied treatment ever proposed for BPS. It is the only medication approved by the Food and Drug Administration for the pain of interstitial cystitis. Parsons initially administered the drug at a dosage of 50mg 4 times daily or 150mg twice daily in an open trial involving 24 patients [299]. Twenty-two of 24 patients experienced a good or excellent response within 8 weeks. In a subsequent randomized, placebo-controlled trial using a dose of 100mg three times daily in 62 patients, pain and urgency improved in 44% vs. a placebo response of 15%. Urgency improved by 38% vs. 18% on placebo. The average number of daily voids was unchanged [300].

Five randomized controlled trials for pentosan polysulfate have yieled conflicting results of efficacy. Holm-bentzen et. al [301] reported the first multicenter double-blind placebo controlled trial in 1987 looking at 115 patients with bladder pain syndrome. Patients were randomized to a dose of 200mg twice daily vs. placebo for 4 months. The results showed no difference between pre and post trial values with regard to symptoms, urodynamic parameters, cystoscopic appearance, or mast cell counts in the two groups. The study concluded that the drug had no clinically significant effect.

The first of two pivotal studies for the FDA was performed in the United States in 1990 [302] A total of 110 patients in 5 medical centers were studied for 3 months on a dosage of 100mg three times daily. Twenty-eight per cent of patients on PPS reported "more than slight improvement" versus 13% of those on placebo. Pain and pressure to urinate were the main parameters to show benefit with PPS.

The FDA asked for a second study which was reported 3 years later [303]. In a multicenter, placebo-controlled RCT 148 patients were randomized to 100mg three times daily of pentosanpolysulfate vs. placebo. In the primary endpoint of patient self-evaluation of global improvement, 32% of those on PPS reported 50% or more overall improvement vs. 16% on placebo at 3 months. Pain, urgency, and pressure showed significant improvement with drug. Frequency, nocturia, and volume voided showed no significant changes between study groups.

The NIDDK performed their own 2 X 2 factorial study to evaluate PPS and hydroxyzine [285]. Each drug was used alone and in combination and compared to a placebo group. Patients were treated for 6 months. There were 121 participants in 7 centers. No statistically significant response to these medications was documented. A non-significant trend was seen in the PPS treatment groups (34%) compared to non-PPS groups (18%). Of the 29 patients on PPS alone, 28% had global response (primary endpoint) of moderately or markedly improved vs. 13% on placebo, very similar in this 6-month study to improvement rates in the 3-month pivotal studies, though not reaching statistical significance in the longer study.

In summary, of 5 RCTs 2 had unfavorable and 3 had favorable results for PPS. Such conflicting results might suggest that a minority of patients do respond to PPS, but currently there is no reliable method to identify such patients.

Long-term, open-label studies with PPS have been reported. Populations of patients receiving extended treatment for up to 90 months or more in the compassionate use program showed no further improvement in symptoms after 1-2 years, though there seemed to be little tachyphylaxis [285,304]. A total of 2809 patients had begun treatment with a 3 month supply of PPS and 21% continued with treatment beyond this point and reordered medication. This seems to correlate with the 28-32% improvement rate previously reported. The dropout rate in the first 6 months was extraordinarily high with only 178 active patients out of 1742 who initially ordered the drug. There was an overall improvement in symptoms in 62% of the patients who did remain in treatment for 6-35 months.

PPS appears to be a very well-tolerated medication [304] with no common central nervous system side effects, and appears to be beneficial with regard to improving the pain associated with interstitial cystitis in up to one-third of patients, a standard often expected with a placebo. A 3-6 month course is required to see an effect in most patients. Claims suggesting greater efficacy and claims urging its use in patients who do not meet the standard definition of bladder pain syndrome should be regarded with caution.

6. OTHER ORAL MEDICATION THAT HAVE BEEN USED FOR BPS

a) L-Arginne

Foster and Weiss were the original proponents of L-arginine in the therapy of interstitial cystitis [305]. Eight patients with IC were given 500mg of L-arginine 3 times daily. After one month, urinary nitric oxide synthase activity increased 8-fold and 7 of the 8 patients noticed improvement in IC symptoms. An open-label study of 11 patients showed improvement in all 10 of the patients who remained on L-arginine for 6 months [306].

An open-label study of 9 women in Sweden failed to find any change in symptom scores or in nitric oxide production in the bladder [307]. A placebo-controlled randomized controlled trial of 53 IC patients could find no difference on an intention to treat analysis between drug and placebo-treated patients [308]. A smaller randomized placebo-controlled crossover trial of 16 IC patients found no clinically significant improvement with L-arginine and concluded that it could not be recommended for IC treatment [309].

Data does not support the use of L-arginine for the relief of symptoms of interstitial cystitis.

b) Quercetin

Quercetin, a bioflavenoid available in many over-the-counter products, may have the anti-inflammatory effects of other members of this class of compounds found in fruits, vegetables, and some spices. Katske et. al [310] administered 500mg twice daily to 22 BPS patients for 4 weeks. All but one patient had some improvement in the O'Leary/Sant symptom and problem scores as well as in a global assessment score. Further studies are necessary to determine efficacy.

c) Antibiotics

Warren et. al [311] randomized 50 patients to receive 18 weeks of placebo or antibiotics including rifampin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin and ciprofloxacin for 3 weeks each. Intent to treat analysis demonstrated that 12 of 25 patients in the antibiotic and 6 of 25 patients in the placebo group reported overall improvement while 10 and 5 respectively noticed improvement in pain and urgency. The study was complicated by the fact that 16 of the patients in the antibiotic group underwent new BPS therapy during the study as did 13 of the placebo patients. There was no statistical significance reached. What was statistically significant were adverse events in 80% of participants who received antibiotic compared to 40% in the placebo group. Nausea and/or vomiting and diarrhea were the predominant side effects. Most patients on antibiotics correctly guessed what treatment arm they were in, and those that guessed correctly were significantly more likely to note improvement after the study. No duration in improvement after completion of the trial of antibiotics was reported.

Burkhard et. al [312] reported a 71% success in 103 women presenting with a history of urinary urgency and frequency and chronic urethral and/or pelvic pain often associated with dyspareunia and/or a history of recurrent urinary tract infection. This was a large, inclusive group and one that is probably broader than the bladder pain syndrome we are focusing on. Nevertheless, he recommended empiric doxycycline in this group. The overwhelming majority of BPS patients have been treated with empiric antibiotics prior to diagnosis.

At this time there is no evidence to suggest that antibiotics have a place in the therapy of BPS in the absence of a culture-documented infection [313].

d) Methotrexate

Low dose oral methotrexate significantly improved bladder pain in 4 of 9 women with BPS, but did not change urinary frequency, maximum voided volume, or mean voided volume [314]. No placebo-controlled, RCT has been done with this agent.

e) Montelukast

Mast cell triggering releases 2 types of proinflammatory mediators, including granule stored pre-formed types such as heparin and histamine, and newly syn-

thesized prostaglandins, and leukotriene B_4 and C_4. Classic antagonists, such as montelukast, zafirlukast and pranlukast, block cysteinyl leukotriene 1 receptors. In a pilot study, [315] 10 women with IC and detrusor mastocytosis received 10mg of montelukast daily for 3 months. Frequency, nocturia, and pain improved dramatically in 8 of the patients. Further study would seem to be warranted, especially in patients with detrusor mastocytosis, defined as > 28 per mm^2.

e) Nifedipine

The calcium channel antagonist nifedipine inhibits smooth muscle contraction and cell-mediated immunity. In a pilot study, [316] 30mg of an extended release preparation was administered to 10 female patients and titrated to 60mg daily in 4 of the patients who did not get symptom relief. Within 4 months five patients showed at least a 50% decrease in symptom scores, and 3 of the 5 were asymptomatic. No further studies have been reported.

f) Misoprostol

The oral prostaglandin analogue misoprostol was studied in 25 patients at a dose of 600 micrograms daily [317]. At 3 months 14 patients were significantly improved, and at 6 months 12 patients still had a response. A cytoprotective action in the urinary bladder was postulated.

IX. INTRAVESICAL / INTRAMURAL THERAPY (Table 5)

Intravesical therapies form one of the staples of BPS therapy, though regulatory approvals and availability throughout the world differ from nation to nation. What follows are treatments that have been reported in the recent literature, some of which are commonly used. Older therapies that are rarely used now include silver nitrate [44,330-333] and chlorpactin WCS90 [6,334-338]. These have not been included in this current edition of the Consultation, but have level 3 evidence to support a grade C recommendation based on original reports.

1. DMSO (Dimethyl sulfoxide)
Grade of Recommendation: B
Level of evidence 2

• A small number of significant side effects.

Not approved in Japan.

DMSO is believed to reduce inflammation, relax muscles, eliminate pain, dissolve collagen, and degranulate mast cells. It has long been used as a therapeutic agent for BPS. Its mechanism of action, however, has not been clarified. Ten articles on DMSO for the treatment of IC were retrieved. Peeker et al [339] reported that in a randomized study, frequency and pain were improved in ulcer-type IC patients, although no improvement was observed in maximum bladder capacity. Perez-Marrero et al [340] reported that in a non-randomized controlled study, 53% of the patients showed remarkable improvement in subjective evaluation (placebo 18%), and 93% in objective evaluation (placebo 35%).?Around an 80% improvement rate has been reported in case series and retrospective studies [341-348].

With regard to side effects after instillation of DMSO, most patients recognize a garlic-like odor, which disappears within a day, and about 10% of patients report bladder irritative symptoms which resolve with or without symptomatic treatment [349]. It is hypothesized that these transient exacerbations occur as the result of mast cell degranulation. The number of significant side effects is considered to be small [348]. Cataracts have been reported in animal studies, [350,351] though not in humans. Negative effects on bladder compliance have been noted in rat detrusor [352]. DMSO may accelerate the absorption of other drugs instilled simultaneously, which could be a source of side effects.

Table 5. Intravesical therapy for BPS; assessments according to Oxford System

Intravesical Agent	Level of Evidence	Grade of Recommendation
DMSO	2	B
Heparin	3	C
Hyaluronic Acid	1	D
Chondroitin Sulfate	4	D
Pentosan Polysulfate	4	D
Capsaicin / Resiniferatoxin	1	-A (ineffective)
Bacillus Calmette-Guerin (BCG)	1	-A (ineffective
Oxybutinin	4	D
Lidocaine	2	C
Botulinum Toxin	4	D

The instillation method has not been standardized. Generally, 50cc of a solution of medical grade 50% DMSO is instilled into the bladder. If pain occurs immediately following instillation, local anesthesia (e.g. 20ml of 2% lidocaine solution) may be instilled. Average retention time is considered to be 10 to 20 minutes [349]. The instillation is performed weekly for 6-8 weeks. After an initial course, treatment is suspended until symptoms recur. If a good result was obtained, another 6 week course (often followed by monthly maintenance) can be initiated. The long-term effect is unknown, although there is no upper limit for the duration of the treatment. DMSO is medically approved in the US, while it has not been approved yet in Japan.

2. HEPARIN

Grade of Recommendation: C
Level of Evidence: 3

Side effects primarily related to effects intravesical catheterization and slight chance of bladder hemorrhage.

The glycosaminoglycan (GAG) layer on the bladder urothelium is a kind of muco-polysaccharide, working as a non-specific defense mechanism. It is believed that a deficiency or abnormality of GAG secondarily causes inflammation of the bladder by increasing the permeability of the bladder mucosa, leading to the pathologic cascade of BPS. Heparin has similarities to the GAG layer of the bladder. When instilled into the bladder, theoretically it might replace the damaged GAG layer. Kuo [353] reported that the International Prostate Symptom Score, as well as bladder capacity at initial desire to void and maximum bladder capacity, improved significantly. According to the report by Parsons et al [354] symptoms were reduced in 56% of patients treated 3 times weekly for 12 weeks. These reports suggest the efficacy of heparin, however, there is no randomized comparative study to give conclusive evidence. One study indicated that intravesical heparin instillations may prolong the response to dimethyl sulfoxide treatment [355].

No significant side effects have been reported, as it does not affect systemic coagulation parameters. In the case of patients with hematuria, however, it may exacerbate local hemorrhage.

The instillation method has not been standardized. Generally, 10,000-40,000 units of heparin are instilled. It is unusual to have pain or irritation as a result of instillation, and retention times can be 30 minutes or more. Instillation frequency can be up to every other day and is often administered at home by the patient. Parsons et al [356] recently reported that when 40,000 units of heparin combined with 1 to 2% lidocaine was instilled 3 times a week for 2 weeks, about 80% efficacy was obtained. There is no upper limit for the duration of the treatment, but a long-term effect is unknown. A bleeding tendency may occur. Heparin for intravesical use is not approved by drug regulatory authorities.

3. HYALURONIC ACID

Grade of Recommendation : D
Level of Evidence: 1

• No significant side effects.

Hyaluronic acid, like heparin, is a muco-polysaccharide, that could theoretically repair a damaged GAG layer of the bladder mucosa. Six reports have indicated efficacy [357-362]. In the summer of 2003 Bioniche Life Science Inc http://www.medicalnewstoday.com/articles/112053.php and in the spring of 2004 Seikagaku Corporation reported double-blind, placebo-controlled, multicenter clinical studies of their hyaluronic acid preparations (40mg or 200mg per cc respectively) and neither showed significant efficacy of sodium hyaluronate compared to placebo. These negative studies have not been published in peer reviewed literature. Neither preparation has been approved for use for BPS in the United States. At the same time, no significant side effects were observed.

4. CHONDROITIN SULFATE

Grade of Recommendation: D
Level of Evidence: 4

• No significant side effects.

Chondroitin sulfate is another mucopolysaccharide. Its efficacy was suggested in one article when used alone [363] and in another trial when used in combination with hyaluronic acid [364]. A randomized comparative study has not been reported.

5. PENTOSAN POLYSUFATE

Grade of Recommendation: D
Level of evidence: 4

• No significant side effects are considered to be present.

Pentosan polysufate (PPS) is a mucopolysaccharide similar to heparin, with a similar postulated mode of action when used locally. Like other muco-polysaccharides, it has not been well-studied clinically. Bade et al in a randomized controlled trial found benefit in 4 patients out of 10 on PPS versus 2 of 10 on placebo [365]. A more recent placebo-controlled study of 41 patients found the addition of a 6 week course of intravesical PPS to a regimen of oral PPS significantly improved results [366].

6. CAPSAICIN, RESINIFERATOXIN

Grade of Recommendation: -A (ineffective)
Level of Evidence: 1

• Significant side effects: local irritation possible.

It would seem reasonable that capsaicin, a C-fiber

afferent neurotoxin, could alleviate the pain of BPS by desensitizing bladder afferents. Resiniferatoxin (RTX) is considered to have a stronger action than capsaicin, by desensitizing C-fibers more quickly, and causing less initial irritation. Efficacy was indicated in five relatively small clinical trials [367-371]. No severe side effects were reported. A randomized multicenter placebo-controlled clinical trial of RTX failed to demonstrate benefit over placebo [372].

7. BACILLUS CALMETTE-GUERIN (BCG)
Grade of Recommendation: -A (ineffective)
Level of Evidence: 1

• Potential serious complications

Seven articles reported on a BCG instillation therapy. Zeidman et al first reported that 5 patients who did not respond to other therapies showed symptomatic improvement [373]. Peters et al conducted a randomized double blind study showing a 60% improvement compared to 27% [374] placebo response with good long-term results at 27 months [375]. Sixty-five percent of the patients experienced burning sensation, 41% irritation of the bladder, and 35% pelvic pain. One patient was reported to have dropped out due to joint pain.

Peeker et al conducted a randomized double blind study comparing intravesical BCG and DMSO and failed to find any efficacy with BCG [339]. A very large, multicenter randomized placebo controlled trial conducted by the National Institute of Diabetes, Digestive, and Kidney Disorders failed to identify benefit from BCG, although the side-effect profile was surprisingly similar to that of placebo [376].

8. OXYBUTYNIN
Grade of Recommendation ? D
Level of Evidence: 4

• Side effect profile is unknown

Barbalias et al observed significant improvement when combining intravesical instillation of oxybutynin with bladder training [377]. Randomized trials are lacking.

9. LIDOCAINE
Grade of Recommendation: C
Level of Evidence: 2

• No significant side effects.

Lidocaine is a local anesthetic that relieves pain by blocking sensory nerves in the bladder. Four articles [378-381] reported on the electromotive drug administration (EDMA) of lidocaine. Using EMDA, ionized lidocaine is actively introduced into the bladder using an electrical current. Three articles reported that lidocaine and dexamethasone were instilled following hydrodistention. According to the report by Rosamilia et al [381], 85% of the patients had a good result, with the effect persisting for 6 months in 25%. There are two other case reports [382,383]. A report on a pharmacokinetic effect, demonstrated safe levels of lidocaine absorption into the bladder [384] Randomized, placebo-controlled trials are needed to ascertain efficacy, optimal treatment parameters, and length of response to intravesical lidocaine preparations [385]. Advantages seem to be immediate response, low-cost of generic medication, and ability of patients to self-administer at home.

10. BOTULINUM TOXIN
Grade of Recommendation: D
Level of Evidence: 4

• Side effects include dysuria, incomplete bladder emptying

In a study using rats, botulinum toxin inhibited pain response induced by acetic acid and calcitonin gene related peptide release from afferent nerves, which indicates the possibility of relieving pain and other symptoms of BPS [386]. Smith et al observed symptom improvement in 9 of 13 BPS patients treated with 100-200 units of botulinum toxin injected into 20 to 30 sites under general anesthesia [387]. Giannantoni and colleagues [388] noted improvement in 13 of 15 patients at 1 and 3 months after injection of 200units diluted in 20cc injected into the lateral bladder walls and trigone. By the 5 month mark only 26.6% of patients had any benefit, and at 12 months all patients had baseline symptoms. Dysuria occurred in a majority of patients and persisted in a minority for several months after initial injection. Three patients required clean intermittent catheterization for 2-3 months following therapy. Further studies will be needed to obtain conclusive evidence for its efficacy, duration of effect, and side-effect profile.

X. NEUROMODULATION

Level of Evidence: 3
Grade of Recommendation: C

Sacral nerve stimulation (SNS) involves implanting permanent electrode(s) to stimulate S3 or S4 roots. As early as 1989, Tanago et al showed that stimulation of S3 may modulate detrusor and urethral sphincter function [389]. FDA approved the usage of sacral neuromodulation for treating refractory detrusor overactivity in 1997 and for urinary urgency and frequency in 1999. Although the effectiveness of SNS for detrusor overactivity is largely confirmed by a good number of papers, only a few papers report the effect of SNS in treating BPS.

Zerman et. al reported significant improvement in a 60-year-old woman treated for severe BPS pain using sacral nerve stimulation implant. Pain and accompanying bladder dysfunction were improved by temporary and permanent sacral nerve stimulation for up to six months [390].

Maher et al showed that temporary stimulation was effective in 73% of 15 women with refractory BPS [391]. Mean voided volume during treatment increased and mean daytime frequency, nocturia and pain decreased significantly. As indicated by the Short Urinary Distress Inventory and SF-36 Health Survey, the quality of life parameters of social functioning, bodily pain and general health significantly improved during the stimulation period.

Chai et. al found that percutaneous S3 nerve root stimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with BPS [213]. In their report in 2003, Comiter et al prospectively investigated the effect of SNS on a series of 17 patients with refractory BPS. At an average of 14 months follow-up mean daytime frequency, nocturia and mean voided volume improved significantly.

The average pain decreased from 5.8 to 1.6 points on a scale of 0 to 10 and Interstitial Cystitis Symptom and Problem Index scores (ICSI and ICPI) decreased from 16.5 to 6.8 and 14.5 to 5.4, respectively. Of the 17 patients 16 (94%) with a permanent stimulator demonstrated sustained improvement in all parameters at the last postoperative visit [392].

Whitmore el al applied percutaneous sacral nerve root stimulation on 33 patients with refractory interstitial cystitis. Statistically significant improvements were seen in pain and urinary symptoms.

Significant improvements were also seen in ICSI and ICPI scores [393]. Peters et al reported a reduction of narcotic usage in 18 BPS patients following SNS for a mean of 15.4 months, although the dose reduction was modest (36%) and only 4 of 18 discontinued the narcotics [394]. However, Elhilali and colleagues found that both of two patients with interstitial cystitis reported no improvement following sacral neuromodulation [395].

Zabihi et al more extensively stimulate S2-S4 by implanting electrodes into epidural space through sacral hiatus. 23 of 30 (77%) patients had successful trial stimulation and were permanently implanted. Among these patients, the symptom score was improved by 35% (p=0.005). The pain score improved by 40% (p=0.04). Patients reported an average of 42% improvement in their symptoms [396].

Sacral nerve modulation is still considered an investigational procedure for BPS by the Consultation. Its therapeutic benefits appear to be significant in selected cases.

Strict patient selection and detailed discussion with patients prior to surgery is mandatory. Long-term results should be collected and reported, and trial results discussed with patients before employing this treatment modality.

XI. PAIN EVALUATION AND TREATMENT

Level of Evidence: 4
Recommendation: C

As is evident in the information presented in this section, studies on the use of analgesics for bladder pain syndrome are sparse, and the majority of data is inferred from non-BPS types of pain and expert opinion

Health professionals should ask about pain, and the patient's self report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales and should document the efficacy of pain relief at regular intervals after starting or changing treatment. Systematic evaluation of the pain involves the following:

- Evaluation of severity
- Detailed history of the pain including assessment of pain intensity and character
- Evaluation of the psychological state of the patient, including assessment of mood and coping responses
- Physical examination emphasizing the neurologic examination
- Diagnostic workup to determine the cause of the pain
- Re-evaluation of therapeutic strategy and response.

The initial evaluation of pain should include a description of the pain, **PQRST** characteristics serve well for this purpose:

P: Palliative or Provocative factors, 'what makes it less intense?'

Q: Quality, 'what is it like?'

R: Radiation, 'does it spread anywhere else?'

S: Severity, 'how severe is it?'

T: Temporal factors, 'is it there all the time, or does it come and go?'

1. PAIN MEASUREMENT

A number of different rating scales have been devised to attempt to methodically measure pain and to allow patient follow-up. These have been used in research, audit and in clinical practice. They all rely on a subjective assessment of the pain and therefore make inter-individual comparisons difficult. Additionally, pain is a multidimensional complex phenomenon and is not adequately described by unidimensional scales, however there is value in making some sort of an assessment to aid clinical practice.

- Categorical scales e.g., verbal rating scales: mild, moderate, severe pain
- Visual analogue scale (VAS)
- Complex pain assessment compendiums e.g., Brief Pain Inventory (BPI), McGill Pain Questionnaire [397-399].

The BPI consists of several visual analogue scales grouped together assessing pain at rest, on movement, and other aspects of the pain including interference with function and effect on work.

2. BASICS OF CHRONIC PELVIC PAIN MANAGEMENT

a) Analgesia

1. Non-acidic antipyretic analgesics

Paracetamol (acetaminophen) is the main representative of this group. It has antipyretic activity and is a simple analgesic. There is very little evidence about its role in chronic pelvic pain. Further studies need to be considered.[400,401] Paracetamol should be considered for mild pain.

2. Acidic antipyretic analgesics

The classical non-steroidal anti-inflammatory drugs (NSAIDs) fall into this group and include salicylic acid. They are known to act on the cyclooxygenase (COX) enzyme. The early NSAIDs tended to have little selectivity for COX2 over COX1, and are therefore said to be associated with more side effects than the newer COX2 selective inhibitors. The COX1 enzyme is mainly involved in normal 'housekeeping' functions, such as mediating gastric mucosal integrity, and renal and platelet function. Blocking the COX1 enzyme is the cause of the platelet, gastric and renal complications that can occur with NSAIDs. It has been suggested that the COX2 enzyme is inducible as a result of tissue damage, and that it is the main enzyme involved in inflammation and peripheral sensitization of nociceptors. As a result, the analgesic efficacy of COX2 selective drugs should be as good as that of the nonselective drugs. This, however, has been disputed [402-405]. The selective COX2 agents should not be prescribed in patients with increased risk of cardiovascular disease including congestive cardiac failure [406]. There is very little evidence for a role of NSAIDs in the management of chronic pelvic pain and even less evidence for a role for the COX2 selective drugs. Most of the analgesic studies have investigated dysmenorrhoea in which NSAIDs have been found to be superior to placebo and possibly paracetamol [401,407].

For practical purposes the NSAIDs may be divided into:

1. Non-selective, low potency (e.g. salicylic acid, ibuprofen, mefenamic acid).
2. Non-selective, high potency (e.g. ketoprofen, diclofenac, ketorolac).
3. COX2 selective drugs (e.g. celecoxib, etoricoxib).

3. Guidelines for use [408]

Non-selective, low potency NSAIDs can be used as first-line analgesics. They are most likely to be of help if there is an inflammatory component to the pain. More potent NSAIDs should be reserved for those conditions in which the low potency drugs have been tried and failed to produce significant benefit. COX2 selective drugs should be used with caution as an alternative to the non-selective drugs where there is an increased risk of gastric complications. They should be avoided in patients with known cardiovascular disease. NSAIDs should be taken with food and consideration must be given to the use of gastric protective agents. The benefits of the NSAIDs must be demonstrated to outweigh the risks. All NSAIDs are contraindicated in active gastrointestinal ulceration/ bleeding and renal disease. They may seriously exacerbate asthma and produce fluid retention. Even if stronger analgesics such as opioids are added, the NSAIDs can be continued as they are likely to have a synergistic action improving pain control above and beyond that obtained with opioids alone [409].

b) Opioids

There is now a general acceptance that opioids have a role in the management of chronic non-malignant pain [410]. The use of opioids in urogenital pain is poorly defined. The following guidelines are suggested by the European Association of Urology [408].

General guidelines for the use of opioids in chronic/non-acute urogenital pain

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient's family doctor).
3. Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The patient should undergo a trial of opioids [410]
5. The dose required needs to be calculated by careful titration.
6. The patient should be made aware (and possibly give written consent):

I. that opioids are strong drugs and associated with addiction and dependency

II. the opioids will normally only be prescribed from one source

III. the drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period

IV. the patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that non-prescribed drugs are not being taken

V. inappropriate aggressive behaviour associated with demanding the drug will not be accepted

VI. hospital specialist review will normally occur at least once a year

VII. the patient may be requested to attend a psychiatric/psychology review

VIII. failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.

7. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow release/modified release form. Short-acting preparations are undesirable and should be avoided where possible. Parenteral dosing is undesirable and should be avoided where possible.

1) Morphine. There is no compelling evidence that one opiate is better than another [410]. Morphine is the traditional gold standard. In an acute situation, the daily morphine requirement may be calculated by titration of the drug with progressively increasing doses of 4-hourly rapid-release morphine. However, in most cases, starting with a low dose of slow-release morphine and confining the increments to occur at intervals of no less than 3 days to 1 week is adequate.

2) Diamorphine is not generally available orally, because of its high first-pass metabolism within the liver. It should not be used routinely for long term pain management in patients with chronic/non-acute pain.

3) A fentanyl patch is used when oral absorption is restricted or when the patient suffers with nausea and vomiting. Patches are generally changed every 72 hours. The problem with the currently available patches is that the dosing increments between patches are large. Care needs to be exercised when increments in dose are undertaken.

4) Methadone is a strong analgesic which has a long track record [411]. It may have a useful role in the management of urogenital pain, though there is very little science to support this. Methadone has the tendency to accumulate with repeated dosing and cause delayed respiratory arrest. Therefore, whereas it may be a very useful drug, it should only be prescribed by a practitioner familiar with its use as an analgesic. Methadone as an analgesic is usually prescribed 6 hourly as its analgesic action is relatively short-lived compared with the longer benefits seen from using the drug in drug addiction.

5) Pethidine 100 mg intramuscular (i.m.) is about as effective as tramadol 100 mg i.m [412] or morphine 10 mg i.m. Its oral bioavailability is, however, poor. Pethidine has a short duration of action and is therefore not an ideal drug for use in chronic/non-acute pain.

6) Other opioids. Oxycodone and hydromorphone are now both available as slow/modified-release preparations. They may be useful for opiate rotation if side effects or tolerance is a problem. They are powerful opioids. Phenazocine is effective in severe pain. It may be administered sublingually if nausea and vomiting are a problem. Buprenorphine and pentazocine both have agonist and antagonist properties and can induce withdrawal symptoms in patients used to opioids. Naloxone may only partly reverse respiratory depression. Buprenorphine topical patches are now available. Codeine and dihydro-codeine are effective for the relief of mild-to-moderate pain. However, dihydrocodeine is a drug that is frequently abused.

7) Opioid-like agents. Tramadol produces analgesia by two mechanisms: an opioid effect; and an enhancement of serotoninergic and adrenergic pathways [413,414]. It has fewer of the typical opioid side effects (notably, less respiratory depression, less constipation and less addiction potential).

c) Neuropathic analgesics

• *Tricyclic antidepressants.* Tricyclics have a definite analgesic effect on neuropathic pain compared with placebo [415]: 30% of patients should obtain more than 50% pain relief; 30% will have minor adverse effects; and 4% will have to stop treatment because of side effects. Tricyclics are said to work in doses that are too low to affect mood. They may work by increasing levels of norepinephrine and/or serotonin. They also have actions at sodium channels. They are extensively used for pelvic pain and good evidence exists to justify their usage (see oral therapy) [416,417].

• *Serotonin reuptake inhibitors*. Selective serotonin reuptake inhibitors appear to be less effective for the management of pelvic pain [418]. Fluoxetine can increase plasma levels of amitriptyline and induce toxicity, and therefore care must be exercised if the drugs are combined.

• *Anticonvulsants* have been used in the management of pain for many years. Gabapentin and pregabalin have recently been introduced for pain management. There is evidence to show that both compounds are effective in neuropathic pain [419]. There is limited evidence to show that gabapentin is effective in acute pain [420]. Whereas there is little evidence to support the use of anticonvulsants in the management of genitourinary pain, they should be considered if there

is a suggestion of neuropathic pain or central sensitization [421,422].

• *N-methyl-D-aspartate (NMDA) antagonists*. The NMDA receptor channel complex is known to be an important channel for the development and maintenance of chronic pain. It is felt to be particularly important when there is evidence of central sensitization and opioid tolerance [423]. Ketamine has been used as a general anaesthetic for over 30 years. It has also been used as an intravenous analgesic in burn units, and accident and emergency units. Ketamine is thought to act primarily at the NMDA receptor, though it may also have actions at sodium channels, as well as opioid (kappa and mu) receptors [424]. Ketamine has been shown in both human and animal models of neuropathic pain to reduce central sensitization and wind-up [424-426]. These phenomena alter signal transmission within the nervous system so that non-painful stimuli may become painful (allodynia) and pain from a painful stimulus is magnified (hyperalgesia). Ketamine has been found to be useful in a number of chronic pain states including: peripheral neuropathies with allodynia, stump and phantom pain, central pain, and cancer-related pain with and without a neurological component [427]. Difficult urogenital pains may therefore be helped by ketamine if there is evidence of nerve injury or central sensitization [428-431]. Ketamine may be useful in opioid-resistant pain in which it may restore the opioid dose-response curve towards normal [428,432]. Oral ketamine has a bioavailability of about 17%. A test dose given by intravenous infusion is a quick way of establishing whether oral ketamine may be viable. Ketamine is a street drug of addiction and great care must be exercised if a patient is to be managed at home on parenteral ketamine. Ketamine should only be used by an experienced practitioner trained in its use.

XII. SURGICAL THERAPY

Bladder Pain Syndrome (BPS) is a chronic and debilitating disease. Major surgical options should be considered only when all conservative treatment has failed. The patient should be informed of all aspects of surgery and understand consequences and potential side effects of surgical intervention. An experienced surgeon familiar with the particular surgical technique should perform the procedure.

1. HYDRODISTENTION

Bladder distension has been used for many years [433] not only as a diagnostic/ classification tool but also for treatment of BPS. In 1957 Franksson reported on a retrospective series of 33 patients, with symptom improvement in all, and lasting up to 1 year in 7 patients [434]. Reports from the seventies were contradictory. Using the Helmstein method [435]. Dunn reported complete absence of symptoms in 16 of 25 patients [436], while Badenoch found no improvement in 44 of 56 patients [437]. More recent literature reports poor results with only a minority of patients reporting a small improvement in symptoms for a relatively short period of time [203,204,215,438]. Most studies are retrospective and uncontrolled. **Level of evidence 3; recommendation C**

2. TRANSURETHRAL RESECTION

In his first papers Hunner described open resection of the bladder ulcer in the treatment of patients with IC[4]. He later abandoned this treatment due to operative morbidity and recurrence of symptoms. Results of transurethral resection were originally reported by Greenberg et al. [439] and Fall [440]. The retrospective results of this treatment in 116 patients with Hunner's lesion from Fall's Swedish clinic was later reported by Peeker et al [441]. Hunner's lesion was first recognized by bladder distension under general anesthesia. All lesions were then resected including at least half of the underlying muscular coat. Large areas of the bladder might be treated to resect all diseased tissue. Ninety-two of the 116 patients experienced amelioration of their symptoms. Average duration of symptom alleviation was 23 months ranging from 0-180 months. Up to 16 re-resections were performed if symptoms recurred. This is the only center having reported a large clinical series of patients with BPS treated in this manner. Shanberg and Malloy reported in 1987 on laser fulgeration of 39 patients with BPS [442]. Nineteen of 39 had Hunner's lesion. Of the 19 patients with Hunner's lesion 17 reported good pain relief lasting between 6 and 18 months. In the 20 patients without Hunner's lesion, reddened areas in the bladder were photocoagulated with the Neodynium:Yag laser.

Thirteen felt marked impro-vement of symptoms but time to symptom recurrence was not reported. Small bowel perforation in 2 patients was the most important complication in this series. This series was extended to 76 patients [443] where 21 of 27 patients with Hunner's lesion (BPS ESSIC type 3X) experienced symptom improvement; 12 had relapse within 18 months. Of patients with BPS ESSIC type 1 or 2, 20 of 49 improved but 10 required further therapy within 1 year. Rofeim et al [444]. reported on Nd:YAG laser ablation of Hunner's lesion in 24 patients with BPS type 3X. All had symptom improvement within days without complications. Pain, urgency, nocturia, and frequency were improved after 23 months, but relapse in 11 patients required up to four additional treatments.

Transurethral resection, coagulation, or laser ablation of Hunner's lesions is a recommended treatment for patients with BPS type 3X.
Level of Evidence: 3
Grade of Recommendation: C

3. CYSTOLYSIS – PERIPHERAL DENERVATION

Hunner [4] simply dissected bladder from surrounding tissue. Initial results were encouraging, however after 3 years of follow-up, symptoms reoccurred. Worth and Turner-Warwick [445] attempted to do more formal cystolysis and were more successful with regard to symptoms. Worth [446] followed patients up to 7 years and found bladder areflexia to be a significant complication of this procedure. Patient**s** had to use Credé technique or even be on intermittent self-catheterisation. Albers & Geyer [447] reported symptom recurrence after 4 years in most of the patients.

• Cystolysis – peripheral denervation is not indicated for BPS; Level of Evidence: 3 Grade of Recommendation: -A (not recommended)

4. SYMPATHETIC DENERVATION

Visceral pain is transmitted in most cases by the sympathetic nervous system. Gino Pieri [448] applied this principle to the bladder pathology and suggested resection of the superior hypogastric plexus (presacral nerves), paravertebral sympathetic chain, and gray rami from S1-3 ganglia (Level 4). This was repeated by Douglass [449] a few years later. Immediate results were very good; however Nesbit [450] showed that the long term results were short lived.

• Sympathetic denervation is not indicated for BPS
Level of Evidence: 4
Grade of Recommendation: -A (not recommended)

5. PARASYMPATHETIC DENERVATION

Based on the contribution of S2-S4 segments to bladder innervation, Moulder and Meirowsky [451] used S3 neurectomy in 3 patients with good long term follow-up. Larger series were reported by Milner [452] and Mason [453] but results after five years were not encouraging. To improve results selective dorsal sacral root neurectomy, unilateral or bilateral, was introduced by Bohm and Franksson [454]. The outcomes of this procedure were unclear.

• Parasympathetic denervation is not indicated for BPS;
Level of Evidence: 4
Grade of Recommendation: -A (not recommended)

6. BOWEL SURGERY

a) Bladder augmentation-cystoplasty has been commonly used for refractory BPS for 50 years. First reports of ileocystoplasty from 1958 were very promising [455]. Later publications were less sanguine with good results varying from up to 100% [456,457] to 25% [458,459]. Cystoplasty is usually done with or without bladder resection.

Cystoplasty alone was reported as early as 1967 by Turner-Warwick and Ashken [460], advocating augmentation with removal of the diseased tissue. Several subsequent studies indicated that cystoplasty with subtrigonal cystectomy offers better results than without subtrigonal cystectomy [457,461-463]. These were all retrospective studies and conclusions should be taken with reservation. Cystoplasty with partial or total removal of the bladder requires bowel tissue substitution. Different bowel segments are used to enlarge the bladder. It is the general consensus that the intestine segment used for bladder augmentation should be detubularized [464]. Experiences with different bowel segments have been reported in numerous articles with level 4 evidence:

Ileum [456-458,463,465-469]

ileocecum [330,457,459,461,470,471]

cecum [456,472,472]

right colon [457,458,473]

sigmoid colon [461,463,466,470]

gastric segments [474,475]

There is no significant different between different bowels segments with regard to outcome except for gastric tissue substitution which is associated dysuria and persistent pain due to production of acids

b) Cystoplasty with Supratrigonal Resection (i.e. trigone-sparing) has been reported in various studies. Von Garrelts [456] described excellent results in eight of 13 patients with a follow-up of 12-72 months. Bruce et. al [463] reported satisfactory relief of BPS symptoms by ileocystoplasty and colocystoplasty in eight patients. Dounis and Gow [476] reported improvement in pain and frequency in seven BPS patients after supratrigonal cystectomy with ileocecal augmentation. Kontturi et. al [461] used segments of colon and sigmoid colon in 12 cases with 100% symptom-free outcome in five patients augmented with sigmoid colon over 4.7 years of follow-up. Two of seven cases augmented with colon required ileal conduit and cystectomy. Linn et. al [477] followed six BPS patients for 30 months, and reported that all were symptom-free and voided spontaneously. The report by Nielsen et. al [459] was less favorable. Six out of eight patients had good results. Van Ophoven et. al [478] reported the long-term (mean 5 years) results of orthotopic substitution enteroplasty in 18 women with BPS, using ileocecal (n = 10) or ileal (n = 8) segments with only two failures. In the group [479] augmented with ileum, three patients required self-catheterization and one a suprapubic catheter. Peeker et. al [480] found that patients with end-stage ulcerative BPS had excellent results following ileocystoplasty but not so the patients with non-ulcer disease. A follow up on this paper was recently published [171] with the same conclusion for the

patients with end stage BPS ESSIC type 3C, while both continent diversion and iliocystoplasty were unrewarding in patients with type 2X BPS. Patients with low cystoscopic capacity (<200 ml) under general anaesthetic have achieved better results [6, 21, 481,482].

There is some weak evidence that cystoplasty with supratrigonal resection may benefit some selected patients with end stage ESSIC type 3C BPS.
Level of Evidence: Level 3;
Grade of Recommendation: C

c) Cystoplasty with Subtrigonal Cystectomy — orthotopic continent bladder augmentation (i.e. with trigone removal but preservation of the bladder neck) in the management of BPS has been reported less often [479,483-485]. Because of the need of ureteral reimplantation, it is associated with some risks of urine leakage, urethral stricture and reflux [484]. Linn et. al [477] had three failures in 17 patients and half of the patients with good symptomatic response required self catheterization. Nielsen et. al [459] had better results following orthotopic substitution with low bladder capacity (200 mL versus 525 mL, respectively). Orthotopic continent bladder augmentation, particularly when removing the trigone, may cause incomplete voiding requiring intermittent self-catheterization. Therefore patients considering such procedures should be advised accordingly and must be considered capable of performing, accepting and tolerating self catheterization. Nurse suggested that the decision on whether to due a subtrigonal or supratrigonal cystectomy be based on the results of trigonal biopsy, with the former procedure indicated in the patient with trigonal inflammation [486].

There is no compelling evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy but it tends to be associated with more complications and poorer functional bladder rehabilitation. Level of evidence: 3; Grade of Recommendation: C

d) Urinary Diversion with or without Total Cystectomy and Urethrectomy

This is the ultimate, final and most invasive option. It should be used as a last therapeutic resort in selected patients. Techniques include simple or continent urinary diversion. Continent diversion may be preferable for cosmetic reasons in younger patients.

Simple urinary diversion with formation of an ileal conduit is the most common surgical treatment for BPS/IC [487]. Initially, diversion can be done without cystectomy and only when bladder pain is persistent, cystectomy may be considered. Bladder de-functionalization alone produced symptom-relief in several reports [6,21,458,488,488,489]. Often diversion is performed as a next step after unsuccessful bladder augmentation. To avoid further bowel resection, a bowel segment used for cystoplasty can often be converted to a conduit [490]. In some patients chronic inflammatory changes have been seen in the cystoplasty pouch resembling interstitial cystitis [6,458,491,492], preventing one from using this technique. Similar bowel changes however have been described when cystoplasty is performed for pathology other than interstitial cystitis, suggesting that these pathologic findings are not a direct result of the exposure of bowel to BPS urine [493]. Relatively good responses to diversion with or without cystectomy have been reported in small series [459,494].

Urinary diversion with and without cystectomy may be the ultimate option for refractory patients. Continent diversion may have better cosmetic and life style outcome but recurrence of pain in the pouch is a real possibility. Level of Evidence: 3; Grade of Recommendation: C

XIII. CLINICAL SYMPTOM SCALES

Symptom scales have enabled patients to be categorized by symptom severity and have also served to follow results of treatment in patients with bladder pain syndrome. Their future development may enable a presumptive diagnosis of the syndrome but at this time that is not possible. A brief survey that reliably segregates BPS from other urologic disorders would make the ability to diagnose the syndrome reliable, inexpensive, and available to all healthcare providers. It would aid in epidemiologic studies as well. Currently such work sponsored by NIDDK is ongoing (http://www.niddk.nih.gov/fund/other/niddkfrontiers/frontiers%20in%20PBS%20Summary%20Report.pdf). The goals of the RAND Interstitial Cystitis Epidemiology (RICE) study are to: (1) develop a case definition for IC in women for patient screening and epidemiological studies; (2) develop and validate a symptom questionnaire to identify female IC patients through self-report; (3) develop IC specific self-report measures of functional status and disease burden; (4) conduct first and second stage screening for IC; and (5) describe the impact of IC on quality of life compared to other disease.

A process for development of a case definition for IC has been developed by adapting the RAND/University of California, Los Angeles Appropriateness Method. This involves a panel consisting of nine experts with experience in BPS and related diseases, literature review of case definitions of BPS, initial ratings of symptoms as indicators of the BPS diagnosis, and discussion and a second set of ratings to establish criteria for diagnosis through patient reports. Symptom questionnaire development, based on the results of the case definition exercise, and validation are the following steps to identify populations of women with

symptoms of BPS who do or do not meet NIDDK criteria, which allows determination of the specificity and sensitivity of the case definition for use in population screening.

Questionnaires and symptom scales are currently utilized to measure treatment outcome and are especially valuable in clinical research studies as well as for guiding therapy for individual patients.

There are 3 published BPS symptom questionnaires: the University of Wisconsin IC Scale (**figure 5**), the O'Leary-Sant IC Symptom Index (ICSI) and IC Problem Index (ICPI) (**figure 6**), and the Pelvic Pain and Urgency/Frequency (PUF) Scale (**figure 7**).

1. The University of Wisconsin IC Scale includes 7 BPS symptom items and has not been validated for identification or diagnosis of BPS. It captures severity of symptom expression [495,496]. Unlike the other two instruments, it addresses some quality-of-life issues, and this is an advantage when such issues are subject of investigation. Its most attractive aspects are its clinically apparent face validity and its ease of implementation.

2. The O'Leary-Sant indexes are validated questionnaires that were originally developed by focus groups, subjected to test-retest reliability analysis, and validated by administration to BPS patients and asymptomatic controls [497,498]. The questionnaires center on 3 questions related to urgency/frequency and one on bladder-associated pain. It does not address generalized pelvic pain or symptomatology associated with sexual activity. This is not because these questions were not considered in the formulation of the questionnaire.

Of 73 questions in the preliminary instrument covering domains of urinary symptoms, pain, sexual function, menstrual variability, and general health, only the four questions now in the instrument were needed to reliably and validly describe the illness experience of those with IC and distinguish these patients from those without the disorder [499].

3. The most recently published instrument is the Pelvic Pain, Urgency, Frequency (PUF) questionnaire [189].

It was specifically designed to include questions that directly reflect a wide variety of the symptoms experienced by patients who are affected by this disorder. One-third of the questions address pelvic pain, including pain anywhere in the pelvis: the vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum. A large study utilizing the PUF questionnaire has concluded that up to 23% of American females have BPS [189]. This makes one wary as to the utility and face-validity of the PUF [500]. A total score of 10-14 =74% likelihood of positive potassium test (PST); 15-19=76%; 20+=91%. To the extent that the PST is suspect, the reliability of PUF data comes into question.

4. Discussion

Neither the PUF nor O'Leary Sant questionnaires have been shown to be of value in diagnosis of the individual patient [501]. In an interesting epidemiologic study in Finland, Leppilahti and colleagues randomly selected 2000 participants from the Finnish population registry and administered the O'Leary Sant IC symptom and problem index [64]. Women with symptom scores 7 or higher with no history of urinary tract infection in the preceding month were invited to undergo clinical examination. Of these 32 women, 21 underwent examination of whom 3 had probable interstitial cystitis and 4 had possible interstitial cystitis. Based on this specificity, a population prevalence in Finnish women of 230/100,000 probable interstitial cystitis and 530/100,000 possible interstitial cystitis was calculated. Thus, one can get some idea as to O'Leary Sant specificity. For probable BPS it would be about 14% using a parameter of 7 or greater on the symptom index.

The O'Leary-Sant and University of Wisconsin instrument correlate strongly in a large population of patients with BPS [502]. Clemons and co-workers administered the ICSI to 45 patients scheduled to undergo laparoscopy for pelvic pain. Seventeen were diagnosed with BPS based on the finding of glomerulations on bladder distention associated with urgency, frequency, or nocturia. A score of 5 on the ICSI had a 94% sensitivity and a 93% negative predictive value in this enriched population of patients with pelvic pain [503]. However, Clemens and colleagues have found a high degree of overlap in International Prostate Symptom Scores, the O'Leary Sant Symptom Index, and the Chronic Prostatitis Symptom Index in a random sample of over 1400 men and women with urologic symptoms, underscoring that we should be cautious in using these questionnaires as a basis for diagnosis in epidemiologic studies [504].

Rosenberg and Hazzard [67] surveyed 1218 consecutive patients presenting to their primary care office and found 7 (0.6%) who had a 7 ICSI score. Likely BPS was noted in 12.6% of patients on the PUF scale, a figure 21 times higher, suggesting that either the PUF drastically overestimates BPS, or the ICSI lacks sensitivity. Based on the correlation of the potassium sensitivity test and the PUF questionnaire, Parsons [54] stated that 30.6% of 3'rd year female medical students at his California institution had probable BPS. Sahinkanat and coworkers [190] in Turkey administered the PUF questionnaire to all 442 female textile workers in two local factories. Eighty-six per cent of those with a PUF score 7 or greater had an 86% positive rate of PST testing verses 9% positive in the group with PUF less than 7. They extrapolated that bladder epithelial permeability dysfunction was present in 32.8% of these unselected women. The ICSI estimate seems much more in line with current epidemiologic data.

Symptom	Score each symptom from 1-6 (0=not at all) (6=a lot)					
1. Bladder discomfort	0	1	2	3	4	5
2. Bladder pain	0	1	2	3	4	5
3. Other pelvic discomfort	0	1	2	3	4	5
4. Headache	0	1	2	3	4	5
5. Backache	0	1	2	3	4	5
6. Dizziness	0	1	2	3	4	5
7. Feelings of suffocation	0	1	2	3	4	5
8. Chest pain	0	1	2	3	4	5
9. Ringing in ears	0	1	2	3	4	5
10. Getting up at night to go to the bathroom	0	1	2	3	4	5
11. Aches in joints	0	1	2	3	4	5
12. Swollen ankles	0	1	2	3	4	5
13. Nasal congestion	0	1	2	3	4	5
14. Flu	0	1	2	3	4	5
15. Abdominal cramps	0	1	2	3	4	5
16. Numbness or tingling in fingers or toes	0	1	2	3	4	5
17. Nausea	0	1	2	3	4	5
18. Going to the bathroom frequently during the day	0	1	2	3	4	5
19. Blind spots or blurred vision	0	1	2	3	4	5
20. Heart pounding	0	1	2	3	4	5
21. Difficulty sleeping because of bladder symptoms	0	1	2	3	4	5
22. Sore throat	0	1	2	3	4	5
23. Urgency to urinate	0	1	2	3	4	5
24. Coughing	0	1	2	3	4	5
25. Burning sensation in bladder	0	1	2	3	4	5

Figure 5 : University of Wisconsin Symptom Instrument (J. Urol. 173:835-840, 2005)

IC SYMPTOM INDEX

During the past month …

Q1. … how often have you felt the strong need to urinate with little or no warning?

0. Not at all
1. Less than 1 time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Almost always

Q2. … how often have you had to urinate less than 2 hours after you finished urinating?

0. Not at all
1. Less than 1 time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Almost always

Q3. … how often did you most typically get up at night to urinate?

0. Not at all
2. A few times
3. Almost always
4. Fairly often
5. Usually

Q4. …have you experienced pain or burning in your bladder?

0. Not at all
2. A few times
3. Almost always
4. Fairly often
5. Usually

Add the numerical values of the checked entries.
Total Score:___

IC PROBLEM INDEX

During the past month how much has each of the following been a problem for you:

Q1. Frequent urination during the day?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Q2. Getting up at night to urinate?

0. No problem
1. Very small problem'
2. Small problem
3. Medium problem
4. Big problem

Q3. Need to urinate with little warning?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Q4. Burning, pain, discomfort, or pressure in your bladder?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Add the numerical values of the checked entries.
Total score: ___

Figure 6 : O'Leary Sant Symptom and Problem Indexes

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom, does it bother you?	Never Bothers	Occasionally	Usually	Always			
3	a. Do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
	b. Has pain or urgency ever made you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
4	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
5	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
6	Do you still have urgency after going to the bathroom?	Never	Occasionally	Usually	Always			
7	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
8	Are you sexually active? Yes___ No___							
							SYMPTOM SCORE = (1, 2a, 3a, 4, 5a, 6, 7a)	
								BOTHER SCORE = (2b, 3b, 5b, 7b)
							TOTAL SCORE (Symptom Score + Bother Score) =	

Figure 7: Pelvic Pain, Urgency, Frequency Scale

While perhaps not ideally suited for epidemiologic studies, these questionnaires can reveal important epidemiologic data. Porru and colleagues [505 compared University of Wisconsin scores including both urinary and non-urinary symptoms, for 30 BPS female patients and 30 female controls. While the IC group had significantly higher scores for the urinary symptoms, they did not appear to indiscriminately report higher scores than controls for different somatic and general complaints, as might be expected if this disease is a manifestation of a more generalized disorder. Diggs and colleagues [506] used the ICSI to investigate how interstitial cystitis patients interpret urgency. The ICSI question regarding: "the strong need to urinate with little or no warning" consistently underestimated the response to the International Continence Society definition of urgency: "the compelling urge to urinate that is difficult to postpone.

Treatment outcome studies have also used the Global Response Assessment (**figure 8**); a balanced patient self-report on overall response to therapy, developed for NIDDK sponsored multicenter therapeutic trials [285]. The O'Leary Sant and University of Wisconsin questionnaires are responsive to change over time in patients with BPS and have been recommended as secondary endpoints in future clinical trials of the disorder. Propert and colleagues in the Interstitial Cystitis Clinical Trials Group determined that a 1.2 point change in the O'Leary Sant indexes and a 3.1 point change in Wisconsin IC inventory corresponded to a one-category change in the GRA. Individual symptoms were also responsive [507].

- 3 : MARKEDLY WORSE
- 2 : MODERATELY WORSE
- 1 : SLIGHTLY IMPROVED
0 : NO CHANGE
+ 1 : SLIGHTLY IMPROVED
+2 : MODERATELY IMPROVED
+ 3 : MARKEDLY IMPROVED

Figure 8 : Global Response Assessment (GRA)

XIV. OUTCOME ASSESSMENT

1. THE PROBLEM

BPS/IC has been a difficult condition for which to assess therapeutic impact. There is a 50% incidence of temporary remission unrelated to therapy, with a mean duration of 8 months [58]. A somewhat surprising finding from the Interstitial Cystitis Database was that although there was initial improvement in symptoms partially due to regression to the mean [508] and the intervention effect, there was no evidence of a long-term change in average symptom severity over the four year course of follow-up [71]. In a chronic, devastating condition with primarily subjective symptomatology, no known cause, and no cure, patients are desperate and often seem to respond to any new therapy. A

skeptical view of outcomes is essential (**figure 9**), as patients can be victims of unorthodox health care providers using unproven forms of therapy, some medical, some homeopathic, and some even surgical.

2. THE PLACEBO ISSUE

Where possible, the results of randomized controlled studies should be used for decision making. Placebo, double-blind studies are optimal in this disorder for which there is no generally effective standard therapy.

Placebo effects influence patient outcomes after any treatment which the clinician and patients believe is effective, including surgery. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects [71,509-511] Unfortunately, few BPS treatments have been subjected to a placebo-controlled trial. This is not to say that what seems effective is not, but rather that a high index of skepticism is healthy, even in treatments tested in controlled trials [512].

While in many diseases an argument can be made against using a true placebo control as opposed to an orthodox treatment of approved or accepted value [513], a good case for true placebo comparison can readily be made for BPS. The vagaries of the natural history, the general lack of progression of symptom severity over time, and the fact that it is not life threatening, mean that there is little to lose and much to gain by subjecting new treatments to the vigorous scrutiny of placebo control. Many patients who volunteer for such trials have already run the gamut of accepted (though generally unproved) therapies. It has long been recognized in protocols that use subjective criteria for assessment that “improvement” may be expected in up to 35% of placebo-treated patients [514]. As the spontaneous remission rate (though temporary) for BPS is 11% [295] to 50% [58], combined with the placebo improvement it can be difficult to prove efficacy.

Even in placebo controlled trials, it is reasonable to surmise that some degree of unblinding may occur as a result of somatic or psychological side effects of the active arm, impairing the validity of the trial results and giving the active arm a slight edge over placebo [515,516]. Failure to recognize unblinding can easily bias results of a study and has not been routinely measured in clinical trials [517]. When occurring late in a study after one would expect onset of a therapeutic effect, unblinding could be the result of side effect profile or drug efficacy. Early in the trial it reflects poor placebo or study design. The degree of blinding needs to be ascertained throughout the trial. This is of specific concern in BPS and any disorder where primary outcomes may be subject to patient-specific psychological and physiological factors.

The ethics and necessity of placebo-controlled trials have been questioned, especially in situations in which an effective treatment exists and also where delay in treatment has been shown to result in disease progression [518-520]. However, there are methodological concerns with equivalence and non-inferiority active agent comparison trials [521]. These include an inability to determine if the treatments are equally good or equally bad, and the possibility that successive non-inferiority trials can lead to a gradual decrease in treatment efficacy. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied [522].

The value of placebo-controlled trials is aptly illustrated by the recent decisions by pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for BPS [523,524] after placebo-controlled trials failed to establish efficacy. These include low concentration hyaluronic acid (Bioniche, Canada), high concentration hyaluronic acid (SKK, Tokyo), and resiniferatoxin (ICOS, Bothell, Washington, USA). Nalmefene, an initially promising oral therapy in the 1990’s, [326] also failed phase 3 trials (IVAX, Miami). Placebo trials are impractical in surgery and it can be difficult to evaluate surgical reports. The many older medications currently used off-label might not meet success if tested in the stringent manner in which new molecular entities are tested. The expense of testing therapies currently used off-label often requires dependence on the largesse of government agencies like the National Institute of Health [285,376,525]

2. OUTCOME INTERPRETATION

As has been discussed with regard to rheumatologic disorders [526], the interpretation of measurements of physical functioning in clinical trials should consider the composition of the study sample, with attention to the stage of disease and the heterogeneity in disease duration. Patients with long-standing disease or compromised bladder capacity or central sensitization can be expected to be less responsive to treatments directed toward the bladder itself. Finally, when considering objective changes, the concept of statistical versus clinical significance is paramount. Investigators should, but rarely do, point out differences between statistical improvement and what they consider to be clinically significant improvement [527]. As Gertrude Stein reportedly stated, “A difference, to be a difference, must make a difference”. An increase in bladder capacity of 30cc may be statistically significant but clinically irrelevant. Number needed to treat and number needed to harm data [528] may be particularly important in BPS and have not typically been included in efficacy analysis.

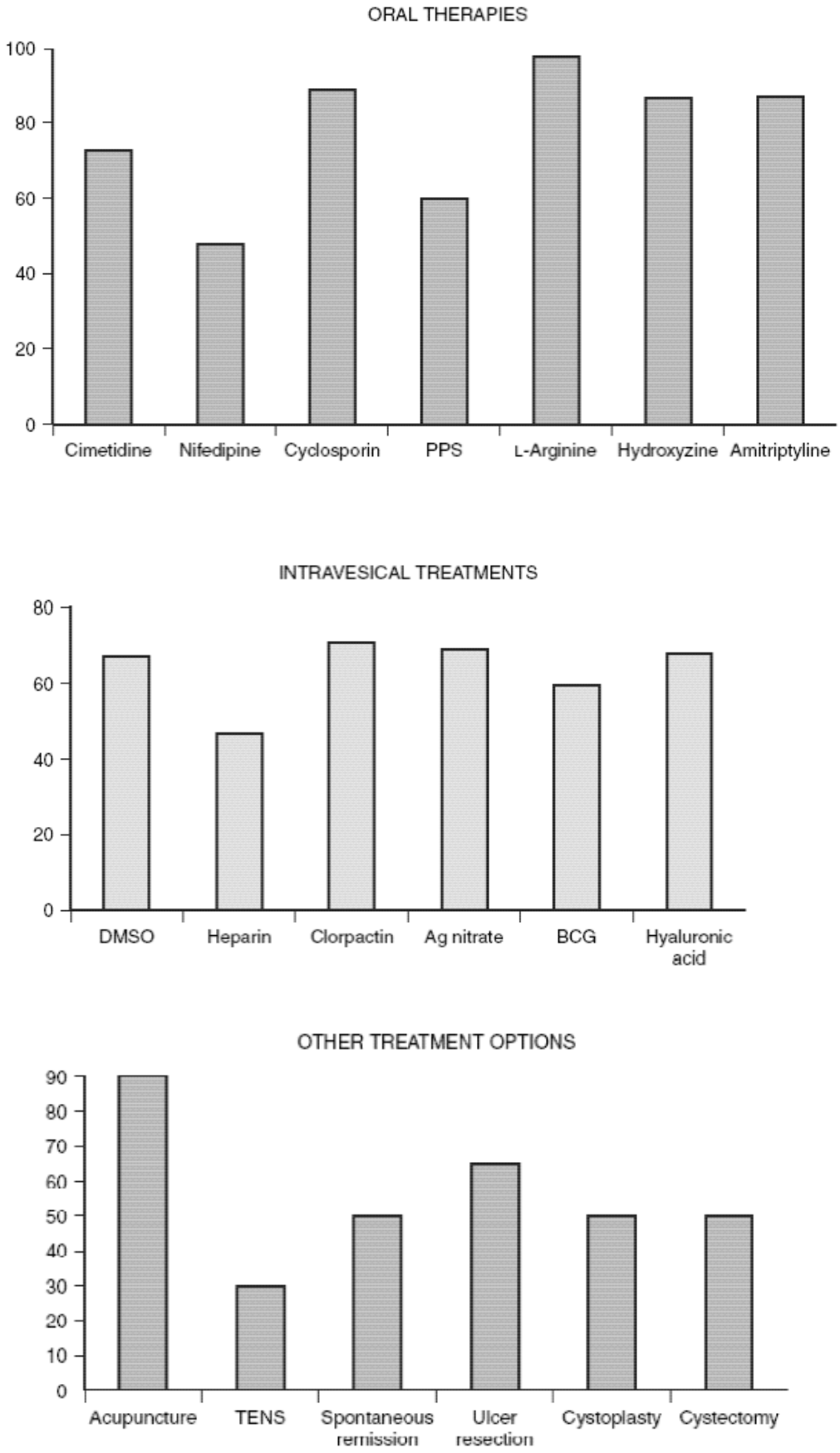

Figure 9 : Selected reported treatment outcomes in uncontrolled studies in IC literature: Percentage of patients initially improved.

3. IMMPACT RECOMMENDATIONS

The core outcome domains for chronic pain clinical trials have been published [399,529].The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations indicate that core outcome domains should be considered in all clinical trials of the efficacy and effectiveness of treatments for chronic pain. These domains include:

1. Pain
2. Physical functioning
3. Emotional functioning
4. Participant ratings of improvement and satisfaction with treatment
5. Symptoms and adverse effects, participant disposition

CONCLUSIONS

Currently for BPS/IC there are no accepted biologic disease markers that can be used for the assessment of response to therapy. The O'Leary Sant, University of Wisconsin, and Global Response Assessment are well-validated questionnaires to follow disease progression and response to therapy. The IMMPACT recommen-dations suggest that as well as symptoms scores, any future study on a pain syndrome must involve more general assessments of psycho-physical functioning. There is limited experience in BPS/IC for the use of well-validated measures available for the study of chronic pain. Future NIDDK research initiatives may help to rectify this. http://grants.nih. gov/grants/guide/rfa-files/RFA-DK-07-003.htmlhttp://www. nih.gov/news/health/sep 2008/ niddk-05.htm.

International recognition of an agreed upon definition and inclusion and exclusion criteria of BPS/IC will help future studies to fulfill the highest standards available, and placebo-controlled, double-blind, randomized controlled trials, where possible, will provide the highest level of evidence to move the field forward.

XV. PRINCIPLES OF MANAGEMENT

The information currently available in the literature does not lend itself to easily formulating a diagnostic or treatment guideline. Different groups of "experts" would undoubtedly create different "best practices". The compromise approach devised by an experienced cross-section of urologists and gynecologists from around the world at the International Consultation on Continence 2004 meeting in Monaco [38] has been reviewed and updated by the committee and allows for significant latitude to reflect varying individual practice patterns and to account for patient preference.

An underlying principle is that, where possible, treatment decisions of bladder pain syndrome should be evidence based. Unfortunately, high level evidence of efficacy is lacking for many common treatments, either because such studies have not been done, or were done and failed to demonstrate efficacy [530,531] The previous Consultation reported that only oral amitriptyline and intravesical dimethyl sulfoxide had supporting evidence to have a B level of recommendation in the Oxford system [38]. A subsequent review by Karsenty and colleagues added oral cimetidine to that list [532].

Another principle is that we should be guided by patient perceived and driven outcomes for bladder pain syndrome, which is, after all, diagnosed on the basis of symptoms after exclusion of confusable diseases. Many patients prefer noninvasive therapies [533], and it would seem reasonable to start with oral therapies if conservative non-medical interventions fail to result in significant symptom amelioration. Use of surgical therapies should be approached with some caution. Ingber and coworkers reported that women with BPS have significantly more pelvic surgeries than controls, and the majority were performed prior to diagnosis of BPS, possibly for pain related to undiagnosed BPS [534].

1. HISTORY / INITIAL ASSESSMENT

Men or women with **an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes [535]** should be evaluated for bladder pain syndrome. The initial assessment consists of a frequency/volume chart, focused physical exam, urinalysis, and urine culture. Cytology and cystoscopy are recommended if clinically indicated.

Patients with infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and/or hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms are they diagnosed with BPS.

2. INITIAL TREATMENT

Patient education and support, dietary manipulation, nonprescription analgesics, and pelvic floor relaxation techniques comprise the initial management of BPS. **It is important to address the patient's pain, and understand that at some point in the progression of treatment, referral to a pain specialty clinic may be desirable.**

When the conservative approach fails, or symptoms are severe and conservative mana-gement unlikely to succeed, oral medication, physical therapy, and/or intravesical treatment can be prescribed.

3. SECONDARY ASSESSMENT

If oral or intravesical therapy fails, or before beginning such therapy at the discretion of the clinician, it is reasonable to consider further evaluation which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia. Laparoscopy may be indicated if there is a suspicion of gynecologic disease. Findings of bladder overactivity suggest a trial of antimuscarinic therapy. Findings of a Hunner's lesion suggest therapy with transurethral fulguration or resection of the ulcer. Distention itself can have therapeutic benefit in up to one-third of patients, though benefits rarely persist for longer than a few months.

4. REFRACTORY PBS/IC

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities, generally in the context of clinical trials. These might include neuromodulation, intravesical botulinum toxin, and/or experimental pharmacologic protocols of promising new treatments. The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urine stream. Augmentation (substitution) cystoplasty and urinary diversion with or without cystectomy have been used with good results in very well selected patients.

It is the opinion of the committee that, because of the natural history of the disorder, it is best to cautiously progress through a variety of treatments. Whereas the shotgun approach, starting newly diagnosed patients on a variety of simultaneous medications, seems to have many adherents, employing one treatment at a time makes the natural history of the disease itself an ally in the treatment process. If a treatment has no efficacy, it should be stopped. It a treatment results in modest improvement, it should be continued and another treatment option employed in an attempt to further improve symptoms. The goal is to maximize quality of life and dispense with ineffective treatments in a somewhat controlled fashion. The patient and clinician must remember that "perfect is the enemy of good" and expectations should be realistic. One should encourage patients to maximize their activity and live as normal a life as possible, not becoming a prisoner of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself. Therefore, patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare. Dogmatic restriction and diet are to be avoided unless they are shown to improve symptoms in a particular patient. Level 4 Grade C

XVI. FUTURE DIRECTIONS IN RESEARCH

There are five major recommendations for future directions in research on BPS that the committee believes will lead to a greater understanding of the condition and will have a major impact on its management.

1. EPIDEMIOLOGICAL STUDY

1. Develop a reliable screening tool with adequate sensitivity and specificity to conduct epidemiologic research in the general population to study the incidence, prevalence and identify risk factors for the development of BPS.

2. Establish patient data bases in different regions and conduct longitudinal follow up to understand the natural history of the disease and to examine the differences in disease natural history among regions.

2. SUB-GROUPING/PHENOTYPING PATIENTS

Patients who have or develop additional pain syndromes, such as vulvodynia, temporomandibular disorder, irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome, or autoimmune diseases such as lupus erythematosus and Sjögren's syndrome might have different pathophysiology, natural history and treatment response from those patients without co-morbidities. Sub-grouping patients not only allows us to develop better treatment strategy but also may answer the question: Is BPS an end-organ disease of the bladder or a systemic condition? [147,536 90] However, to properly phenotype patients, it is necessary to develop an easy-to-use tool for non-specialists to identify those with co-morbidities. It is also important to validate the concept that categorizes all types of pelvic pain into one "chronic urological pelvic pain syndrome", as some patients' symptoms involve multiple pelvic organs, concurrently or sequentially along with other body systems.

3. DEVELOPING A SIMPLE, NON-INVASIVE DIAGNOSTIC TEST FOR BPS

This will most likely involve urinary markers. Urinary markers may help to sub-classify various types of BPS. This test will determine the diagnosis of BPS in the female population, as well as determine the subset of men currently diagnosed with non-bacterial chronic prostatitis/chronic pelvic pain syndrome who may actually have BPS.

4. COMPREHENSIVE STUDY ON HYDRODISTENTION

Hydrodistention is still a popular practice in many places around the world simply due to the limited effective therapeutic armamentarium that can be

offered to the patients. It is necessary to standardize the technique and conduct international cooperative studies to verify the true value of this treatment modality. Some important information can be gathered from these studies, such as identifying the patient variables that lead to a good therapeutic response.

5. DEVELOP A PRACTICAL MULTI-DISCIPLINARY CARE MODEL

In addition to physical morbidities (urinary frequency, pain), many BPS patients have associated psychological co-morbidities [537]. These can often be managed by psychological intervention. BPS patients also need help from dietitians and physiotherapists. A practical multi-disciplinary care model, which includes physicians, dietitians, physiotherapists, pain specialists, psychologists, psychiatrists and patient support groups, should be developed and tested in various settings.

XVII. SUMMARY (figure 10)

1. DEFINITION

Bladder Pain Syndrome (in the absence of a universally agreed definition, the European Society for the Study of Interstitial Cystitis –ESSIC definition is given along with a slight modification made at a recent international meeting held by the Society for Urodynamics and Female Urology – SUFU

ESSIC: *Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.*

Consensus Definition from SUFU International Conference (Asia, Europe, North America) held in Miami, Florida February 2008: *An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes.*

2. BLADDER PAIN SYNDROME (BPS)

a) Nomenclature (Figure 11)

The scientific committee of the International Consultation voted to use the term “bladder pain syndrome” for the disorder that has been commonly referred to as interstitial cystitis (IC). The term painful bladder syndrome was dropped from the lexicon. The term IC implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. Painful Bladder Syndrome, as defined by the International Continence Society, is too restrictive for the clinical syndrome. Properly defined, the term Bladder Pain Syndrome appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP), and focuses on the actual symptom complex rather than what appears to be long-held misconception of the underlying pathology.

b) History / Initial Assessment

Males or females with pain, pressure, or discomfort that they perceive to be related to the bladder with at least one urinary symptom, such as frequency not obviously related to high fluid intake, or a persistent urge to void should be evaluated for possible bladder pain syndrome. The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms also suggests the diagnosis. Abnormal gynecologic findings in women and well-characterized confusable diseases that may explain the symptoms must be ruled out.

The initial assessment consists of a frequency/volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology and cystoscopy are recommended if clinically indicated. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms, are they diagnosed with BPS. **Grade of recommendation: C**

c) Initial Treatment

Patient education, dietary manipulation, nonprescription analgesics, and pelvic floor relaxation techniques comprise the initial treatment of BPS. The treatment of pain needs to be addressed directly, and in some instances referral to an anesthesia/pain center can be an appropriate early step in conjunction with ongoing treatment of the syndrome. When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed, oral medication, intravesical treatment, or physical therapy can be prescribed. It is recommended to initiate a single form of therapy and observe results, adding another modality or substituting another modality as indicated by degree of response or lack of response to treatment. Excellence can be the enemy of good. **Grade of recommendation: C**

d) Secondary Assessment

If initial oral or intravesical therapy fails, or before beginning such therapy, it is reasonable to consider further evaluation which can include Urodynamics, pelvic imaging, and cystoscopy with bladder distention

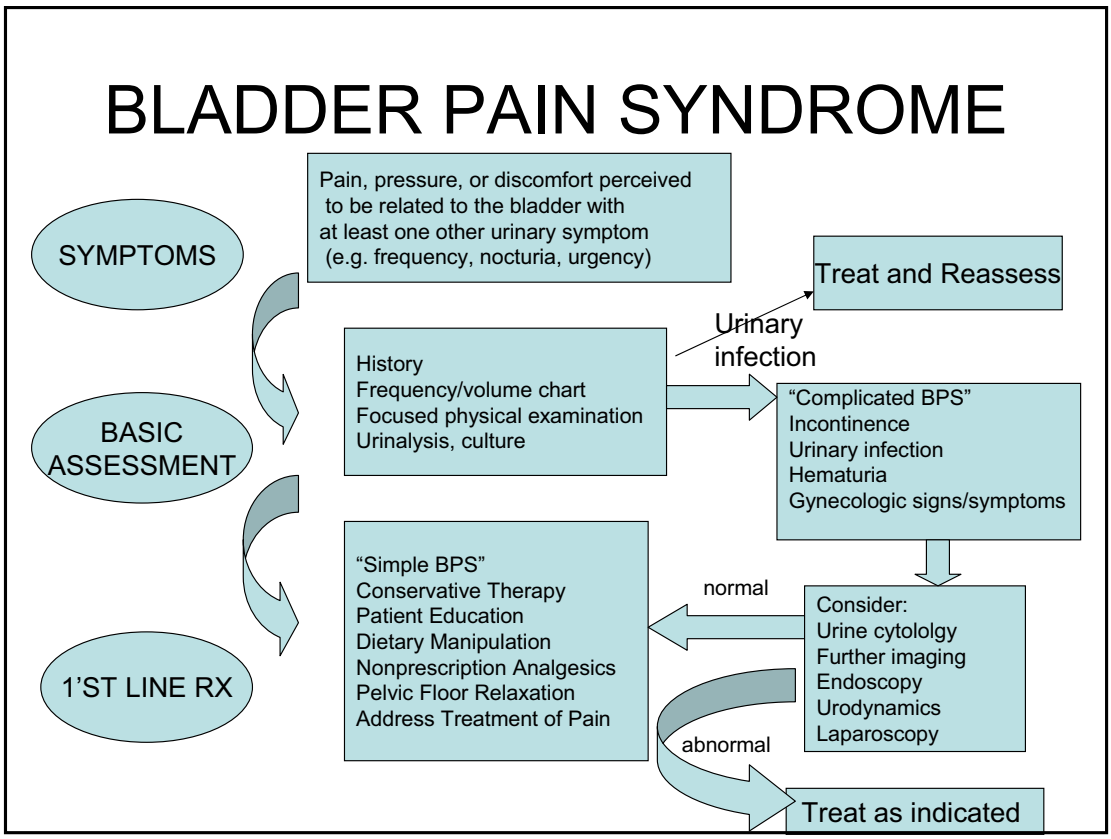

Figure 10 : The new perspective of Bladder Pain Syndrome From Hanno, PM: Proceedings of the International Consultation on Interstitial Cystitis, Japan; Comfortable Urology Network, pages 2-9, 2008

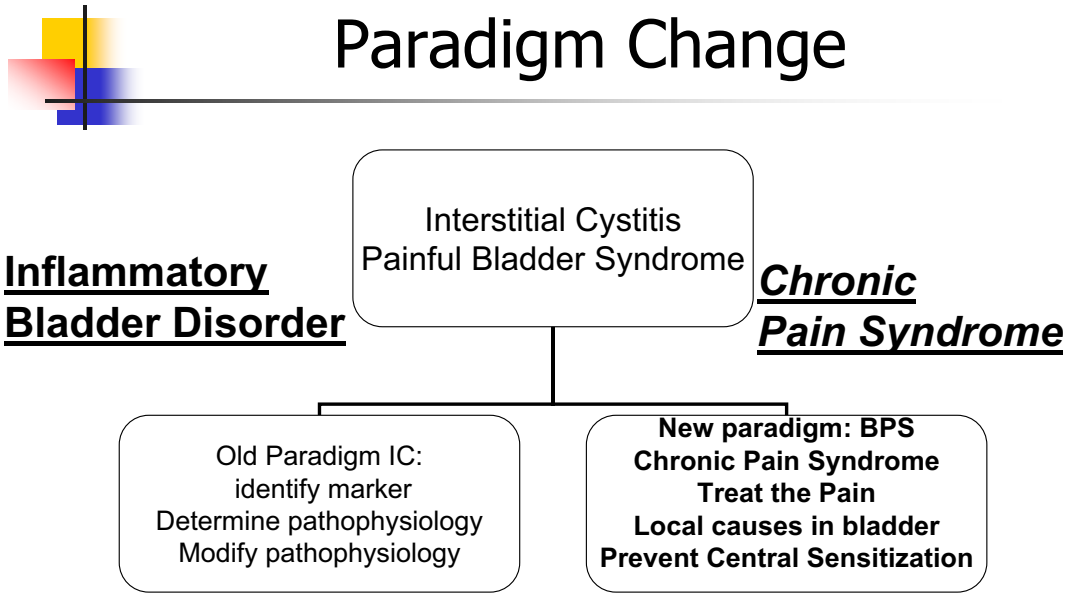

Figure 11 : The new perspective of Bladder Pain Syndrome From Hanno, PM: Proceedings of the International Consultation on Interstitial Cystitis, Japan; Comfortable Urology Network, pages 2-9, 2008

and possible bladder biopsy under anesthesia. Findings of bladder overactivity suggest a trial of antimuscarinic therapy. Findings of a Hunner's lesion suggest therapy with transurethral resection or fulguration of the lesion. Distention itself can have therapeutic benefit in 30-50% of patients, though benefits rarely persist for longer than a few months. **Grade of recommendation: C**

e) Refractory BPS

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include neuromodulation, intravesical botulinum toxin, or newly described pharmacologic management techniques. At this point, most patients will benefit from the expertise of an anesthesia pain clinic. The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream. Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients. Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series. **Grade of recommendation: C**

REFERENCES

1. Van De Merwe, J., Nordling, J., Bouchelouche, K., Bouchelouche, P., and et.al: Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an essic proposal. Eur Urol, 53**:** 60, 2008.
2. Hanno, P., Nordling, J., and van Ophoven, A.: What is new in bladder pain syndrome/interstitial cystitis? Curr Opin Urol, 18**:** 353, 2008.
3. Skene, A. J. C.: Diseases of the Bladder and Urethra in Women. New York: William Wood, 1887.
4. Hunner, G. L.: A rare type of bladder ulcer in women; report of cases. Boston Med Surg Journal, 172**:** 660, 1915.
5. Bourque, J. P.: Surgical management of the painful bladder. Journal of Urology, 65**:** 25, 1951.
6. Messing, E. M. and Stamey, T. A.: Interstitial cystitis: early diagnosis, pathology, and treatment. Urology, 12**:** 381, 1978.
7. Wein, A., Hanno, P. M., and Gillenwater, J. Y.: Interstitial Cystitis: an introduction to the problem. In: Interstitial Cystitis. Edited by Hanno, P. M., Staskin, D. R., Krane, R. J., and Wein, A. J.: London: Springer-Verlag, pp 3-15, 1990.
8. Simon, L. J., Landis, J. R., Erickson, D. R., and Nyberg, L. M.: The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. Urology, 49**:** 64, 1997.
9. Abrams, P. H., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U. et al.: The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. Neurourology and Urodynamics, 21**:** 167, 2002.
10. Warren, J. W., Meyer, W. A., Greenberg, P., Horne, L., Diggs, C., and Tracy, J. K.: Using the International Continence Society's definition of painful bladder syndrome. Urology, 67**:** 1138, 2006.
11. Nordling, J., Anjum, F. H., Bade, J. J., Bouchelouche, K., Bouchelouche, P., Cervigni, M. et al.: Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol, 45**:** 662, 2004.
12. Abrams, P., Hanno, P., and Wein, A.: Overactive bladder and painful bladder syndrome: there need not be confusion. Neurourol Urodyn, 24**:** 149, 2005.
13. Nigro, DA., Wein, A. J., Foy, M., Parsons, C. L., Williams, M., Nyberg, L. M., Jr. et al.: Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology, 49**:** 86, 1997.
14. Salavatore, S., Khullar, V., Cardozo, L., Anders, K., Zocchi, G., and Soligo, M.: Evaluating ambulatory urodynamics: a prospective study in asymptomatic women. British Journal of Obstetrics and Gynaecology, 110**:** 83, 2003.
15. Parsons, J. K. and Parsons, C. L.: The historical origins of interstitial cystitis. J Urol, 171**:** 20, 2004.
16. Christmas, T. J.: Historical aspects of interstitial cystitis. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 1-8, 1997.
17. Parrish, J.: Tic doloureux of the urinary bladder. In: Practical observations on strangulated hernia and some of the diseases of the urinary organs Philadelphia: Key and Biddle, pp 309-313, 1836.
18. Teichman, J. M., Thompson, I. M., and Taichman, N. S.: Joseph Parrish, tic doloureux of the bladder and interstitial cystitis. J Urol, 164**:** 1473, 2000.
19. Hunner, G. L. A rare type of bladder ulcer. Further notes, with a report of eighteen cases. JAMA 70[4], 203-212. 1-26-1918. Ref Type: Journal (Full)
20. Walsh, A.: Interstitial cystitis. In: Campbell's Urology, 4th ed. Edited by Harrison, J. H., Gittes, R. F., Perlmutter, A. D., and al., et: Philadelphia: W. B. Saunders Company, pp 693-707, 1978.
21. Hand, J. R.: Interstitial cystitis: report of 223 cases (204 women and 19 men). Journal of Urology, 61**:** 291, 1949.
22. Gillenwater, J. Y. and Wein, A. J.: Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol, 140**:** 203, 1988.
23. Simon, L. J., Landis, J. R., Tomaszewski, J. E., and Nyberg, L. M.: The interstitial cystitis database (ICDB) study. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 17-24, 1997.
24. Hanno, P. M., Landis, J. R., Matthews-Cook, Y., Kusek, J., and Nyberg, L., Jr.: The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol, 161**:** 553, 1999.
25. Hanno, P. M.: Re-imagining Interstitial Cystitis. Urol Clin North Am, 35**:** 91, 2008.
26. Hanno, P. and Dmochowski, R. R.: Status of interntional consensus on interstitial cystitis / bladder pain syndrome / painful bladder syndrome: 2008 snapshot . Neurourol Urodyn. In press 2009
27. Hanno, P.: Interstitial cystitis/painful bladder syndrome/bladder pain syndrome: the evolution of a new paradigm. International Consultation Interstitial Cystitis Japan, 2, 2008.
28. Powell, N. B. and Powell, E. B.: The female urethra: A clinico-pathological study. Journal of Urology, 61**:** 557, 1949.
29. Dell, J. R. and Parsons, C. L.: Multimodal therapy for interstitial cystitis. J Reprod Med, 49**:** 243, 2004.
30. Tomaszewski, J. E., Landis, J. R., Russack, V., Williams, T. M., Wang, L. P., Hardy, C. et al.: Biopsy features are associated with primary symptoms in interstitial cystitis: results from the interstitial cystitis database study. Urology, 57**:** 67, 2001.

31. Rosamilia, A., Igawa, Y., and Higashi, S.: Pathology of interstitial cystitis. Int J Urol, 10 Suppl: S11, 2003.

32. Lynes, W. L., Flynn, S. D., Shortliffe, L. D., and Stamey, T. A.: The histology of interstitial cystitis. Am J Surg Pathol, 14: 969, 1990.

33. Denson, M. A., Griebling, T. L., Cohen, M. B., and Kreder, K. J.: Comparison of cystoscopic and histological findings in patients with suspected interstitial cystitis. J Urol, 164: 1908, 2000.

34. Clauw, D. J., Schmidt, M., Radulovic, D., Singer, A., Katz, P., and Bresette, J.: The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res, 31: 125, 1997.

35. Wu, E. Q., Birnbaum, H., Kang, Y. J., Parece, A., Mallett, D., Taitel, H. et al.: A retrospective claims database analysis to assess patterns of interstitial cystitis diagnosis. Curr Med Res Opin, 22: 495, 2006.

36. Ueda, T., Sant, G. R., Hanno, P. M., and Yoshimura, N.: Interstitial cystitis and frequency-urgency syndrome (OAB syndrome). Int J Urol, 10 Suppl: S39, 2003.

37. Hanno, P., Keay, S., Moldwin, R., and van, O. A.: International Consultation on IC - Rome, September 2004/Forging an International Consensus: progress in painful bladder syndrome/interstitial cystitis. Report and abstracts. Int Urogynecol J Pelvic Floor Dysfunct, 16 Suppl 1: S2, 2005.

38. Hanno, P., Baranowski, A., Fall, M., Gajewski, J. B., Nordling, J., Nyberg, L. et al.: Painful bladder syndrome (including interstitial cystitis). In: Incontinence, 3 ed. Edited by Abrams, P. H., Wein, A. J., and Cardozo, L.: Paris: Health Publications Limited, vol. 2, chapt. 23, pp 1456-1520, 2005.

39. Abrams, P., Baranowski, A., Berger, R., Fall M, Hanno, P., and Wesselmann, U.: A new classification is needed for pelvic pain syndromes — are existing terminologies of spurious diagnostic authority bad for patients? J Urol, 175: 1989, 2006.

40. van de Merwe, J. P., Nordling, J., Bouchelouche, P., Bouchelouche, K., Cervigni, M., Daha, L. K. et al.: Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol, 53: 60, 2008.

41. Baranowski, A., Abrams, P., Berger, R., Buffington, C. A., Williams, CD., Hanno, P. et al.: Urogenital pain- time to accept a new approach to phenotyping and, as a consequence, management. European Urology, 2007.

42. Verhaak, P. F. M., Kerssens, J. J., Dekker, J., Sorbi, M. J., and Bensing, J. M.: Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain, 77: 231, 1998.

43. Farkas, A., Waisman, J., and Goodwin, W. E.: Interstitial cystitis in adolescent girls. J Urol, 118: 837, 1977.

44. Hanash, K. A. and Pool, T. L.: Interstitial cystitis in men. J Urol, 102: 427, 1969.

45. Geist, R. W. and Antolak, S. J., Jr.: Interstitial cystitis in children. J Urol, 104: 922, 1970.

46. Koff, S. A. and Byard, M. A.: The daytime urinary frequency syndrome of childhood. Journal of Urology, 140: 1280, 1988.

47. Robson, W. L. M. and Leung, A. K. C.: Extraordinary urinary frequency syndrome. Urology, 42: 321, 1993.

48. Close, C. E., Carr, M. C., Burns, M. W., Miller, J. L., Bavendam, T. G., Mayo, M. E. et al.: Interstitial cystitis in children. J Urol, 156: 860, 1996.

49. Koziol, J. A., Clark, D. C., Gittes, R. F., and Tan, E. M.: The natural history of interstitial cystitis: a survey of 374 patients. J Urol, 149: 465, 1993.

50. Tincello, D. and Walker, A.: Interstitial cystitis in the UK: results of a questionnaire survey of members of the interstitial cystitis support group. Eur J Obstet Gynecol Reprod Biol, 118: 91, 2005.

51. Bernardini, P., Bondavalli, C., Luciano, M., Schiavon, L., Dall'Oglio, B., Parma, P. et al.: [Interstitial cystitis: epidemiology]. Arch Ital Urol Androl, 71: 313, 1999.

52. Barry, M. J., Link, C. L., Naughton-Collins, M. F., and McKinlay, J. B.: Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. BJU Int, 101: 45, 2008.

53. Ito, T., Miki, M., and Yamada, T.: Interstitial cystitis in Japan. BJU Int, 86: 634, 2000.

54. Parsons, C. L. and Tatsis, V.: Prevalence of interstitial cystitis in young women. Urology, 64: 866, 2004.

55. Clemens, J. Q., Link, C. L., Eggers, P. W., Kusek, J. W., Nyberg, L. M., Jr., and McKinlay, J. B.: Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol, 177: 1390, 2007.

56. Koziol, J. A.: Epidemiology of interstitial cystitis. Urol Clin North Am, 21: 7, 1994.

57. Oravisto, K. J.: Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn, 64: 75, 1975.

58. Held, P. J., Hanno, P. M., and Wein, A. J.: Epidemiology of interstitial cystitis: 2. In: Interstitial Cystitis. Edited by Hanno, P. M., Staskin, D. R., Krane, R. J., and Wein, A. J.: London: Springer-Verlag, pp 29-48, 1990.

59. Jones, C. A. and Nyberg, L.: Epidemiology of interstitial cystitis. Urology, 49: 2, 1997.

60. Bade, J. J., Rijcken, B., and Mensink, H. J.: Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. J Urol, 154: 2035, 1995.

61. Curhan, G. C., Speizer, F. E., Hunter, D. J., Curhan, S. G., and Stampfer, M. J.: Epidemiology of interstitial cystitis: a population based study. J Urol, 161: 549, 1999.

62. Ibrahim, I. A., Diokno, A. C., Killinger, K. A., Carrico, D. J., and Peters, K. M.: Prevalence of self-reported interstitial cystitis (IC) and interstitial-cystitis-like symptoms among adult women in the community. Int Urol Nephrol, 39: 489, 2007.

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

64. Leppilahti, M., Sairanen, J., Tammela, T. L., Aaltomaa, S., Lehtoranta, K., and Auvinen, A.: Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. J Urol, 174: 581, 2005.

65. Yu, Hong-Jeng. Prevalence of Interstitial Cystitis in Taiwan. 2006. 2006. Ref Type: Conference Proceeding

66. Warren, J. W., Jackson, T. L., Langenberg, P., Meyers, D. J., and Xu, J.: Prevalence of interstitial cystitis in first-degree relatives of patients with interstitial cystitis. Urology, 63: 17, 2004.

67. Rosenberg, M. T. and Hazzard, M.: Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol, 174: 2231, 2005.

68. Nickel, J. C., Teichman, J. M., Gregoire, M., Clark, J., and Downey, J.: Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE Study. Urology, 66: 935, 2005.

69. Leppilahti, M., Tammela, T. L., Huhtala, H., and Auvinen, A.: Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. J Urol, 168: 139, 2002.

70. Clemens, J. Q., Meenan, R. T., O'Keeffe Rosetti, M. C., Brown, S. O., Gao, S. Y., and Calhoun, E. A.: Prevalence of

interstitial cystitis symptoms in a managed care population. J Urol, 174: 576, 2005.

71. Propert, K. J., Schaeffer, A. J., Brensinger, C. M., Kusek, J. W., Nyberg, L. M., and Landis, J. R.: A prospective study of interstitial cystitis: results of longitudinal followup of the interstitial cystitis data base cohort. The Interstitial Cystitis Data Base Study Group. J Urol, 163: 1434, 2000.
72. Shea-O'Malley, C. C. and Sant, G. R.: Quality of life in interstitial cystitis. Urologia Integrada y de Investigacion, 4: 303, 1999.
73. Rothrock, N. E., Lutgendorf, S. K., Hoffman, A., and Kreder, K. J.: Depressive symptoms and quality of life in patients with interstitial cystitis. J Urol, 167: 1763, 2002.
74. Michael, Y. L., Kawachi, I., Stampfer, M. J., Colditz, G. A., and Curhan, G. C.: Quality of life among women with interstitial cystitis. J Urol, 164: 423, 2000.
75. Onwude, J. L. and Selo-Ojeme, D. O.: Pregnancy outcomes following the diagnosis of interstitial cystitis. Gynecol Obstet Invest, 56: 160, 2003.
76. Clemens, J., Meenan, R., Rosetti, M., and Calhoun, E.: Prevalence and incidence of interstitial cystitis in a managed care population. J Urol, 173: 98, 2005.
77. Forrest, J. B. and Schmidt, S.: Interstitial cystitis, chronic nonbacterial prostatitis and chronic pelvic pain syndrome in men: a common and frequently identical clinical entity. J Urol, 172: 2561, 2004.
78. Miller, J. L., Rothman, I., Bavendam, T. G., and Berger, R. E.: Prostatodynia and interstitial cystitis: one and the same? Urology, 45: 587, 1995.
79. Miller, J. L., Bavendam, T. G., and Berger, R. E.: Interstitial cystitis in men. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 165-168, 1997.
80. Novicki, D. E., Larson, T. R., and Swanson, S. K.: Interstitial cystitis in men. Urology, 52: 621, 1998.
81. Roberts, R. O., Bergstralh, E. J., Bass, S. E., Lightner, D. J., Lieber, M. M., and Jacobsen, S. J.: Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. BJU Int, 91: 181, 2003.
82. Clauw, D.: The pathogenesis of chronic pain and fatigue syndromes, with special reference to fibromyalgia. Medical Hypotheses, 44: 369, 1995.
83. Clauw, D., Schmidt, M., Radulovic, D., Singer, A., Katz, P., and Bresette, J.: The relationship between fibromyalagia and interstitial cystitis. Journal of Psychiatric Research, 31: 125, 1997.
84. Alagiri, M., Chottiner, S., Ratner, V., Slade, D., and Hanno, P. M.: Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology, 49: 52, 1997.
85. Erickson, D. R., Morgan, K. C., Ordille, S., Keay, S. K., and Xie, S. X.: Nonbladder related symptoms in patients with interstitial cystitis. J Urol, 166: 557, 2001.
86. Aaron, L. A. and Buchwald, D.: A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med, 134: 868, 2001.
87. Aaron, L. A., Herrell, R., Ashton, S., Belcourt, M., Schmaling, K., Goldberg, J. et al.: Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med, 16: 24, 2001.
88. Peeker, R., Atanasiu, L., and Logadottir, Y.: Intercurrent autoimmune conditions in classic and non-ulcer interstitial cystitis. Scand J Urol Nephrol, 37: 60, 2003.
89. Weissman, M. M., Gross, R., Fyer, A., Heiman, G. A., Gameroff, M. J., Hodge, S. E. et al.: Interstitial cystitis and panic disorder: a potential genetic syndrome. Arch Gen Psychiatry, 61: 273, 2004.
90. Clemens, J. Q., Meenan, R. T., O'Keeffe Rosetti, M. C., Kimes, T. A., and Calhoun, E. A.: Case-control study of medical comorbidities in women with interstitial cystitis. J Urol, 179: 2222, 2008.
91. Peters, K. M., Kalinowski, S. E., Carrico, D. J., Ibrahim, I. A., and Diokno, A. C.: Fact or fiction—is abuse prevalent in patients with interstitial cystitis? Results from a community survey and clinic population. J Urol, 178: 891, 2007.
92. Brand, K., Littlejohn, G., Kristjanson, L., Wisniewski, S., and Hassard, T.: The fibromyalgia bladder index. Clin Rheumatol, 26: 2097, 2007.
93. Aaron, L. A. and Buchwald, D.: Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. Best Pract Res Clin Rheumatol, 17: 563, 2003.
94. Fall, M., Johansson, S. L., and Vahlne, A.: A clinicopathological and virological study of interstitial cystitis. J Urol, 133: 771, 1985.
95. Fall, M.: Transcutaneous electrical nerve stimulation in interstitial cystitis. Update on clinical experience. Urology, 29: 40, 1987.
96. Peeker, R., Enerback, L., Fall, M., and Aldenborg, F.: Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. J Urol, 163: 1009, 2000.
97. Hofmeister, M. A., He, F., Ratliff, T. L., Mahoney, T., and Becich, M. J.: Mast cells and nerve fibers in interstitial cystitis (IC): an algorithm for histologic diagnosis via quantitative image analysis and morphometry (QIAM). Urology, 49: 41, 1997.
98. Fall, M., Johansson, S. L., and Aldenborg, F.: Chronic interstitial cystitis: a heterogeneous syndrome. J Urol, 137: 35, 1987.
99. Dundore, P. A., Schwartz, A. M., and Semerjian, H.: Mast ce counts are not useful in the diagnosis of nonulcerative interstitial cystitis. J Urol, 155: 885, 1996.
100. Bouchelouche, K., Kristensen, B., Nordling, J., Horn, T., and Bouchelouche, P.: Increased urinary leukotriene E4 and eosinophil protein X excretion in patients with interstitial cystitis. J Urol, 166: 2121, 2001.
101. Parsons, C. L., Lilly, J. D., and Stein, P.: Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol, 145: 732, 1991.
102. Johansson, S. L. and Fall, M.: Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol, 143: 1118, 1990.
103. Fellows, G.: The permeability of human bladder epithelium to water and sodium. Invest Urol, 9: 339, 1972.
104. Anderstrom, C. R., Fall, M., and Johansson, S. L.: Scanning electron microscopic findings in interstitial cystitis. Br J Urol, 63: 270, 1989.
105. Parsons, C. L., Stein, P., Zupkas, P., Chenoweth, M., Argade, S. P., Proctor, J. G. et al.: Defective Tamm-Horsfall protein in patients with interstitial cystitis. J Urol, 178: 2665, 2007.
106. Keay, S., Kleinberg, M., Zhang, C. O., Hise, M. K., and Warren, J. W.: Bladder epithelial cells from patients with interstitial cystitis produce an inhibitor of heparin-binding epidermal growth factor-like growth factor production. J Urol, 164: 2112, 2000.
107. Keay, S., Seillier-Moiseiwitsch, F., Zhang, C. O., Chai, T. C., and Zhang, J.: Changes in human bladder epithelial cell gene expression associated with interstitial cystitis or antiproliferative factor treatment. Physiol Genomics, 14: 107, 2003.
108. Keay, S., Reeder, J. E., Koch, K., Zhang, C. O., Grkovic, D., Peters, K. et al.: Prospective evaluation of candidate urine and cell markers in patients with interstitial cystitis enrolled in a randomized clinical trial of Bacillus Calmette Guerin (BCG). World J Urol, 25: 499, 2007.

109. Silk, M. R.: Bladder antibodies in interstitial cystitis. J Urol, 103: 307, 1970.

110. Oravisto, K. J.: Interstitial cystitis as an autoimmune disease. A review. Eur Urol, 6: 10, 1980.

111. Jokinen, E. J., Alfthan, O. S., and Oravisto, K. J.: Antitissue antibodies in interstitial cystitis. Clin Exp Immunol, 11: 333, 1972.

112. Anderson, J. B., Parivar, F., Lee, G., Wallington, T. B., MacIver, A. G., Bradbrook, R. A. et al.: The enigma of interstitial cystitis—an autoimmune disease? Br J Urol, 63: 58, 1989.

113. Tan, E. M.: Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol, 44: 93, 1989.

114. Leppilahti, M., Tammela, T. L., Huhtala, H., Kiilholma, P., Leppilahti, K., and Auvinen, A.: Interstitial cystitis-like urinary symptoms among patients with Sjogren's syndrome: a population-based study in Finland. Am J Med, 115: 62, 2003.

115. Ochs, R. L.: Autoantibodies and interstitial cystitis. Clin Lab Med, 17: 571, 1997.

116. Mattila, J., Harmoinen, A., and Hallstrom, O.: Serum immunoglobulin and complement alterations in interstitial cystitis. Eur Urol, 9: 350, 1983.

117. Mattila, J. and Linder, E.: Immunoglobulin deposits in bladder epithelium and vessels in interstitial cystitis: possible relationship to circulating anti-intermediate filament autoantibodies. Clin Immunol Immunopathol, 32: 81, 1984.

118. Harrington, D. S., Fall, M., and Johansson, S. L.: Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. J Urol, 144: 868, 1990.

119. Lynes, W. L., Sellers, R. G., and Dairiki Shortliffe, L. M. The evidence for occult bacterial infections as a cause for interstitial cystitis. J Urol 141, 268. 1989. Ref Type: Abstract

120. Warren, J. W., Brown, V., Jacobs, S., Horne, L., Langenberg, P., and Greenberg, P.: Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. Urology, 71: 1085, 2008.

121. Duncan, J. L. and Schaeffer, A. J.: Do infectious agents cause interstitial cystitis? Urology, 49: 48, 1997.

122. English, S. F., Liebert, M., Cross, C. A., and McGuire, E. J.: The incidence of Helicobacter pylori in patients with interstitial cystitis. J Urol, 159: 772, 1998.

123. Palea, S., Artibani, W., Ostardo, E., Trist, D. G., and Pietra, C.: Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis. J Urol, 150: 2007, 1993.

124. Hohenfellner, M., Nunes, L., Schmidt, R. A., Lampel, A., Thuroff, J. W., and Tanagho, E. A.: Interstitial cystitis: increased sympathetic innervation and related neuropeptide synthesis. J Urol, 147: 587, 1992.

125. Christmas, T. J., Rode, J., Chapple, C. R., Milroy, E. J., and Turner-Warwick, R. T.: Nerve fibre proliferation in interstitial cystitis. Virchows Arch A Pathol Anat Histopathol, 416: 447, 1990.

126. Sugimura, K., Haimoto, H., and Nagura, H.: Immunohistochemical differential distribution of S-100 alpha and S-100 beta in the peripheral nervous system of the rat. Muscle Nerve, 12: 929, 1989.

127. Stefansson, K., Wollmann, R. L., and Moore, B. W.: Distribution of S-100 protein outside the central nervous system. Brain Res, 234: 309, 1982.

128. Peeker, R., Aldenborg, F., Haglid, K., Johansson, S. L., Rosengren, L., and Fall, M.: Decreased levels of S-100 protein in non-ulcer interstitial cystitis. Scand J Urol Nephrol, 32: 395, 1998.

129. Elbadawi, A. E. and Light, J. K.: Distinctive ultrastructural pathology of nonulcerative interstitial cystitis: new observations and their potential significance in pathogenesis. Urol Int, 56: 137, 1996.

130. Peeker, R., Aldenborg, F., Dahlstrom, A., Johansson, S. L., Li, J. Y., and Fall, M.: Increased tyrosine hydroxylase immunoreactivity in bladder tissue from patients with classic and nonulcer interstitial cystitis. J Urol, 163: 1112, 2000.

131. Malykhina, A. P., Qin, C., Greenwood-Van, M. B., Foreman, R. D., Lupu, F., and Akbarali, H. I.: Hyperexcitability of convergent colon and bladder dorsal root ganglion neurons after colonic inflammation: mechanism for pelvic organ cross-talk. Neurogastroenterol Motil, 18: 936, 2006.

132. Malykhina, A. P.: Neural mechanisms of pelvic organ cross-sensitization. Neuroscience, 149: 660, 2007.

133. Noronha, R., Akbarali, H., Malykhina, A., Foreman, R. D., and Greenwood-Van, M. B.: Changes in urinary bladder smooth muscle function in response to colonic inflammation. Am J Physiol Renal Physiol, 293: F1461, 2007.

134. Pezzone, M. A., Liang, R., and Fraser, M. O.: A model of neural cross-talk and irritation in the pelvis: implications for the overlap of chronic pelvic pain disorders. Gastroenterology, 128: 1953, 2005.

135. Qin, C., Malykhina, A. P., Akbarali, H. I., Greenwood-Van, M. B., and Foreman, R. D.: Acute colitis enhances responsiveness of lumbosacral spinal neurons to colorectal distension in rats. Dig Dis Sci, 53: 141, 2008.

136. Rudick, C. N., Chen, M. C., Mongiu, A. K., and Klumpp, D. J.: Organ cross talk modulates pelvic pain. Am J Physiol Regul Integr Comp Physiol, 293: R1191, 2007.

137. Moncada, S. and Higgs, A.: The L-arginine-nitric oxide pathway. New England Journal of Medicine, 329: 2002, 1993.

138. Smith, S. D., Wheeler, M. a., Foster, H. E., Jr., and Weiss, R. M.: Urinary nitric oxide synthase activity and cyclic GMP levels are decreased with interstitial cystitis and increased with urinary tract infections. J Urol, 155: 1432, 1996.

139. Logadottir, Y. R., Ehren, I., Fall, M., Wiklund, N. P., Peeker, R., and Hanno, P. M.: Intravesical nitric oxide production discriminates between classic and nonulcer interstitial cystitis. J Urol, 171: 1148, 2004.

140. Parsons, C. L., Bautista, S. L., Stein, P. C., and Zupkas, P.: Cyto-injury factors in urine: a possible mechanism for the development of interstitial cystitis. J Urol, 164: 1381, 2000.

141. Hang, L., Wullt, B., Shen, Z., Karpman, D., and Svanborg, C.: Cytokine repertoire of epithelial cells lining the human urinary tract. J Urol, 159: 2185, 1998.

142. Rosamilia, A., Cann, L., Scurry, J., Rogers, P., and Dwyer, P.: Bladder microvasculature and the effects of hydrodistention in interstitial cystitis. Urology, 57: 132, 2001.

143. Pontari, M. A., Hanno, P. M., and Ruggieri, M. R.: Comparison of bladder blood flow in patients with and without interstitial cystitis. J Urol, 162: 330, 1999.

144. Warren, J. W., Keay, S. K., Meyers, D., and Xu, J.: Concordance of interstitial cystitis in monozygotic and dizygotic twin pairs. Urology, 57: 22, 2001.

145. Talati, A., Ponniah, K., Strug, L. J., Hodge, S. E., Fyer, A. J., and Weissman, M. M.: Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. Biol Psychiatry, 63: 594, 2008.

146. Clauw, D. J.: The pathogenesis of chronic pain and fatigue syndromes, with special reference to fibromyalgia. Med Hypotheses, 44: 369, 1995.

147. Clauw, D. J., Schmidt, M., Radulovic, D., Singer, A., Katz,

P., and Bresette, J.: The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res, 31: 125, 1997.

148. Sand, P. K.: Proposed pathogenesis of painful bladder syndrome/interstitial cystitis. J Reprod Med, 51: 234, 2006.
149. Hellstrom, H. R., Davis, B. K., and Shonnard, J. W.: Eosinophilic cystitis. A study of 16 cases. Am J Clin Pathol, 72: 777, 1979.
150. Tsiriopoulos, I., Lee, G., O', R. A., Smith, R., and Pancharatnam, M.: Primary splenic marginal zone lymphoma with bladder metastases mimicking interstitial cystitis. Int Urol Nephrol, 38: 475, 2006.
151. Jacobo, E., Stamler, F. W., and Culp, D. A.: Interstitial cystitis followed by total cystectomy. Urology, 3: 481, 1974.
152. Smith, B. H. and Dehner, L. P.: Chronic ulcerating interstitial cystitis (Hunner's ulcer). A study of 28 cases. Arch Pathol, 93: 76, 1972.
153. Lepinard, V., Saint-Andre, J. P., and Rognon, L. M.: [Interstitial cystitis. Current aspects]. J Urol (Paris), 90: 455, 1984.
154. Johansson, S. L. and Fall, M.: Pathology of interstitial cystitis. Urol Clin North Am, 21: 55, 1994.
155. Holm-Bentzen, M., Jacobsen, F., Nerstrom, B., Lose, G., Kristensen, J. K., Pedersen, R. H. et al.: Painful bladder disease: clinical and pathoanatomical differences in 115 patients. J Urol, 138: 500, 1987.
156. Moore, K. H., Nickson, P., Richmond, D. H., Sutherst, J. R., Manasse, P. R., and Helliwell, T. R.: Detrusor mast cells in refractory idiopathic instability. Br J Urol, 70: 17, 1992.
157. Theoharides, T. C., Kempuraj, D., and Sant, G. R.: Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. Urology, 57: 47, 2001.
158. Larsen, M. S., Mortensen, S., Nordling, J., and Horn, T.: Quantifying mast cells in bladder pain syndrome by immunohistochemical analysis. BJU Int, 2008.
159. Rudick, C. N., Bryce, P. J., Guichelaar, L. A., Berry, R. E., and Klumpp, D. J.: Mast cell-derived histamine mediates cystitis pain. PLoS ONE, 3: e2096, 2008.
160. Collan, Y., Alfthan, O., Kivilaakso, E., and Oravisto, K. J.: Electron microscopic and histological findings on urinary bladder epithelium in interstitial cystitis. Eur Urol, 2: 242, 1976.
161. Dixon, J. S., Holm-Bentzen, M., Gilpin, C. J., Gosling, J. A., Bostofte, E., Hald, T. et al.: Electron microscopic investigation of the bladder urothelium and glycocalyx in patients with interstitial cystitis. J Urol, 135: 621, 1986.
162. Nickel, J. C., Emerson, L., and Cornish, J.: The bladder mucus (glycosaminoglycan) layer in interstitial cystitis. J Urol, 149: 716, 1993.
163. Elbadawi, A.: Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology, 49: 14, 1997.
164. Holm-Bentzen, M.: Pathology and pathophysiology of painful bladder diseases. Urol Int, 44: 327, 1989.
165. Holm-Bentzen, M., Larsen, S., Hainau, B., and et.al.: Nonobstructive detrusor myopathy in a group of patients with chronic abacterial cystitis. Scand J Urol Nephrol, 19: 21, 1985.
166. Christmas, T. J., Smith, G. L., and Rode, J.: Detrusor myopathy: an accurate predictor of bladder hypocompliance and contracture in interstitial cystitis. Br J Urol, 78: 862, 1996.
167. Tomaszewski, J. E., Landis, J. R., Brensinger, C., Hardy, C., and et.al.: Baseline associations among pathologic features and patient symptoms in the national interstitial cystitis data base. Journal of Urology, 161 S: 28, 1999.
168. Hanus, T., Zamecnik, L., Jansky, M., Jarolim, L., Povysil, C., and Benett, R.: The comparison of clinical and histopathologic features of interstitial cystitis. Urology, 57: 131, 2001.
169. Mattila, J.: Vascular immunopathology in interstitial cystitis. Clin Immunol Immunopathol, 23: 648, 1982.
170. Johansson, S. L., Ogawa, K., and Fall, M.: The pathology of interstitial cystitis. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 143-152, 1997.
171. Rossberger, J., Fall, M., Jonsson, O., and Peeker, R.: Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology, 70: 638, 2007.
172. Erickson, D. R., Tomaszewski, J. E., Kunselman, A. R., Stetter, C. M., Peters, K. M., Rovner, E. S. et al.: Urine markers do not predict biopsy findings or presence of bladder ulcers in interstitial cystitis/painful bladder syndrome. J Urol, 179: 1850, 2008.
173. Mcdougald M, Landon CR. The diagnosis of interstitial cystitis: Is histology helpful ? Int.Urogynecol.J.Pelvic.Floor. Dysfunct. 14[Suppl 1], S40-S41. 2003. Ref Type: Abstract
174. Nordling, J., Anderson, J. B., Mortensen, S, Bouchelouche, K., Horn, T., Hald, T., and and the Copenhagen IC study group. Clinical outcome in patients with interstitial cystitis, relative to detrusor myopathy. Poster 42 Research Insights into Interstitial cystitis, NIDDK Washington Oct 30-Nov 1, 2003 . 11-1-2003. Ref Type: Abstract
175. MacDermott, J. P., Charpied, G. C., Tesluk, H., and Stone, A. R.: Can histological assessment predict the outcome in interstitial cystitis? Br J Urol, 67: 44, 1991.
176. Kaplan, S. A., Ikeguchi, E. F., Santarosa, R. P., D'Alisera, P. M., Hendricks, J., Te, A. E. et al.: Etiology of voiding dysfunction in men less than 50 years of age. Urology, 47: 836, 1996.
177. Hanno, P.: Is the potassium sensitivity test a valid and useful test for the diagnosis of interstitial cystitis? Int Urogynecol J Pelvic Floor Dysfunct, 16: 428, 2005.
178. Hohlbrugger, G.: Disintegrity of the vesical blood-urine barrier in interstitial cystitis: a vicious circle. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 87-92, 1997.
179. Vander, A. J.: Renal Physiology. New York: McGraw Hill Health Professions Division, 1995.
180. Roberto, P. J., Reich, J. D., Hirshberg, S., Knight, L., Hanno, P. M., and Ruggieri, M.: Assessment of bladder permiability and sensation in interstitial cystitis patients. Journal of Urology, 157: 317, 1997.
181. Teichman, J. M. and Nielsen-Omeis, B. J.: Potassium leak test predicts outcome in interstitial cystitis. J Urol, 161: 1791, 1999.
182. Chambers, G. K., Fenster, H. N., Cripps, S., Jens, M., and Taylor, D.: An assessment of the use of intravesical potassium in the diagnosis of interstitial cystitis. J Urol, 162: 699, 1999.
183. Parsons, C. L., Greenberger, M., Gabal, L., Bidair, M., and Barme, G.: The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol, 159: 1862, 1998.
184. Yilmaz, U., Liu, Y. W., Rothman, I., Lee, J. C., Yang, C. C., and Berger, R. E.: Intravesical potassium chloride sensitivity test in men with chronic pelvic pain syndrome. J Urol, 172: 548, 2004.
185. Parsons, C. L., Stein, P. C., Bidair, M., and et.al.: Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. Neurourol Urodyn, 13: 515, 1994.
186. Parsons, C. L. and Albo, M.: Intravesical potassium sensitivity in patients with prostatitis. J Urol, 168: 1054, 2002.

187. Parsons, C. L., Rosenberg, M. T., Sassani, P., Ebrahimi, K., Koziol, J. A., and Zupkas, P.: Quantifying symptoms in men with interstitial cystitis/prostatitis, and its correlation with potassium-sensitivity testing. BJU Int, 95**:** 86, 2005.

188. Parsons, C. L., Dell, J., Stanford, E. J., Bullen, M., Kahn, B. S., and Willems, J. J.: The prevalence of interstitial cystitis in gynecologic patients with pelvic pain, as detected by intravesical potassium sensitivity. Am J Obstet Gynecol, 187**:** 1395, 2002.

189. Parsons, C. L., Dell, J., Stanford, E. J., Bullen, M., Kahn, B. S., Waxell, T. et al.: Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. Urology, 60**:** 573, 2002.

190. Sahinkanat, T., Guven, A., Ekerbicer, H., and Aral, M.: Prevalence of positive potassium sensitivity test which is an indicator of bladder epithelial permeability dysfunction in a fixed group of Turkish women. Urol Int, 80**:** 52, 2008.

191. Gregoire, M., Liandier, F., Naud, A., Lacombe, L., and Fradet, Y.: Does the potassium stimulation test predict cystometric, cystoscopic outcome in interstitial cystitis? J Urol, 168**:** 556, 2002.

192. Kuo, H. C.: Urodynamic study and potassium sensitivity test for women with frequency-urgency syndrome and interstitial cystitis. Urol Int, 71**:** 61, 2003.

193. Philip, J., Willmott, S., and Irwin, P.: Interstitial cystitis versus detrusor overactivity: a comparative, randomized, controlled study of cystometry using saline and 0.3 M potassium chloride. J Urol, 175**:** 566, 2006.

194. Philip, J., Willmott, S., Owen, D., Samsudin, C., and Irwin, P. P.: A double-blind, randomized controlled trial of cystometry using saline versus 0.3 M potassium chloride infusion in women with overactive bladder syndrome. Neurourol Urodyn, 26**:** 110, 2007.

195. Daha, L. K., Riedl, C. R., Hohlbrugger, G., Knoll, M., Engelhardt, P. F., and Pfluger, H.: Comparative assessment of maximal bladder capacity, 0.9% NaCl versus 0.2 M Kcl, for the diagnosis of interstitial cystitis: a prospective controlled study. J Urol, 170**:** 807, 2003.

196. Riedl, C. R., Engelhardt, P. F., Daha, K. L., Morakis, N., and Pfluger, H.: Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct, 19**:** 717, 2008.

197. Awad, S. A., MacDiarmid, S., Gajewski, J. B., and Gupta, R.: Idiopathic reduced bladder storage versus interstitial cystitis. J Urol, 148**:** 1409, 1992.

198. Waxman, J. A., Sulak, P. J., and Kuehl, T. J.: Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. J Urol, 160**:** 1663, 1998.

199. Messing, E., Pauk, D., Schaeffer, A., Nieweglowski, M., Nyberg, L. M., Jr., Landis, J. R. et al.: Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology, 49**:** 81, 1997.

200. Erickson, D. R.: Glomerulations in women with urethral sphincter deficiency: report of 2 cases [corrected]. J Urol, 153**:** 728, 1995.

201. Bade, J., Ishizuka, O., and Yoshida, M.: Future research needs for the definition/diagnosis of interstitial cystitis. Int J Urol, 10 Suppl**:** S31, 2003.

202. Turner, K. J. and Stewart, L. H.: How do you stretch a bladder? A survey of UK practice, a literature review, and a recommendation of a standard approach. Neurourol Urodyn, 2004.

203. Cole, E. E., Scarpero, H. M., and Dmochowski, R. R.: Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn, 24**:** 638, 2005.

204. Ottem, D. P. and Teichman, J. M.: What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology, 66**:** 494, 2005.

205. Lamale, L. M., Lutgendorf, S. K., Hoffman, A. N., and Kreder, K. J.: Symptoms and cystoscopic findings in patients with untreated interstitial cystitis. Urology, 67**:** 242, 2006.

206. Shear, S. and Mayer, R.: Development of glomerulations in younger women with interstitial cystitis. Urology, 68**:** 253, 2006.

207. Zabihi, N., Allee, T., Maher, M. G., Mourtzinos, A., Raz, S., Payne, C. K. et al.: Bladder necrosis following hydrodistention in patients with interstitial cystitis. J Urol, 177**:** 149, 2007.

208. Erickson, D. R.: Urinary markers of interstitial cystitis. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 123-128, 1997.

209. Erickson, D. R., Xie, S. X., Bhavanandan, V. P., Wheeler, M. a., Hurst, R. E., Demers, L. M. et al.: A comparison of multiple urine markers for interstitial cystitis. J Urol, 167**:** 2461, 2002.

210. Keay, S. K., Szekely, Z., Conrads, T. P., Veenstra, T. D., Barchi, J. J., Jr., Zhang, C. O. et al.: An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. Proc Natl Acad Sci U S A, 101**:** 11803, 2004.

211. Keay, S., Zhang, C. O., Trifillis, A. L., Hise, M. K., Hebel, J. R., Jacobs, S. C. et al.: Decreased 3H-thymidine incorporation by human bladder epithelial cells following exposure to urine from interstitial cystitis patients. J Urol, 156**:** 2073, 1996.

212. Keay, S., Warren, J. W., Zhang, C. O., Tu, L. M., Gordon, D. A., and Whitmore, K. E.: Antiproliferative activity is present in bladder but not renal pelvic urine from interstitial cystitis patients. J Urol, 162**:** 1487, 1999.

213. Chai, T. C., Zhang, C., Warren, J. W., and Keay, S.: Percutaneous sacral third nerve root neurostimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis. Urology, 55**:** 643, 2000.

214. Chai, T. C., Zhang, C. O., Shoenfelt, J. L., Johnson, H. W., Jr., Warren, J. W., and Keay, S.: Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis. J Urol, 163**:** 1440, 2000.

215. Erickson, D. R., Kunselman, A. R., Bentley, C. M., Peters, K. M., Rovner, E. S., Demers, L. M. et al.: Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol, 177**:** 556, 2007.

216. Keay, S., Zhang, C. O., Hise, M. K., Hebel, J. R., Jacobs, S. C., Gordon, D. et al.: A diagnostic in vitro urine assay for interstitial cystitis. Urology, 52**:** 974, 1998.

217. Keay, S., Zhang, C. O., Marvel, R., and Chai, T.: Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor: sensitive and specific urine markers for interstitial cystitis. Urology, 57**:** 104, 2001.

218. Conrads, T. P., Tocci, G. M., Hood, B. L., Zhang, C. O., Guo, L., Koch, K. R. et al.: CKAP4/p63 is a receptor for the frizzled-8 protein-related antiproliferative factor from interstitial cystitis patients. J Biol Chem, 281**:** 37836, 2006.

219. Kim, J., Keay, S. K., Dimitrakov, J. D., and Freeman, M. R.: p53 mediates interstitial cystitis antiproliferative factor (APF)-induced growth inhibition of human urothelial cells. FEBS Lett, 581**:** 3795, 2007.

220. Zhang, C. O., Wang, J. Y., Koch, K. R., and Keay, S.: Regulation of tight junction proteins and bladder epithelial paracellular permeability by an antiproliferative factor from patients with interstitial cystitis. J Urol, 174**:** 2382, 2005.

221. Moskowitz, M. O., Byrne, D. S., Callahan, H. J., Parsons, C. L., Valderrama, E., and Moldwin, R. M.: Decreased expression of a glycoprotein component of bladder surface mucin (GP1) in interstitial cystitis. J Urol, 151: 343, 1994.

222. Byrne, D. S., Sedor, J. F., Estojak, J., Fitzpatrick, K. J., Chiura, A. N., and Mulholland, S. G.: The urinary glycoprotein GP51 as a clinical marker for interstitial cystitis. J Urol, 161: 1786, 1999.

223. Keay, S. K., Zhang, C. O., Shoenfelt, J., Erickson, D. R., Whitmore, K., Warren, J. W. et al.: Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. Urology, 57: 9, 2001.

224. Keay, S., Zhang, C. O., Kagen, D. I., Hise, M. K., Jacobs, S. C., Hebel, J. R. et al.: Concentrations of specific epithelial growth factors in the urine of interstitial cystitis patients and controls. J Urol, 158: 1983, 1997.

225. Fries, J., Hochberg, M., Medsger, T., and Hunder, G.: Criteria for rheumatic disease. Different types and different functions. Arthritis Rheum, 37: 454, 1994.

226. Peeker, R. and Fall, M.: Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. J Urol, 167: 2470, 2002.

227. Homma, Y.: Lower urinary tract symptomatology: Its definition and confusion. International Journal of Urology, 15: 35, 2008.

228. Chaiken, D. C., Blaivas, J. G., and Blaivas, S. T.: Behavioral therapy for the treatment of refractory interstitial cystitis. J Urol, 149: 1445, 1993.

229. Parsons, C. L. and Koprowski, P. F.: Interstitial cystitis: successful management by increasing urinary voiding intervals. Urology, 37: 207, 1991.

230. Weiss, J. M.: Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol, 166: 2226, 2001.

231. Lukban, J., Whitmore, K., Kellogg-Spadt, S., Bologna, R., Lesher, A., and Fletcher, E.: The effect of manual physical therapy in patients diagnosed with interstitial cystitis, high-tone pelvic floor dysfunction, and sacroiliac dysfunction. Urology, 57: 121, 2001.

232. Holzberg, A., Kellog-Spadt, S., Lukban, J., and Whitmore, K.: Evaluation of transvaginal theile massage as a therapeutic intervention for women with interstitial cystitis. Urology, 57: 120, 2001.

233. Mendelowitz, F. and Moldwin, R.: Complementary approaches in the management of interstitial cystitis. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 235-240, 1997.

234. Meadows, E.: Treatments for patients with pelvic pain. Urologic Nursing, 19: 33, 1999.

235. Markwell, S. J.: Physical therapy managment of pelvi/perineal and perianal syndromes. World J Urol, 19: 194, 2001.

236. Lukban, J. C. and Whitmore, K.: Pelvic floor muscle reeducation treatment of the overactive bladder and painful bladder syndrome. Clinical Obstetrics and Gynecology, 45: 273, 2002.

237. Rothrock, N. E., Lutgendorf, S. K., and Kreder, K. J.: Coping strategies in patients with interstitial cystitis: relationships with quality of life and depression. J Urol, 169: 233, 2003.

238. Webster, D. C. and Brennan, T.: Self-care effectiveness and health outcomes in women with interstitial cystitis: implications for mental health clinicians. Issues Ment Health Nurs, 19: 495, 1998.

239. McCormick, N. B.: Psychological aspects of interstitial cystitis. In: Interstitial Cystitis. Edited by Sant, G. R.: Philadelphia: Lippincott-Raven, pp 193-204, 1997.

240. Ratner, V. and Slade, D.: The Interstitial Cystitis Association: patients working for a cure. Semin Urol, 9: 72, 1991.

241. Rothrock, N. E., Lutgendorf, S. K., Kreder, K. J., Ratliff, T., and Zimmerman, B.: Stress and symptoms in patients with interstitial cystitis: a life stress model. Urology, 57: 422, 2001.

242. Whitmore, K. E.: Self-care regimens for patients with interstitial cystitis. Urol Clin North Am, 21: 121, 1994.

243. McCormick, N. B. and Vinson, R. K.: Interstitial cystitis: how women cope. Urol Nurs, 9: 11, 1989.

244. Webster, D. C. and Brennan, T.: Use and effectiveness of psychological self-care strategies for interstitial cystitis. Health Care Women Int, 16: 463, 1995.

245. Bade, J. J., Peeters, J. M., and Mensink, H. J.: Is the diet of patients with interstitial cystitis related to their disease? Eur Urol, 32: 179, 1997.

246. Chung, M. K.: Interstitial cystitis in persistent posthysterectomy chronic pelvic pain. JSLS, 8: 329, 2004.

247. Gillespie, L.: Metabolic appraisal of the effects of dietary modification on hypersensitive bladder symptoms. Br J Urol, 72: 293, 1993.

248. Nguan, C., Franciosi, L. G., Butterfield, N. N., Macleod, B. A., Jens, M., and Fenster, H. N.: A prospective, double-blind, randomized cross-over study evaluating changes in urinary pH for relieving the symptoms of interstitial cystitis. BJU Int, 95: 91, 2005.

249. Nickel, J. C.: Interstitial cystitis. Etiology, diagnosis, and treatment. Can Fam Physician, 46: 2430, 2000.

250. Panzera, A. K.: Interstitial cystitis/painful bladder syndrome. Urol Nurs, 27: 13, 2007.

251. Rovner, E., Propert, K. J., Brensinger, C., Wein, A. J., Foy, M., Kirkemo, A. et al.: Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. Urology, 56: 940, 2000.

252. Webster, D. C. and Brennan, T.: Use and effectiveness of physical self-care strategies for interstitial cystitis. Nurse Pract, 19: 55, 1994.

253. Webster, D. C. and Brennan, T.: Self-care strategies used for acute attack of interstitial cystitis. Urol Nurs, 15: 86, 1995.

254. Erickson, D. R. and Davies, M. F.: Interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct, 9: 174, 1998.

255. Moldwin, R. M. and Sant, G. R.: Interstitial cystitis: a pathophysiology and treatment update. Clin Obstet Gynecol, 45: 259, 2002.

256. Nguan, C., Franciosi, L. G., Butterfield, N. N., Macleod, B. A., Jens, M., and Fenster, H. N.: A prospective, double-blind, randomized cross-over study evaluating changes in urinary pH for relieving the symptoms of interstitial cystitis. BJU Int, 95: 91, 2005.

257. Rummans, T. A.: Nonopioid agents for treatment of acute and subacute pain. Mayo Clin Proc, 69: 481, 1994.

258. Backonja, M., Beydoun, A., Edwards, K. R., Schwartz, S. L., and et.al.: Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. JAMA, 280: 1831, 1998.

259. Rowbotham, M., Harden, N., Stacey, B., Bernstein, P., and Magnus-Miller, L.: Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA, 280: 1837, 1998.

260. Gilron, I., Bailey, J., Tu, D., Holden, R., Weaver, D., and Houlden, R.: Morphine, gabapentin, or their combination for neuropathic pain. NEJM, 352: 1324, 2005.

261. Sasaki, K., Smith, C. P., Chuang, Y. C., Lee, J. Y., Kim, J.

C., and Chancellor, M. B.: Oral gabapentin (neurontin) treatment of refractory genitourinary tract pain. Tech Urol, 7: 47, 2001.

262. Freynhagen, R., Strojek, K., Griesing, T., Whalen, E., and Balkenohl, M.: Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain, 115: 254, 2005.

263. Arnold, L. M., Russell, I. J., Diri, E. W., Duan, W. R., Young, J. P., Jr., Sharma, U. et al.: A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia. J Pain, 2008.

264. Portenoy, R. K., Dole, V., Joseph, H., Lowinson, J., and et.al.: Pain management and chemical dependency. JAMA, 278: 592, 1997.

265. Gourlay, G. K.: Long-term use of opiods in chronic pain patients with nonterminal disease states. Pain Rev, 1: 62, 1994.

266. Reid, M. C., Engles-Horton, L. L., Weber, M. B., Kerns, R. D., Rogers, E. L., and O'Connor, P. G.: Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med, 17: 173, 2002.

267. Portenoy, R. K. a. F. K. M.: Chronic use of opioid analgesics in nonmalignant pain: Report of 38 cases. Pain, 171: 1986.

268. Nickel, J. C.: Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th World Congress on Pain. Urology, 68: 697, 2006.

269. Richelson, E.: Tricyclic antidepressants and histamine H1 receptors. Mayo Clin Proc, 54: 669, 1979.

270. Hanno, P. M.: Amitriptyline in the treatment of interstitial cystitis. Urol Clin North Am, 21: 89, 1994.

271. Hanno, P. M. a. W. A. J.: Conservative therapy of interstitial cystitis. Semin Urol, 9: 143, 1991.

272. Kirkemo, A. K., Miles, B. J., and Peters, J. M.: Use of amitriptyline in the treatment of interstitial cystitis. Journal of Urology, 143: 279A, 1990.

273. Pranikoff, K. and Constantino, G.: The use of amitriptyline in patients with urinary frequency and pain. Urology, 51: 179, 1998.

274. van Ophoven, A., Pokupic, S., Heinecke, A., and Hertle, L.: A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol, 172: 533, 2004.

275. van Ophoven, A. and Hertle, L.: Long term results of amitriptyline treatment for interstitial cystitis. J Urol, 173: 86, 2005.

276. Wammack, R., Remzi, M., Seitz, C., Djavan, B., and Marberger, M.: Efficacy of oral doxepin and piroxicam treatment for interstitial cystitis. Eur Urol, 41: 596, 2002.

277. Renshaw, D. C.: Desipramine for interstitial cystitis. JAMA, 260: 341, 1988.

278. van, O. A. and Hertle, L.: The dual serotonin and noradrenaline reuptake inhibitor duloxetine for the treatment of interstitial cystitis: results of an observational study. J Urol, 177: 552, 2007.

279. Simmons, J. L. and Bunce, P. L.: On the use of an antihistamine in the treatment of interstitial cystitis. Am Surg, 24: 664, 1958.

280. Indent1440Lim0Lim1 Simmons, J. L.: Interstitial cystitis: An explanation for the beneficial effect of an antihistamine. Journal of Urology, 85: 149, 1961.

281. Minogiannis, P., El Mansoury, M., Betances, J. A., Sant, G. R., and Theoharides, T. C.: Hydroxyzine inhibits neurogenic bladder mast cell activation. Int J Immunopharmacol, 20: 553, 1998.

282. Theoharides, T. C.: Hydroxyzine for interstitial cystitis. J Allergy Clin Immunol, 91: 686, 1993.

283. Theoharides, T. C.: Hydroxyzine in the treatment of interstitial cystitis. Urol Clin North Am, 21: 113, 1994.

284. Theoharides, T. C. and Sant, G. R.: Hydroxyzine therapy for interstitial cystitis. Urology, 49: 108, 1997.

285. Sant, G. R., Propert, K. J., Hanno, P. M., Burks, D., Culkin, D., Diokno, A. C. et al.: A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol, 170: 810, 2003.

286. Seshadri, P., Emerson, L., and Morales, A.: Cimetidine in the treatment of interstitial cystitis. Urology, 44: 614, 1994.

287. Lewi, H. J.: Cimetidine in the treatment of interstitial cystitis. British Journal of Urology, 77: 28, 1996.

288. Lewi, H.: Medical therapy in interstitial cystitis: the essex experience. Urology, 57: 120, 2001.

289. Thilagarajah, R., Witherow, R. O., and Walker, M. M.: Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int, 87: 207, 2001.

290. Forsell, T., Ruutu, M., Isoniemi, H., Ahonen, J., and Alfthan, O.: Cyclosporine in severe interstitial cystitis. J Urol, 155: 1591, 1996.

291. Sairanen, J., Forsell, T., and Ruutu, M.: Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol, 171: 2138, 2004.

292. Sairanen, J., Tammela, T. L., Leppilahti, M., Multanen, M., Paananen, I., Lehtoranta, K. et al.: Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol, 174: 2235, 2005.

293. Sairanen, J., Hotakainen, K., Tammela, T. L., Stenman, U. H., and Ruutu, M.: Urinary epidermal growth factor and interleukin-6 levels in patients with painful bladder syndrome/interstitial cystitis treated with cyclosporine or pentosan polysulfate sodium. Urology, 71: 630, 2008.

294. Ueda, T., Tamaki, M., Ogawa, O., Yamauchi, T., and Yoshimura, N.: Improvement of interstitial cystitis symptoms and problems that developed during treatment with oral IPD-1151T. J Urol, 164: 1917, 2000.

295. Oravisto, K. J. and Alfthan, O. S.: Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. Eur Urol, 2: 82, 1976.

296. Parsons, C. L.: Bladder surface glycosaminoglycan: efficient mechanism of environmental adaptation. Urology, 27: 9, 1986.

297. Chiang, G., Patra, P., Letourneau, R., Jeudy, S., Boucher, W., Green, M. et al.: Pentosanpolysulfate inhibits mast cell histamine secretion and intracellular calcium ion levels: an alternative explanation of its beneficial effect in interstitial cystitis. J Urol, 164: 2119, 2000.

298. Sadhukhan, P. C., Tchetgen, M. B., Rackley, R. R., Vasavada, S. P., Liou, L., and Bandyopadhyay, S. K.: Sodium pentosan polysulfate reduces urothelial responses to inflammatory stimuli via an indirect mechanism. J Urol, 168: 289, 2002.

299. Parsons, C. L., Schmidt, J. D., and Pollen, J. J.: Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. J Urol, 130: 51, 1983.

300. Parsons, C. L. and Mulholland, S. G.: Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol, 138: 513, 1987.

301. Holm-Bentzen, M., Jacobsen, F., Nerstrom, B., Lose, G., Kristensen, J. K., Pedersen, R. H. et al.: A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol, 138: 503, 1987.

302. Mulholland, S. G., Hanno, P., Parsons, C. L., Sant, G. R., and Staskin, D. R.: Pentosan polysulfate sodium for therapy

of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology, 35: 552, 1990.

303. Parsons, C. L., Benson, G., Childs, S. J., Hanno, P., Sant, G. R., and Webster, G.: A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol, 150: 845, 1993.
304. Hanno, P. M.: Analysis of long-term Elmiron therapy for interstitial cystitis. Urology, 49: 93, 1997.
305. Foster, H. E. S. S. W. M.: Nitric oxide and interstitial cystitis. Advances in Urology, 10: 1, 1997.
306. Smith, S. D., Wheeler, M. a., Foster, H. E., Jr., and Weiss, R. M.: Improvement in interstitial cystitis symptom scores during treatment with oral L-arginine. J Urol, 158: 703, 1997.
307. Ehren, I., Lundberg, J. O., Adolfsson, J., and Wiklund, N. P.: Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. Urology, 52: 1026, 1998.
308. Korting, G. E., Smith, S. D., Wheeler, M. a., Weiss, R. M., and Foster, H. E., Jr.: A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol, 161: 558, 1999.
309. Cartledge, J. J., Davies, A. M., and Eardley, I.: A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. BJU Int, 85: 421, 2000.
310. Katske, F., Shoskes, D. A., Sender, M., Poliakin, R., Gagliano, K., and Rajfer, J.: Treatment of interstitial cystitis with a quercetin supplement. Tech Urol, 7: 44, 2001.
311. Warren, J. W., Horne, L. M., Hebel, J. R., Marvel, R. P., Keay, S. K., and Chai, T. C.: Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol, 163: 1685, 2000.
312. Burkhard, F. C., Blick, N., Hochreiter, W. W., and Studer, U. E.: Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help? J Urol, 172: 232, 2004.
313. Maskell, R.: Broadening the concept of urinary tract infection. British Journal of Urology, 76: 2, 1995.
314. Moran, P. A., Dwyer, P. L., Carey, M. P., Maher, C. F., and Radford, N. J.: Oral methotrexate in the management of refractory interstitial cystitis. Aust N Z J Obstet Gynaecol, 39: 468, 1999.
315. Bouchelouche, K., Nordling, J., Hald, T., and Bouchelouche, P.: Treatment of interstitial cystitis with montelukast, a leukotriene D(4) receptor antagonist. Urology, 57: 118, 2001.
316. Fleischmann, J.: Calcium channel antagonists in the treatment of interstitial cystitis. Urol Clin North Am, 21: 107, 1994.
317. Kelly, J. D., Young, M. R., Johnston, S. R., and Keane, P. F.: Clinical response to an oral prostaglandin analogue in patients with interstitial cystitis. Eur Urol, 34: 53, 1998.
318. Hanno, P. M., Buehler, J., and Wein, A. J.: Use of amitriptyline in the treatment of interstitial cystitis. J Urol, 141: 846, 1989.
319. Wilkins, E. G., Payne, S. R., Pead, P. J., Moss, S. T., and Maskell, R. M.: Interstitial cystitis and the urethral syndrome: a possible answer. Br J Urol, 64: 39, 1989.
320. Durier, J. L.: The application of anti-anaerobic antibiotics to the treatment of female bladder dysfunctions. Neurourol Urodyn, 11: 418, 1992.
321. Walsh, A.: Benzydamine: a new weapon in the treatment of interstitial cystitis. Trans Am Assoc Genitourin Surg, 68: 43, 1976.
322. Walsh, A.: Interstitial cystitis. Observations on diagnosis and on treatment with anti-inflammatory drugs, particularly benzydamine. Eur Urol, 3: 216, 1977.
323. Dasgupta, P., Sharma, S. D., Womack, C., Blackford, H. N., and Dennis, P.: Cimetidine in painful bladder syndrome: a histopathological study. BJU Int, 88: 183, 2001.
324. Burkhard, F. C., Blick, N., Hochreiter, W. W., and Studer, U. E.: Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help? J Urol, 172: 232, 2004.
325. van, O. A. and Hertle, L.: The dual serotonin and noradrenaline reuptake inhibitor duloxetine for the treatment of interstitial cystitis: results of an observational study. J Urol, 177: 552, 2007.
326. Stone, N. N.: Nalmefene in the treatment of interstitial cystitis. Urol Clin North Am, 21: 101, 1994.
327. Fleischmann, J. D., Huntley, H. N., Shingleton, W. B., and Wentworth, D. B.: Clinical and immunological response to nifedipine for the treatment of interstitial cystitis. J Urol, 146: 1235, 1991.
328. Nagaoka, M., Tamaoki, J., Gotoh, S., Nakazawa, H., and Nagai, A.: [A case of Sjogren syndrome accompanied by interstitial cystitis and interstitial pneumonia improved by suplatast tosilate and prednisolone]. Arerugi, 52: 450, 2003.
329. VAN DUZEN, R. E. and MUSTAIN, R.: Alphatocopherol in treatment of interstitial cystitis: preliminary report. J Urol, 65: 1033, 1951.
330. DeJuana, C. P. and Everett, J. C., Jr.: Interstitial cystitis: experience and review of recent literature. Urology, 10: 325, 1977.
331. Ingelman-Sundberg, A.: Urge incontinence in women. Acta Obstet Gynecol Scand, 54: 153, 1975.
332. Kerr, W. S., Jr.: Interstitial cystitis: treatment by transurethral resection. J Urol, 105: 664, 1971.
333. Pool, T. L. and Rives, H. F.: Interstitial cystitis: Treatment with silver nitrate. Journal of Urology, 51: 520, 1944.
334. MERTZ, J. H., Nourse, M. H., and WISHARD, W. N., Jr.: Use of clorpactin WCS 90 for relief of symptoms due to interstitial cystitis. Trans Am Assoc Genitourin Surg, 48: 86, 1956.
335. Messing, E. M. and Freiha, F. S.: Complication of Clorpactin WCS90 therapy for interstitial cystitis. Urology, 13: 389, 1979.
336. O'Connor, V. J.: Clorpactin WCS-90 in the treatment of interstitial cystitis. Q Bull Northwest Univ Med Sch, 29: 392, 1955.
337. Sokol, J. K.: Treatment of interstitial cystitis with clorpactin. Postgrad Semin Am Urol Assoc North Cent, 36: 104, 1957.
338. Wishard, WN., Jr., Nourse, M. H., and Mertz, JH.: Use of clorpactin WCS 90 for relief of symptoms due to interstitial cystitis. J Urol, 77: 420, 1957.
339. Peeker, R., Haghsheno, M. A., Holmang, S., and Fall, M.: Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. J Urol, 164: 1912, 2000.
340. Perez-Marrero, R., Emerson, L. E., and Feltis, J. T.: A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol, 140: 36, 1988.
341. Fowler, J. E., Jr.: Prospective study of intravesical dimethyl sulfoxide in treatment of suspected early interstitial cystitis. Urology, 18: 21, 1981.
342. Ghoniem, G. M., McBride, D., Sood, O. P., and Lewis, V.: Clinical experience with multiagent intravesical therapy in interstitial cystitis patients unresponsive to single-agent therapy. World J Urol, 11: 178, 1993.
343. Nishimura, M., Takano, Y., and Toshitani, S.: Systemic contact dermatitis medicamentosa occurring after intravesical dimethyl sulfoxide treatment for interstitial cystitis. Arch Dermatol, 124: 182, 1988.

344. Okamura, K., Mizunaga, M., Arima, S., Tokunaka, S., Inada, F., Takamura, T. et al.: [The use of dimethyl sulfoxide in the treatment of intractable urinary frequency]. Hinyokika Kiyo, 31**:** 627, 1985.

345. Ruiz, J. L., Alonso, M., Moreno, B., Server, G., Osca, J. M., and Jimenez, J. F.: [Dimethyl sulfoxide in the treatment of interstitial cystitis]. Actas Urol Esp, 15**:** 357, 1991.

346. Shirley, S. W., Stewart, B. H., and Mirelman, S.: Dimethyl sulfoxide in treatment of inflammatory genitourinary disorders. Urology, 11**:** 215, 1978.

347. Sotolongo, J. R., Jr., Swerdlow, F., Schiff, H. I., and Schapira, H. E.: Successful treatment of lupus erythematosus cystitis with DMSO. Urology, 23**:** 125, 1984.

348. Rossberger, J., Fall, M., and Peeker, R.: Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. Scand J Urol Nephrol, 39**:** 73, 2005.

349. Sant, G. R.: Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of interstitial cystitis. Urology, 29**:** 17, 1987.

350. Rubin, L. and Mattis, P.: Dimethyl sulfoxide: lens changes in dogs during oral administration. Science, 153**:** 83, 1966.

351. Wood, D. and Wirth, N.: Changes in rabbit lenses following DMSO therapy. Ophthalmologica, 158S**:** 488, 1969.

352. Melchior, D., Packer, C. S., Johnson, T. C., and Kaefer, M.: Dimethyl sulfoxide: does it change the functional properties of the bladder wall? J Urol, 170**:** 253, 2003.

353. Kuo, H. C.: Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. J Formos Med Assoc, 100**:** 309, 2001.

354. Parsons, C. L., Housley, T., Schmidt, J. D., and Lebow, D.: Treatment of interstitial cystitis with intravesical heparin. Br J Urol, 73**:** 504, 1994.

355. Perez-Marrero, R., Emerson, L. E., Maharajh, D. O., and et.al.: Prolongation of response to DMSO by heparin maintenance. Urology, 41 (suppl)**:** 64, 1993.

356. Parsons, C. L.: Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology, 65**:** 45, 2005.

357. Iavazzo, C., Athanasiou, S., Pitsouni, E., and Falagas, M. E.: Hyaluronic Acid: An Effective Alternative Treatment of Interstitial Cystitis, Recurrent Urinary Tract Infections, and Hemorrhagic Cystitis? Eur Urol, 2007.

358. Kallestrup, E. B., Jorgensen, S. S., Nordling, J., and Hald, T.: Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. Scand J Urol Nephrol, 39**:** 143, 2005.

359. Leppilahti, M., Hellstrom, P., and Tammela, T. L.: Effect of diagnostic hydrodistension and four intravesical hyaluronic acid instillations on bladder ICAM-1 intensity and association of ICAM-1 intensity with clinical response in patients with interstitial cystitis. Urology, 60**:** 46, 2002.

360. Morales, A., Emerson, L., and Nickel, J. C. e. a.: Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol, 156**:** 45, 1996.

361. Morales, A., Emerson, L., and Nickel, J. C.: Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology, 49**:** 111, 1997.

362. Porru, D., Campus, G., Tudino, D., Valdes, E., Vespa, A., Scarpa, R. M. et al.: Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. Urol Int, 59**:** 26, 1997.

363. Steinhoff, G., Ittah, B., and Rowan, S.: The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol, 9**:** 1454, 2002.

364. Porru, D., Cervigni, M., Nasta, L., Natale, F., Lo, V. R., Tinelli, C. et al.: Results of endovesical hyaluronic acid/chondroitin sulfate in the treatment of Interstitial Cystitis/Painful Bladder Syndrome. Rev Recent Clin Trials, 3**:** 126, 2008.

365. Bade, J. J., Laseur, M., Nieuwenburg, A., van der Weele, L. T., and Mensink, H. J.: A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol, 79**:** 168, 1997.

366. Davis, E. L., El, K., Sr., Talbott, E. O., Davis, J., and Regan, L. J.: Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. J Urol, 179**:** 177, 2008.

367. Apostolidis, A., Gonzales, G. E., and Fowler, C. J.: Effect of intravesical Resiniferatoxin (RTX) on lower urinary tract symptoms, urodynamic parameters, and quality of life of patients with urodynamic increased bladder sensation. Eur Urol, 50**:** 1299, 2006.

368. Chen, T. Y., Corcos, J., Camel, M., Ponsot, Y., and Tu, I. M.: Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). Int Urogynecol J Pelvic Floor Dysfunct, 16**:** 293, 2005.

369. Lazzeri, M., Spinelli, M., Beneforti, P., Malaguti, S., Giardiello, G., and Turini, D.: Intravesical infusion of resiniferatoxin by a temporary in situ drug delivery system to treat interstitial cystitis: a pilot study. Eur Urol, 45**:** 98, 2004.

370. Peng, C. H. and Kuo, H. C.: Multiple intravesical instillations of low-dose resiniferatoxin in the treatment of refractory interstitial cystitis. Urol Int, 78**:** 78, 2007.

371. Fagerli, J., Fraser, M. O., deGroat, W. C., Chancellor, M. B., Flood, H. D., Smith, D. et al.: Intravesical capsaicin for the treatment of interstitial cystitis: a pilot study. Can J Urol, 6**:** 737, 1999.

372. Payne, C. K., Mosbaugh, P. G., Forrest, J. B., Evans, R. J., Whitmore, K. E., Antoci, J. P. et al.: Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol, 173**:** 1590, 2005.

373. Zeidman, E. J., Helfrick, B., Pollard, C., and Thompson, I. M.: Bacillus Calmette-Guerin immunotherapy for refractory interstitial cystitis. Urology, 43**:** 121, 1994.

374. Peters, K., Diokno, A., Steinert, B., Yuhico, M., Mitchell, B., Krohta, S. et al.: The efficacy of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol, 157**:** 2090, 1997.

375. Peters, K. M., Diokno, A. C., Steinert, B. W., and Gonzalez, J. A.: The efficacy of intravesical bacillus Calmette-Guerin in the treatment of interstitial cystitis: long-term followup. J Urol, 159**:** 1483, 1998.

376. Mayer, R., Propert, K. J., Peters, K. M., Payne, C. K., Zhang, Y., Burks, D. et al.: A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol, 173**:** 1186, 2005.

377. Barbalias, G. A., Liatsikos, E. N., Athanasopoulos, A., and Nikiforidis, G.: Interstitial cystitis: bladder training with intravesical oxybutynin. J Urol, 163**:** 1818, 2000.

378. Gurpinar, T., Wong, H. Y., and Griffith, D. P.: Electromotive administration of intravesical lidocaine in patients with interstitial cystitis. J Endourol, 10**:** 443, 1996.

379. Riedl, C. R., Knoll, M., Plas, E., and Pfluger, H.: Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. J Endourol, 12**:** 269, 1998.

380. Riedl, C. R., Knoll, M., Plas, E., Stephen, R. L., and Pfluger, H.: Intravesical electromotive drug administration for the treatment of non-infectious chronic cystitis. Int Urogynecol J Pelvic Floor Dysfunct, 8**:** 134, 1997.

381. Rosamilia, A., Dwyer, P. L., and Gibson, J.: Electromotive drug administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct, 8: 142, 1997.

382. Asklin, B. and Cassuto, J.: Intravesical lidocaine in severe interstitial cystitis. Case report. Scand J Urol Nephrol, 23: 311, 1989.

383. Giannakopoulos, X. and Champilomatos, P.: Chronic interstitial cystitis. Successful treatment with intravesical idocaine. Arch Ital Urol Nefrol Androl, 64: 337, 1992.

384. Henry, R., Patterson, L., Avery, N., Tanzola, R., Tod, D., Hunter, D. et al.: Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. J Urol, 165: 1900, 2001.

385. Welk, B. K. and Teichman, J. M.: Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. Urology, 71: 67, 2008.

386. Chuang, Y. C., Yoshimura, N., Huang, C. C., Chiang, P. H., and Chancellor, M. B.: Intravesical botulinum toxin a administration produces analgesia against acetic acid induced bladder pain responses in rats. J Urol, 172: 1529, 2004.

387. Smith, C. P., Radziszewski, P., Borkowski, A., Somogyi, G. T., Boone, T. B., and Chancellor, M. B.: Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology, 64: 871, 2004.

388. Giannantoni, A., Porena, M., Costantini, E., Zucchi, A., Mearini, L., and Mearini, E.: Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year followup. J Urol, 179: 1031, 2008.

389. Tanagho, E. A., Schmidt, R. A., and Orvis, B. R.: Neural stimulation for control of voiding dysfunction: a preliminary report in 22 patients with serious neuropathic voiding disorders. J Urol, 142: 340, 1989.

390. Zermann, D. H., Weirich, T., Wunderlich, H., Reichelt, O., and Schubert, J.: Sacral nerve stimulation for pain relief in interstitial cystitis. Urol Int, 65: 120, 2000.

391. Maher, C. F., Carey, M. P., Dwyer, P. L., and Schluter, P. L.: Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol, 165: 884, 2001.

392. Comiter, C. V.: Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. J Urol, 169: 1369, 2003.

393. Whitmore, K. E., Payne, C. K., Diokno, A. C., and Lukban, J. C.: Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J Pelvic Floor Dysfunct, 14: 305, 2003.

394. Peters, K. M. and Konstandt, D.: Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. BJU Int, 93: 777, 2004.

395. Elhilali, M. M., Khaled, S. M., Kashiwabara, T., Elzayat, E., and Corcos, J.: Sacral neuromodulation: long-term experience of one center. Urology, 65: 1114, 2005.

396. Zabihi, N., Mourtzinos, A., Maher, M. G., Raz, S., and Rodriguez, L. V.: Short-term results of bilateral S2-S4 sacral neuromodulation for the treatment of refractory interstitial cystitis, painful baldder syndrome, and chronic pelvic pain. Int Urogynecol J Pelvic Floor Dysfunct, 19: 553, 2008.

397. Melzack, R.: The McGill pain questionnaire: major properties and scoring methods. Pain, 1: 277, 1975.

398. Melzack, R.: The short-form McGill pain questionnaire. Pain, 30: 191, 1987.

399. Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T. et al.: Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain, 9: 105, 2008.

400. Milsom, I. and Andersch, B.: Effect of ibuprofen, naproxen sodium and paracetamol on intrauterine pressure and menstrual pain in dysmenorrhoea. Br J Obstet Gynaecol, 91: 1129, 1984.

401. Zhang, W. and Li, P.: Efficacy of minor analgesics in primary dysmenorrhoea: a systemic review. Br J Obstet Gynaecol, 105: 780, 1998.

402. Gilroy, D., Tomlinson, A., and Willoughby, D.: Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation. Eur J Clin Pharmacol, 355: 211, 1998.

403. Gilroy, D., Colville-Nash, P., Willis, D., Chivers, J., Paul-Clark, M., and Willoughby, D.: Inducible cyclooxygenase may have anti-inflammatory properties. Nat Med, 5: 698, 1999.

404. Colville-Nash, P. and Gilroy, D.: Cox-2 and the cyclopentenone prostaglandins - a new chapter in the book of inflammation? Prostaglandins Other Lipid Mediat, 62: 33, 2000.

405. Futaki, N., Takahashi, S., Kitagawa, K., Yamakawa, Y., Tanaka, M., and Higuchi, S.: Selective inhibition of cyclooxygenase-2 by NS-398 in endotoxin shock rats in vivo. Inflamm res, 46: 496, 1997.

406. Jones, S. and Power, I.: Postoperative NSAIDs and Cox-2 inhibitors: cardiovascular risks and benefits. Br J Anaesth, 95: 281, 2005.

407. Furniss, L.: Nonsteroidal anti-inflammatory agents in the treatment of primary dysmenorrhea. Clin Pharmacol Ther, 1: 327, 1982.

408. Fall M, Baranowski A, Fowler CJ, Lepinard JG, Malone-Lee JG, Messelink EJ et al.: EAU guidelines on chronic pelvic pain. Eur Urol, 46: 681, 2004.

409. Christie, M., Vaughan, C., and Ingram, S.: NSAIDs and 5-lipoxygenase inhibitors act synergistically in brain via arachidonic acid metabolism. Inflamm res, 48: 1, 1999.

410. McQuay H: Opioids in pain management. Lancet, 353: 2229, 1999.

411. Hewitt, D.: The use of NMDA-receptor antagonists in the treatment of chronic pain. Clin J Pain, 16: S73, 2000.

412. Radbruch, L., Grond, S., and Lehmann, K.: A risk-benefit assessment of tramadol in the management of pain. Drug Safety, 15: 8, 1996.

413. Sagata, K., Minami, K., Yanagihara, N., Shiraishi, M., Toyohira, Y., and Ueno, S.: Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. Anesth Analg, 94: 901, 2002.

414. Desmeules, J., Piguet, V., Collart, L., and Dayer, P.: Contribution of monoaminergic modulation to the analgesic effect of tramadol. Br J Clin Pharmacol, 41: 7, 1996.

415. McQuay, H.: A systematic review of antidepressants in neuropathic pain. Pain, 68: 217, 1996.

416. van Ophoven, A., Pokupic, S., Heinecke, A., and Hertle, L.: A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol, 172: 533, 2004.

417. van Ophoven, A. and Hertle, L.: Long-term results of amitriptyline treatment for interstitial cystitis. J Urol, 174: 1837, 2005.

418. Engel, C., Walker, E., Engel, A., Bullis, J., and Armstrong, A.: A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. J Psychosom Res, 44: 203, 1998.

419. Dworkin, R. H., OConnor, A., Backonja, M., Farrar, J. T., Finnerup, N., and Jensen, T.: Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain, 132: 237, 2007.

420. Wiffen, P., McQuay, H., Edwards, J., and Moore, R.: Gabapentin for acute and chronic pain. Cochrane Database Syst Rev, 3: 2005.

421. Hansen, H. C.: Interstitial cystitis and the potential role of gabapentin. South Med J, 93: 238, 2000.

422. Sasaki, K., Smith, C., Chuang, Y., Lee, J., Kim, J., and Chancellor, M.: Oral gabapentin (neurontin) treatment of refractory genitorurinary tract pain. Tech Urol, 7: 47, 2001.

423. Price, D., Mayer, D., Mao, J., and Caruso, F.: NMDA-receptor antagonists and opioid receptor interactions as related to analgesia and tolerance. J Pain Symptom Management, 19: S7, 2000.

424. Mikkelsen, S., Ilkjaer, S., Brennum, J., Borgbjerg, F., and Dahl, J.: The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. Anaesthesiology, 90: 1539, 1999.

425. Guirimand, F., Dupont, X., Brasseur, L., Chauvin, M., and Bouhassira, D.: The effects of ketamine on the temporal summation (wind-up) of the R(III) nociceptive flexion reflex and pain in humans. Anesth Analg, 90: 408, 2000.

426. Laurido, C., Pelissier, T., Perez, H., Flores, F., and Hernandez, A.: Effect of ketamine on spinal cord nociceptive transmission in normal and monoarthritic rats. Neuroreport, 12: 1551, 2001.

427. Backonja, M., Arndt, G., Gombar, K., Check, B., and Zimmermann, M.: Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. Pain, 56: 51, 1994.

428. Eide, P., Jorum, E., Stubhaug, A., Bremnes, J., and Breivik, H.: Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain, 58: 347, 1994.

429. Eide, P., Stubhaug, A., and Stenehjem, A.: Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. Neurosurgery, 37: 1080, 1995.

430. Graven-Nielsen, T., Aspegren, K., Henriksson, K., Bengtsson, M., Sorensen, J., and Johnson, A.: Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain, 85: 483, 2000.

431. Sorensen, J., Bengtsson, A., Backman, E., Henriksson, K., and Bengtsson, M.: Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. Scand J Rheumatol, 24: 360, 1995.

432. Dickenson, A.: Neurophysiology of opioid poorly responsive pain. Cancer Surv, 21: 5, 1994.

433. Bumpus, H. C.: Interstitial cystitis: its treatment by overdistention of the bladder. Med Cl N A, 13: 1495, 1930.

434. FRANKSSON, C.: Interstitial cystitis: a clinical study of fifty-nine cases. Acta Chir Scand, 113: 51, 1957.

435. Helmstein, K.: Treatment of bladder carcinoma by a hydrostatic pressure technique. Report on 43 cases. British Journal of Urology, 44: 434, 1972.

436. Dunn, M., Ramsden, P. D., Roberts, J. B., Smith, J. C., and Smith, P. J.: Interstitial cystitis, treated by prolonged bladder distension. Br J Urol, 49: 641, 1977.

437. Badenoch, A. W.: Chronic interstitial cystitis. Br J Urol, 43: 718, 1971.

438. McCahy, P. J. and Styles, R. A.: Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol, 28: 325, 1995.

439. Greenberg, E., Barnes, R., Stewart, S., and Furnish, T.: Transurethral resection of Hunner's ulcer. J Urol, 111: 764, 1974.

440. Fall, M.: Conservative management of chronic interstitial cystitis: transcutaneous electrical nerve stimulation and transurethral resection. J Urol, 133: 774, 1985.

441. Peeker, R., Aldenborg, F., and Fall, M.: Complete transurethral resection of ulcers in classic interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct, 11: 290, 2000.

442. Shanberg, A. M. and Malloy, T.: Treatment of interstitial cystitis with neodymium:YAG laser. Urology, 29: 31, 1987.

443. Malloy, T. R. and Shanberg, A. M.: Laser therapy for interstitial cystitis. Urol Clin North Am, 21: 141, 1994.

444. Rofeim, O., Hom, D., Freid, R. M., and Moldwin, R. M.: Use of the neodymium: YAG laser for interstitial cystitis: a prospective study. J Urol, 166: 134, 2001.

445. Worth, P. H. and Turner-Warwick, R.: The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. Br J Urol, 45: 65, 1973.

446. Worth, P. H.: The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. A review after 7 years. Br J Urol, 52: 232, 1980.

447. Albers, D. D. and Geyer, J. R.: Long-term results of cystolysis (supratrigonal denervation) of the bladder for intractable interstitial cystitis. J Urol, 139: 1205, 1988.

448. Pieri, G.: Enervation ou ramisection? Lookup, 34: 1141, 1926.

449. Douglass, H.: Excision of the superior hypogastric plexus in the treatment of intractable interstitial cystitis. Am J Surg, 25: 249, 1934.

450. Nesbit, R. M.: Anterolateral chordotomy for refractory interstitial cystitis with intractable pain. J Urology, 57: 741, 1947.

451. Moulder, M. K. and Meirowsky, A. M.: The management of Hunner's ulcer by differential sacral neurotomy: preliminary report. J Urology, 75: 261, 1956.

452. MILNER, W. A. and GARLICK, W. B.: Selective sacral neurectomy in interstitial cystitis. J Urol, 78: 600, 1957.

453. Mason TH, Haines GL, and Laversee BW: Selective sacral neurotomy for Hunner's ulcer. J Neurosurg, 17: 22, 1960.

454. BOHM, E. and FRANKSSON, C.: Interstitial cystitis and sacral rhizotomy. Acta Chir Scand, 113: 63, 1957.

455. Goodwin WE, Turner RD, and Winter CC: Results of ileocystoplasty. J Urol, 80: 461, 1958.

456. von Garrelts, B.: Interstitial cystitis: thirteen patients treated operatively with intestinal bladder substitutes. Acta Chir Scand, 132: 436, 1966.

457. Webster, G. D. and Maggio, M. I.: The management of chronic interstitial cystitis by substitution cystoplasty. J Urol, 141: 287, 1989.

458. Badenoch, A. W.: Chronic interstitial cystitis. Br J Urol, 718: 43, 1971.

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

460. Turner-Warwick R and Ashken HM: The functional results of partial, subtotal, and total cystoplasty with special reference to ureterocystoplasty, selective sphincterotomy, and cystocystoplasty. Br J Urol, 39: 3, 1967.

461. Kontturi, M. J., Hellstrom, P. A., Tammela, T. L., and Lukkarinen, O. A.: Colocystoplasty for the treatment of severe interstitial cystitis. Urol Int, 46: 50, 1991.

462. Hanley H: Ileocystoplasty. A clinical review. J Urol, 82: 317, 1959.

463. Bruce, P. T., Buckham, G. J., Carden, A. B., and Salvaris, M.: The surgical treatment of chronic interstitial cystitis. Med J Aust, 1: 581, 1977.

464. Hinman FJ: Selection of intestinal segments for bladder substitution: physical and physiological characteristics. J Urol, 139: 519, 1988.

465. Awad, S. A., Al Zahrani, H. M., Gajewski, J. B., and Bourque-Kehoe, A. A.: Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. Br J Urol, 81: 569, 1998.

466. Guillonneau, B., Toussaint, B., Bouchot, O., and Buzelin, J. M.: [Treatment of interstitial cystitis with sub-trigonal cystectomy and enterocystoplasty]. Prog Urol, 3: 27, 1993.

467. Christmas, T. J., Holmes, S. A., and Hendry, W. F.: Bladder replacement by ileocystoplasty: the final treatment for interstitial cystitis. Br J Urol, 78: 69, 1996.

468. Shirley, S. W. and Mirelman, S.: Experiences with colocystoplasties, cecocystoplasties and ileocystoplasties in urologic surgery: 40 patients. J Urol, 120: 165, 1978.

469. Koskela E and Kontturi M: Function of the intestinal substituted bladder. Scand J Urol Nephrol, 16: 129, 1982.

470. Hradec H: Bladder substitution: Indications and results in 114 operations. J Urol, 94: 406, 1965.

471. Whitmore, W. F. and Gittes, R. F.: Reconstruction of the urinary tract by cecal and ileocecal cystoplasty: review of a 15-year experience. J Urol, 129: 494, 1983.

472. Holm-Bentzen M, Klarskov P, Opsomer R, and Hald T: Cecocystoplasty: an evaluation of operative results. Urol Int, 41: 21, 1986.

473. Seddon, J. M., Best, L., and Bruce, A. W.: Intestinocystoplasty in treatment of interstitial cystitis. Urology, 10: 431, 1977.

474. Singla A and Galloway N: Early experience with the use of gastric segment in lower urinary tract reconstruction in adult patient population. Urology, 50: 630, 1997.

475. Leong, C. H.: Use of stomach for bladder replacement and urinary diversion. Ann R Coll Surg Engl, 282, 1978.

476. Dounis, A. and Gow, J. G.: Bladder augmentation—a long-term review. Br J Urol, 51: 264, 1979.

477. Linn, J. F., Hohenfellner, M., Roth, S., Dahms, S. E., Stein, R., Hertle, L. et al.: Treatment of interstitial cystitis: comparison of subtrigonal and supratrigonal cystectomy combined with orthotopic bladder substitution. J Urol, 159: 774, 1998.

478. van, O. A., Oberpenning, F., and Hertle, L.: Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. J Urol, 167: 603, 2002.

479. Lotenfoe, R. R., Christie, J., Parsons, A., Burkett, P., Helal, M., and Lockhart, J. L.: Absence of neuropathic pelvic pain and favorable psychological profile in the surgical selection of patients with disabling interstitial cystitis. J Urol, 154: 2039, 1995.

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

481. Counseller, V. S.: Bilateral transplantation of the ureters of the female. Am J Obstet Gynecol, 33: 234, 1937.

482. Hohenfellner, M., Black, P., Linn, J. F., Dahms, S. E., and Thuroff, J. W.: Surgical treatment of interstitial cystitis in women. Int Urogynecol J Pelvic Floor Dysfunct, 11: 113, 2000.

483. Bejany, D. E. and Politano, V. A.: Ileocolic neobladder in the woman with interstitial cystitis and a small contracted bladder. J Urol, 153: 42, 1995.

484. Nurse, D. E., McCrae, P., Stephenson, T. P., and Mundy, A. R.: The problems of substitution cystoplasty. Br J Urol, 61: 423, 1988.

485. Hughes, O. D., Kynaston, H. G., Jenkins, B. J., Stephenson, T. P., and Vaughton, K. C.: Substitution cystoplasty for intractable interstitial cystitis. Br J Urol, 76: 172, 1995.

486. Nurse, D. E., Parry, J. R., and Mundy, A. R.: Problems in the surgical treatment of interstitial cystitis. Br J Urol, 68: 153, 1991.

487. Gershbaum, D. and Moldwin, R.: Practice trends for the management of interstitial cystitis. Urology, 57: 119, 2001.

488. Freiha, F. S., Faysal, M. H., and Stamey, T. A.: The surgical treatment of intractable interstitial cystitis. J Urol, 123: 632, 1980.

489. Tait L: On the cure of the chronic perforating ulcer of the bladder by the formation of an artificial vesico-vaginal fistula. Lancet, 54: 738, 1870.

490. Ahmed E, Bissada NK, Herchorn S, Aboul-Enein H, Ghoneim M, Bissada MA et al.: Urinary conduit formation using a retubularized bowel from continent urinary diversion or intestinal augmentations: ii. does it have a role in patients with interstitial cystitis? J Urol, 171: 1559, 2004.

491. Kisman, O. K., Nijeholt, A. A., and van Krieken, J. H.: Mast cell infiltration in intestine used for bladder augmentation in interstitial cystitis. J Urol, 146: 1113, 1991.

492. McGuire, E. J., Lytton, B., and Cornog, J. L., Jr.: Interstitial cystitis following colocystoplasty. Urology, 2: 28, 1973.

493. MacDermott, J. P., Charpied, G. L., Tesluk, H., and Stone, A. R.: Recurrent interstitial cystitis following cystoplasty: fact or fiction? J Urol, 144: 37, 1990.

494. Webster, G. D. and Galloway, N.: Surgical treatment of interstitial cystitis. Indications, techniques, and results. Urology, 29: 34, 1987.

495. Goin, J. E., Olaleye, D., Peters, K. M., Steinert, B., Habicht, K., and Wynant, G.: Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. J Urol, 159: 1085, 1998.

496. Keller, M. L., McCarthy, D. O., and Neider, R. S.: Measurement of symptoms of interstitial cystitis. A pilot study. Urol Clin North Am, 21: 67, 1994.

497. Lubeck, D. P., Whitmore, K., Sant, G. R., Alvarez-Horine, S., and Lai, C.: Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. Urology, 57: 62, 2001.

498. O'leary, M. P., Sant, G. R., Fowler, F. J., Jr., Whitmore, K. E., and Spolarich-Kroll, J.: The interstitial cystitis symptom index and problem index. Urology, 49: 58, 1997.

499. O'leary, M. P. and Sant, G.: The interstitial cystitis symptom and problem indices: rationale, development, and application. In: Interstitial Cystitis. Edited by Sant, G.: Philadelphia: Lippincott-Raven, chapt. 34, pp 271-276, 1997.

500. Ito, T., Tomoe, H., Ueda, T., Yoshimura, N., Sant, G., and Hanno, P.: Clinical symptoms scale for interstitial cystitis for diagnosis and for following the course of the disease. Int J Urol, 10 Suppl: S24, 2003.

501. Kushner, L. and Moldwin, R. M.: Efficiency of questionnaires used to screen for interstitial cystitis. J Urol, 176: 587, 2006.

502. Sirinian, E., Azevedo, K., and Payne, C. K.: Correlation between 2 interstitial cystitis symptom instruments. J Urol, 173: 835, 2005.

503. Clemons, J. L., Arya, L. A., and Myers, D. L.: Diagnosing interstitial cystitis in women with chronic pelvic pain. Obstet Gynecol, 100: 337, 2002.

504. Clemens, J. Q., Markossian, T. W., Meenan, R. T., O'Keeffe Rosetti, M. C., and Calhoun, E. A.: Overlap of voiding symptoms, storage symptoms and pain in men and women. J Urol, 178: 1354, 2007.

505. Porru, D., Tinelli, C., Gerardini, M., Giliberto, G. L., Stancati, S., and Rovereto, B.: Evaluation of urinary and general symptoms and correlation with other clinical parameters in interstitial cystitis patients. Neurourol Urodyn, 24: 69, 2005.

506. Diggs, C., Meyer, W. A., Langenberg, P., Greenberg, P., Horne, L., and Warren, J. W.: Assessing urgency in interstitial cystitis/painful bladder syndrome. Urology, 69**:** 210, 2007.

507. Propert, K. J., Mayer, R. D., Wang, Y., Sant, G. R., Hanno, P. M., Peters, K. M. et al.: Responsiveness of symptom scales for interstitial cystitis. Urology, 67**:** 55, 2006.

508. Sech, S. M., Montoya, J. D., Bernier, P. A., Barnboym, E., and et.al.: The so-called "placebo effect" in benign prostatic hyperplasia treatment trials represents partially a conditional regression to the mean induced by censoring. Urology, 51**:** 242, 1998.

509. Gillespie, L., Bray, R., Levin, N., and Delamarter, R.: Lumbar nerve root compression and interstitial cystitis—response to decompressive surgery. Br J Urol, 68**:** 361, 1991.

510. Gillespie, L.: Destruction of the vesicoureteric plexus for the treatment of hypersensitive bladder disorders. Br J Urol, 74**:** 40, 1994.

511. Turner, J. A., Deyo, R. A., Loeser, J. D., and et.al.: The importance of placebo effects in pain treatment and research. JAMA, 271**:** 1609, 1994.

512. Schulz, K. F., Chalmers, I., Hayes, R. J., and et.al.: Empirical evidence of bias; dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA, 273**:** 408, 1995.

513. Rothman, K. J. and Michels, K. B.: The continuing unethical use of placebo controls. N Engl J Med, 394, 1994.

514. Benson, H. and Epstein, M. D.: The placebo effect. JAMA, 232**:** 1225, 1976.

515. DuBeau, C., Khullar, V., and Versi, E.: "Unblinding" in randomized controlled drug trials for urinary incontinence: implications for assessing outcomes when adverse effects are evident. Neurourol Urodyn, 24**:** 2005.

516. Rees, J., Wade, T., Levy, D., Colford, J., and Hilton, J.: Changes in beliefs identify unblinding in randomized controlled trials: a method to meet CONSORT guidelines. Contemporary Clinical Trials, 26**:** 25, 2005.

517. Desbiens, N. A.: In randomized controlled trials, should subjects in both placebo and drug groups be expected to guess that they are taking drug 50% of the time? Med Hypotheses, 59**:** 227, 2002.

518. Polman, C. H., Reingold, S. C., Barkhof, F., Calabresi, P. A., Clanet, M., Cohen, J. A. et al.: Ethics of placebo-controlled clinical trials in multiple sclerosis: a reassessment. Neurology, 70**:** 1134, 2008.

519. Anderson, J. A.: The ethics and science of placebo-controlled trials: assay sensitivity and the Duhem-Quine thesis. J Med Philos, 31**:** 65, 2006.

520. Streiner, D. L.: Placebo-controlled trials: when are they needed? Schizophr Res, 35**:** 201, 1999.

521. Streiner, D. L.: Alternatives to placebo-controlled trials. Can J Neurol Sci, 34 Suppl 1**:** S37, 2007.

522. Miller, F. G., Emanuel, E. J., Rosenstein, D. L., and Straus, S. E.: Ethical issues concerning research in complementary and alternative medicine. JAMA, 291**:** 599, 2004.

523. Chancellor, M. B. and de Groat, W. C.: Intravesical capsaicin and resiniferatoxin therapy: spicing up the ways to treat the overactive bladder. Journal of Urology, 162**:** 3, 1999.

524. Morales, A., Emerson, L., Nickel, J. C., and Lundie, M.: Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol, 156**:** 45, 1996.

525. Propert, K. J., Payne, C., Kusek, J. W., and Nyberg, L. M.: Pitfalls in the design of clinical trials for interstitial cystitis. Urology, 60**:** 742, 2002.

526. Ward, M. M.: Interpreting measurements of physical function in clinical trials. Ann Rheum Dis, 66 Suppl 3**:** iii32, 2007.

527. Wein, A. J. and Broderick, G. A.: Interstitial cystitis. Current and future approaches to diagnosis and treatment. Urol Clin North Am, 21**:** 153, 1994.

528. McQuay H: Numbers need to care. Pain, 106**:** 213, 2003.

529. Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P. et al.: Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain, 113**:** 9, 2005.

530. Dimitrakov, J., Kroenke, K., Steers, W. D., Berde, C., Zurakowski, D., Freeman, M. R. et al.: Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med, 167**:** 1922, 2007.

531. Fall, M., Oberpenning, F., and Peeker, R.: Treatment of Bladder Pain Syndrome/Interstitial Cystitis 2008: Can We Make Evidence-Based Decisions? Eur Urol, 2008.

532. Karsenty, G., Aitaweel, W., Hajebrahimi, S., and Corcos, J.: Efficacy of interstitial cystitis treatments. EAU Update Series, 4**:** 47, 2006.

533. Hill, J. R., Isom-Batz, G., Panagopoulos, G., Zakariasen, K., and Kavaler, E.: Patient perceived outcomes of treatments used for interstitial cystitis. Urology, 71**:** 62, 2008.

534. Ingber, M. S., Peters, K. M., Killinger, K. A., Carrico, D. J., Ibrahim, I. A., and Diokno, A. C.: Dilemmas in diagnosing pelvic pain: multiple pelvic surgeries common in women with interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct, 19**:** 341, 2008.

535. Hanno, P. and Dmochowski, R. R.: **Status of interntional consensus on interstitial cystitis / bladder pain syndrome / painful bladder syndrome: 2008 snapshot** Neurourol Urodyn, 2008.

536. van de Merwe, J. P.: Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol, 4**:** 484, 2007.

537. Rothrock, N. E., Lutgendorf, S. K., Hoffman, A., and Kreder, K. J.: Depressive symptoms and quality of life in patients with interstitial cystitis. J Urol, 167**:** 1763, 2002.