Committee 21

Painful Bladder Syndrome (including interstitial cystitis)

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ABBREVIATIONS	
APF	antiproliferative factor
BCG	Bacille Calmette-Guerin
BDI	Beck Depression Inventory
BOO	bladder outlet obstruction
BPI	Brief Pain Inventory
BTX-A	Botulinum toxin type A
CIS	carcinoma in situ
DMMCR	detrusor to mucosa mast cell ratio
DMSO	dimethyl sulfoxide
EM	electron microscopy
EMDA	electromotive drug administration
FDA	Food and Drug Administration (USA)
GAG	glycosaminoglycan
GRA	Global Response Assessment
HADS	Hospital Anxiety and Depression Scale
HB-EGF	heparin-binding epidermal growth factor-like growth factor
HPF	high power field
IC	interstitial cystitis
ICA	Interstitial Cystitis Association
ICDB	Interstitial Cystitis Data Base
ICS	International Continence Society
Ig	immunoglobulin
IL	interleukin
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
mEQ	milliequivalents
MPI	Multidimensional Pain Inventory
MPQ	McGill Pain Questionnaire
NHS	Nurses Health Study
NIDDK	National Institute of Diabetes, Digestive, and Kidney Diseases
NIH	National Institutes of Health
NO	nitric oxide
NOS	nitric oxide synthase
NRS	numerical rating scales
NSAIDS	nonsteroidal anti-inflammatory drugs
OAB	overactive bladder
PBS	painful bladder syndrome
PBS/IC	painful bladder syndrome/interstitial cystitis
PDI	Pain Disability Index
PORIS	Patient's Overall Rating of Improvement of Symptoms
PPI	present pain intensity
PPS	pentosanpolysulfate
PST	potassium sensitivity test
PUF	Pelvic Pain and Urgency/Frequency Scale
QIAM	quantitative image analysis and morphometry
RCT	randomized controlled trial
RNA	ribosomal nucleic acid
RTX	resiniferatoxin
SF36	Short Form 36 of Medical Outcomes Study
SIP	Sickness Impact Profile
TB	tuberculosis
UK	United Kingdom
UW	University of Wisconsin
VAS	visual analogue scale

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I. DEFINITION

Interstitial Cystitis (IC) is a clinical diagnosis primarily based on symptoms of urgency/ frequency and pain in the bladder and or pelvis. The International Continence Society [1] (ICS) prefers 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 reserves the diagnosis IC to patients with "typical cystoscopic and histological features", without further specifying these. The condition will therefore in the remainder of this chapter be referred to as PBS/IC. This seems to be a usable way ahead until more specific criteria can be established. As the terminology is in flux, some of the older literature will be discussed using the original terminology in the interests of clarity. Logically IC should include some form of demonstrable inflammation in the bladder wall, while PBS should include pain in the region of the bladder. The diagnosis of PBS/IC is often based on exclusion of other diseases in the bladder, urethra, and other pelvic organs including the musculoskeletal system. As with other diseases without 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 PBS/IC are screened to exclude other relevant diagnoses 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 ulcer. 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 [2]. One view of the relationship of PBS/IC with OAB is graphically depicted in **figure 1** [3]. The 14% incidence of urodynamic detrusor overactivity in the PBS/IC [4] patients is probably close to what one might expect in the general population if studied urodynamically [5].

In the end, these investigations might prove to be normal, but because no other diagnosis is available, the patients are identified as having PBS/IC 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 not standardised making it difficult or impossible to compare studies.

The committee believes that the Oxford system for categorizing levels of evidence is 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 would be inappropriate.

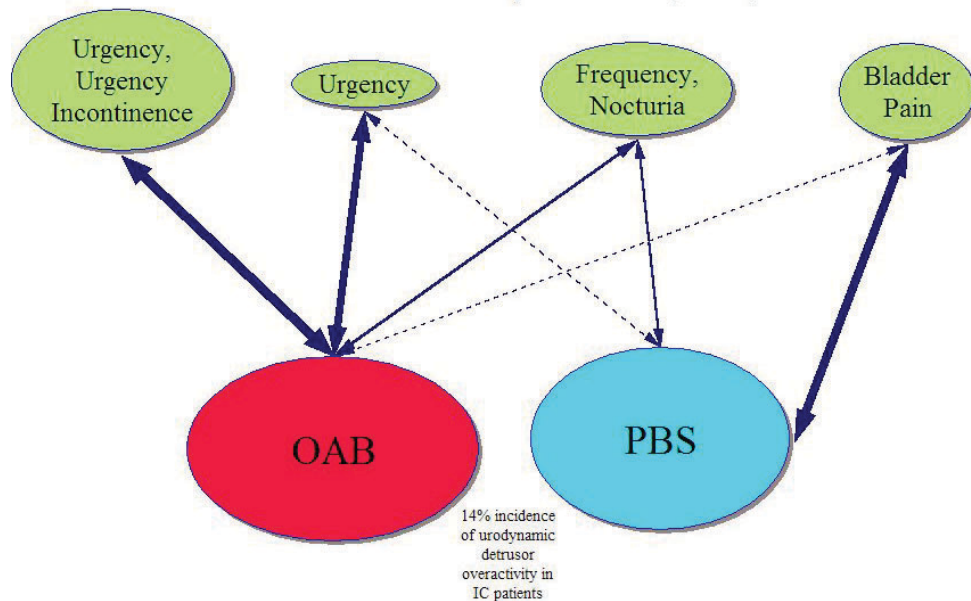## Overactive Bladder (OAB) and its relationship to Painful Bladder Syndrome (PBS)

Figure 1

II. AETIOLOGY OF INTERSTITIAL CYSTITIS

Despite extensive scientific effort, the precise aetiology of PBS/IC is still an enigma. Much data has been compiled resulting in an abundance of theories concerning aetiology and pathogenesis. Since aetiology is unknown, hypotheses abound with sparse evidence. A fact that hampers studies on PBS/IC is that, in clinical practice, there is no general consensus on how to define and classify this condition.

1. INFLAMMATION would seem an essential feature since the term cystitis refers to an inflammatory process. Still, inflammation is a non-disputable feature only in the classic or ulcerative form of interstitial cystitis. Histological examination of bladder lesions has revealed pan-cystitis and perineural inflammatory infiltrates of lymphocytes and plasma cells. Inflammation is scant in non-ulcer IC [6,7]. The cause of a documented inflammatory response is a central issue and has been subject to repeated investigations and much speculation.

2. MAST CELL ACTIVATION

Mast cells are thought to have a pivotal role in IC. They are multifunctional immune cells that contain highly potent inflammatory mediators such as hista-

mine, leucotrienes, serotonins and cytokines[8]. These cells are thus the repositories of many potent inflammatory factors, all of which are of importance in chronic inflammatory diseases. Many of the symptoms and findings in ulcerative IC, 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 [9] seems to be of importance when it comes to etiology and pathogenesis. There is a ten-fold increase in mast cell count in bladder tissue from patients with ulcerative IC as compared to controls. In non-ulcer IC, however, the mast cell count is normal or only slightly increase [8,10,11]. Activation of mast cells has been described as a characteristic and essential feature in IC [12].

Other mechanisms have also been put forward. Leukotriene E4, the end product of cysteinyl containing leukotrienes, and eosinophil protein X are markers of the activation of mast cells and eosinophils. Bouchelouche [13] compared the urinary excretion of leukotriene E4 and eosinophil protein X in patients with interstitial cystitis and in healthy controls and concluded that patients with interstitial cystitis and detrusor mastocytosis had increased urinary leukotriene E4 and eosinophil protein X. Urinary leukotriene E4 and eosinophil protein X may be useful

markers for assessing the grade of activation of mast cells and eosinophils in patients with interstitial cystitis and/or for confirming the diagnosis.

3. Urothelial Dysfunction/GAG-layer defects

A defect in the glycosaminoglycane- (GAG) –layer is a pathogenetic explanation to IC that has been proposed by Parsons and co-workers [14]. By such a defect the sub-mucosal nerve filaments might become accessible to noxious substances of urine, which may explain pain and urinary frequency. According to the NIDDK definition, during bladder distension all patients with IC present some feature of fragility of the bladder mucosa, expressed as mucosal fissures, more extensive rupture of the bladder mucosa or sub-mucosal bleeding. In ulcerative IC there is also granulation tissue indicating a reparative process following repeated disruption of the mucos [15]. In patients with ulcerative IC urothelial detachment and gross defects of the urothelial lining are characteristic findings, whereas in nonulcer IC there are multiple, superficial defects seen microscopically after bladder distension [15]. Widened tight junctions and increased permeability have been demonstrated by scanning electron microscopy and other techniques [16, 17].

4. Urothelial Dysfunction/inhibition of urothelial bladder cell proliferation

It has been suggested that 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 IC [18]. Recently, an exciting step forward to further elucidate the mechanism as to this feature of IC was presented. Explanted urothelial cells from IC patients differ from controls not only as to production of epithelial growth factors but also in other ways like the rate of proliferation and the production of an antiproliferative factor (APF). Keay and cooworkers [19] studied gene expression patterns in normal bladder urothelial cells treated with APF and mock APF as compared to patterns expressed by IC urothelial cells. The results indicate that the mechanism of APF inhibition of urothelial cells may involve both downregulation of genes that stimulate cell proliferation along with upregulation of genes that inhibit cell growth. Recent observations by the same group of researchers indicate that APF seems to be specifically elevated in the urine of patients with IC but not most others, and these findings open up new avenues for development of urine markers for IC.

5. Autoimmune mechanisms

There are numerous reports on autoantibodies in patients with IC [20-23]. However, the precise identity of these autoantibodies is not yet determined. Some of the common clinical and histopathological characteristics present in IC patient show certain similarities with other known autoimmune phenomena, and this is the background to the theory that PBS/IC may arise from autoimmune disturbances. Moreover, studies on autoantibodies in PBS/IC have shown that these mainly consist of antinuclear antibodies [22] and these findings are in turn similar to the autoantibody profiles in some systemic diseases like Sjogren syndrome, well known to be of autoimmune origin [24,27]. The role of autoimmunity in PBS/IC is controversial, and the disease is probably not caused by a direct autoimmune attack on the bladder. Rather, it is suggested that some of the autoimmune symptoms and pathologic features of PBS/IC arise indirectly as a result of tissue destruction and inflammation from as yet unknown causes. This is considered as an explanation for the fact that only a portion of PBS/IC patients has auto-antibodies. It has also been proposed that the titres or presence of auto-antibodies in these patients could be a reflection of disease severity [28].

Vascular immuno-pathology with immune deposits in the bladder wall was found by Mattila [29]. Further studies by the same group also suggest activation of complement [30]. By means of immuno-phenotyping and flow cytometry analyses of the bladder mucosa and peripheral blood, differences between ulcerative and non-ulcer PBS/IC patients have been demonstrated. In the former group intense T-cell infiltrates and B-cell nodules were seen, compared to far less T-cell infiltrate in non-ulcer PBS/IC [31]. Involvement of the immune system is certainly one feature of PBS/IC, but findings are conflicting and have so far not been helpful in explaining the aetiology of this condition. The lack of thorough description of patients in many studies, making subdivision to relevant PBS/IC subgroups and comparison between series impossible, has contributed to this confusion.

6. Infection

No micro-organism has ever been revealed as the

cause of PBS/IC. Although urine cultures may occasionally contain bacteria, most do not and antibiotic treatment is ineffective in this disease. There has been a large number of studies utilizing special techniques to detect microorganisms, some known as pathogens in the urinary tract and others not. It has been suggested that fastidious bacteria may play an etiologic role [32]. However, several authors including Lynes and coworkers did not find any evidence of recent or remote Gram negative or positive infections in patients with PBS/IC, nor did they find increased urinary IgA and IgG elevation, making infection by an untested organism unlikely [33]. Sophisticated culture techniques have been used, as well as incubation of specimens from PBS/IC patients in mammalian cells to search for viruses. Further attempts have applied polymerase chain reaction techniques to amplify bacterial 16S rRNA genes that would be present if there were bacteria in bladder tissue or urine in PBS/IC patients despite negative cultures. All efforts have been without success [34]. Still, it might be relevant to compare this disorder with chronic gastritis, one that is characterised by the combination of chronic pain, epithelial damage and often mucosal ulceration. In this condition, a microbial cause was rarely suspected until helicobacter pylori was revealed as a cause of many cases of chronic gastritis. There is no evidence for helicobacter in PBS/IC [35]. The possibility of a microbiological contribution to the aetiology of PBS/IC remains an open question.

7. NEUROBIOLOGY

Several authors have described autonomic nerve changes [36-38], but the findings are far from uniform. Increase of sympathetic innervation and activation of purinergic neurotransmission have been reported. The S-100 family of proteins appear in Schwann cells of the peripheral nervous system [39-40]. Decreased levels of S-100 protein in the non-ulcer group as compared to controls has been found [41], which is consistent with a decreased nerve content in patients with non-ulcer PBS/IC, a finding conflicting with the results of Hohenfellner [37]who used polyclonal antihuman protein gene product 9,5 antibody and found the overall nerve content increased in IC patients as compared to controls. However, their study did not include sub-typing of the disease into ulcerative and non-ulcer type. A distinctive ultra-structural appearance of specimens from patients with non-ulcer PBS/IC prompted Elbadawi and Light to propose neurogenic inflammation as

trigger to a cascade of events taking place in this disease [42]. 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.

Tyrosine hydroxylase is the rate-limiting enzyme to all catecholamine synthesis, dopamine as well as norepinephrine and epinephrine. Recently, a prominent increase of tyrosine hydroxylase immunoreactivity in bladder tissue of PBS/IC patients, as compared to controls, has been described [43]. This can presumably be interpreted as a sign of generally increased sympathetic outflow, which in turn lends further support to the notion of primary neurogenic aetiology, even though at this stage the patho-physiological steps remain speculative.

8. NITRIC OXIDE METABOLISM

Regulation of urinary nitric oxide synthase activity has been proposed to be of importance for immunologic responses in PBS/IC and oral administration of L-arginine, which is the substrate for nitric oxide production [44], has been shown to increase nitric oxide related enzymes and metabolites in the urine of patients with interstitial cystitis [45].

It has recently been reported that differences in NO evaporation between ulcerative and nonulcer PBS/IC allows for subtyping of cases meeting NIDDK criteria without performing cystoscopy [46]

9. TOXIC AGENTS

Toxic constituents in the urine may cause injury to the bladder in PBS/IC. One hypothesis is that heat labile, cationic urine components of low molecular weight may exert a cytotoxic effect [47]. Defective constitutive cytokine production may decrease mucosal defence to toxic agents [48].

10. HYPOXIA

has been a suggested mechanism for etiology and pathogenesis in PBS/IC. Decreased microvascular density in the suburothelium is said to be one feature [49]. In a recent study it was found that bladder perfusion decreased with bladder filling in these patients compared to the opposite in controls [50]. In spite of these observations it has not been suggested that bladder ischemia alone would account for symptoms of PBS/IC.

11. Complex pathogenetic interactions

In recent years, several reports have indicated that the aetiology of PBS/IC probably is more complex than has previously been anticipated. In fact, it has been proposed that this is a neuroimmunoendocrine disorder. Theoharides et al have shown that activation of mast cells in close proximity to nerve terminals can be influenced by estradiol as well as corticotrophin releasing hormone [51]. Moreover, Okragly et al found elevated levels of tryptase, nerve growth factor, neurotrophin-3 and glial cell line-derived neurotrophic factor in PBS/IC as compared to controls [52]. These findings indicate that the pathogenesis may include interactions between the peripheral nerve system, the immune system and hormone release from different endocrine systems, at varying levels. Recently, it was proposed that the distribution of mast cells in the epithelium in ulcerative disease could be explained by the epithelial coexpression of stem cell factor and interleukin-6 (IL-6) [112].

According to Abdel-Mageed et al, an increased expression of p65, a nuclear factor-kappaB subunit, was found in patients with PBS/IC. Interestingly, these authors subsequently presented a study in which they detected a five-fold increase in the expression of the gene for IL-6 after nuclear factor-kappaB activation [53], findings suggesting that intricate systems on the cytokine gene expression level may be operating.

III. EPIDEMIOLOGY OF PAINFUL BLADDER SYNDROME / INTERSTITIAL CYSTITIS

INTRODUCTION

An editorial in the Journal of Urology in 2000 was titled "Interstitial Cystitis-The Great Enigma". The author begins with the statements: "Many aspects of interstitial cystitis remain a mystery. Fundamental questions facing us are what is and who has interstitial cystitis. Is it a specific disease entity resulting from a definable insult or a collection of symptoms resulting from multiple causes?" [54] These questions must be answered before effective treatment strategies can be developed and implemented for the many people suffering the agonies of this disorder. The answers will necessarily have to come from well-designed, accurate, epidemiological studies.

1. DEFINITION OF EPIDEMIOLOGY

The United Nations defines epidemiology as: *The study of the incidence, prevalence, distribution and determinants of an infection, disease or other health-related event in a population. Epidemiology can be thought of in terms of who, where, when, what and why". (www.un.org/ Pubs/CyberSchoolBus/special/health/glossary).* The epidemiology of chronic disease lends itself to a diversity of population based studies which can be used to evaluate the disease: survey studies, cohort (follow-up) studies and case-control (retrospective) studies. Each of these types of studies has its advantages and limitations and they will be discussed with specific examples.

2. EPIDEMIOLOGY OF INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME – CONFLICTING DATA

The study of the epidemiology of PBS/IC is confounded by the lack of a uniform definition, the lack of any readily available validated diagnostic marker that can be reproducibly utilized in the general population, and an unknown etiology and pathophysiology. That confusion is seen in the data reported in three articles published on the epidemiology of IC which were reviewed in 1997 by Jones and Nyberg [55]. There is a great divergence in the estimate of population prevalence of IC. Oravisto [56] had reported in 1975 a prevalence of 10 per 100,000 for both genders and 18 / 100,000 for women. Held et. al [57], in 1987 reported a prevalence of 30 per 100,000. Jones and Nyberg [58]in 1994 reported a prevalence 501/100,000 for both genders and of 865/100,000 for women. These early studies demonstrate the problems with interpreting epidemiologic studies of IC. The Oravisto report is from a region of Finland in which most persons received care from only a few hospitals. He used as a diagnosis a history of chronic voiding symptoms, sterile urine and a bladder biopsy showing fibrosis, edema and/or lymphocytic infiltration. Held et al, derived data from a questionnaire mailed to randomly selected urologists in the United States asking them to report on the prevalence and incidence of IC in their practices. The response rate was 26%. The authors then used three different methods to estimate the prevalence of U.S. IC patients, which gave a range of from about 20,000 to 90,000 women in the U. S. with IC. Using a weighted average calculation, Held et al then concluded there were at least 43,500 women with IC in the U.S. They followed this with

another calculation based on a reported 5:1 ratio of patients with PBS/IC-like symptoms to patients with diagnosed IC, and suggested that the prevalence of patients with undiagnosed IC might be as high as 217,500 individuals. Jones et al obtained their data from self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey. After the sample responses were weighted by age, race, and gender, 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 the self-report by medical records. This self-reported diagnosis of IC could be misclassified due to poor participant recall and/or confusion between the terms cystitis and interstitial cystitis. In summary, these marked disparities in the prevalence data are due primarily to the lack of a consistent symptom based definition for use by either the patient or the physician, the method of the survey, and the size and demographics of the population surveyed.

3. THE NIH / NIDDK DIAGNOSTIC CRITERIA – FILLING THE VOID

Diagnostic criteria to be used for research studies of IC were established in 1987 at a workshop held at the NIDDK of the NIH established in 1987 [59]. The purpose of these criteria was so to allow comparison of the data from published clinical research studies. These diagnostic criteria, variously referred to as either NIDDK or NIH diagnostic criteria, were intended only to be applied to research studies for the purpose of obtaining uniformity in the patient populations studied, to allow comparison of the published results of studies from various authors. These research criteria have over time been mistakenly used to fill the void of the lack of established, uniform clinical criteria for the diagnosis of IC. This is a purpose for which they were neither developed nor intended. The cohort of persons who meet these research criteria excludes many who would routinely be diagnosed as having IC in a clinical setting [60].

• Diagnostic Criteria and Epidemiological Studies

Bade et.al [61] sought to determine the prevalence of IC in the Netherlands by sending questionnaires to all 235 urologists in the country. The response rate was 65%. The epidemiological portion of the questionnaire questioned the number and demographics of persons with IC and the criteria used to make a diagnosis of IC. The diagnostic criteria used varied amongst urologists. Pathology on bladder biopsies

was reported most frequently as the diagnostic criterion (91%), although it was not designated what pathological criteria were used by all the urologists. 26% of the respondents used the NIH criteria for the diagnosis. The presence of mast cells in biopsies was used as a criterion for 79% of the urologists. The presence of voiding symptoms was reported in most of the patients who met the diagnostic criteria of the individual urologists. Frequency was the most common (87% of patients) symptom and pain in the region of the bladder was reported in 61% of the patients. This study reported the prevalence of IC in women in The Netherlands to be between 8 and 16 /100,000, a result similar to the Finnish study of Oravisto et al. Although the Bade et al study attempts to define the criteria used to diagnose IC, it is not a population based study and does not use uniform criteria for selection of persons included in the study. Only those persons who sought treatment were reported.

The prevalence of IC in Japan was estimated by Ito et. al [62] who sent a questionnaire to the chief urologists of major hospitals. The questionnaire was somewhat similar to that used by Bade et al in the Netherlands. Based on the response rate of 82.3%, the overall prevalence was estimated to be 1.2 per 100,000 with a female prevalence of 4.5 / 100,000. The prevalence increased with age up to the seventh decade. Frequency was the most commonly reported symptom (72%). Suprapubic pain was reported in 54.4%. Fifty-eight percent of the urologists used bladder biopsy results for diagnosis, and 25% used cystoscopy under anesthesia as a diagnostic measure. Only 10% of the urologists reported using the NIH criteria to aid in the diagnosis.

4. THE UTILIZATION OF LARGE STUDY POPULATIONS – PHYSICIAN VERIFIED DIAGNOSIS

The relatively low frequency of the occurrence of PBS/IC in the general population presents a major obstacle to the study of the epidemiology of the disorder. In order to perform valid studies of the distribution of this symptom complex in the general population, epidemiologic investigators need to be able to access and study large numbers of individuals. Curhan et. al[63], addressed the limitations of the previously published studies by utilizing the Nurses Health Study (NHS) I and II, two large population based studies of female, predominantly white, nurses. The initial evaluation for PBS/IC was by questionnaire. Patient medical records of those who indicated a diagnosis PBS/IC were then evaluated to

classify the diagnosis as definite, probable and possible. The confirmation rate of initial self-reports by medical record review was only 6.4%. Among patients for whom medical records were obtained, many of those confirmed to have IC did not meet the NIH criteria. However, at a minimum all patients reported as confirmed for IC had the appropriate symptoms and had undergone cystoscopy. The reported data showed that delay between the initial occurrence of symptoms and the diagnosis was substantial: 7.1 years in NHS I, and 5.3 years in NHS II. This suggests that there are many persons with symptoms who go undiagnosed for many years and are thus not included in surveys that list only diagnoses as a response. The prevalence of confirmed IC was 67 per 100,000 in NHS II and 52 per 100,000 in NHS I. These rates are substantially higher than many of the previously reported estimates. This study improved on previous studies by using a large sample derived from a general population and careful ascertainment of the diagnosis. Limitations of the study include the absence of men and children and a population selected limited to nurses who have higher health awareness, were predominantly white, and are more likely to seek medical care than the general population. The authors note that 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.

5. Large Study Populations – Utilization of Symptom Based Questionnaires

Leppilahti et. al [64] used the validated O'Leary –Sant interstitial cystitis symptom and problem index [65,66] questionnaire to select persons with IC symptoms from the Finnish population register. The response rate after 2 mailings was 67.2%. Women who had had urinary tract infections during the previous month were excluded. They concluded that the prevalence of probable interstitial cystitis, based on a symptom index score of 12 or greater, is 450/100,000. This symptom-derived rate is considerably higher than the physician diagnosed rate reported by Curhan, et al, and supports the concept that many persons go undiagnosed and the symptom complex is very prevalent in the population. Leppilahti et al conclude that given the excellent estimated sensitivity of the O'Leary-Sant score, the true prevalence of IC related symptoms in their population is likely to be up to 50% higher, closer to the 870/100,000 reported in the National Health Interview Survey by Jones [58].

The contrast between physician diagnosed interstitial cystitis and questionnaire based diagnosis is accentuated by the report by Roberts et al on the incidence of physician-diagnosed interstitial cystitis in Olmsted County, Minnesota [67]. The overall age and sex adjusted rate was 1.1 per 100,000 population, with an annual incidence of 1.6 per 100,000 for women and 0.6 per 100,000 for men. There are few studies of incidence of IC; most report prevalence. However, the rates reported in this study for women are comparable to the rates reported by Oravisto, et al for Finnish women (1.2 per 100,000). The cumulative incidence by age >80years in the Minnesota study was 114 per 100,000. This is comparable to the Curhan et al study, which reported on a younger age group. The authors conclude that although there is a low incidence, the chronicity of the condition may contribute to the high prevalence rates.

6. Gender Differences in Epidemiological Studies

A major distinguishing feature of interstitial cystitis, which is evident in all population-based studies, is the disproportional disease burden reported among women. The population prevalence estimates indicate a male-to-female ratio of from 1:4.5 in the Japanese cohort [62] to 1:9 in the U.S. population survey [55]. Because few studies include enough men to explore the clinical characteristics it is difficult to assess why there are these significant gender differences. Novicki [68] described the characteristics of 29 men diagnosed with IC over an 8-year period. Before they were diagnosed with IC, 14 of these men had been diagnosed with prostatitis and 11 were diagnosed with benign prostatic hyperplasia. The average age of diagnosis was about 67 years. All of the men had pain as a component of their presenting symptoms. The Roberts et. al study [67] reported the age at first diagnosis as 71 for men. Approximately 75 % of the men diagnosed with IC in both studies had Hunner's ulcers. The significantly later age of diagnosis for men, the higher rate of Hunner's ulcers and the frequency of previous misdiagnoses for benign prostate disorders suggests that the gender difference for IC might be partially explained by missed or delayed diagnoses in men.

- **Understanding the Disease with Data from Epidemiological Studies**

A prospective epidemiologic study of patients enrolled in the Interstitial Cystitis Database (ICDB) showed that there was no long-term change in overall

disease severity over a period of 48 months in this primarily (92%) female cohort [69]. The longitudinal study confirmed the clinical impression that IC is a chronic and debilitating condition with no long-term effective therapy.

Studies have shown that interstitial cystitis extracts a significant physical, mental and financial toll from those affected. Koziol et. al [70] did an extensive survey of 374 patients diagnosed with IC according to the NIDDK criteria. Travel, employment, leisure activities and sleeping were adversely affected in more than 80% of the patients. Michael et. al [71] evaluated the women in the Nurses Health studies who met the criteria for IC and reported that the quality of life among these women was especially limited in the psychosocial dimensions, such as vitality and mental health.

Interstitial cystitis has been reported to have association with numerous other chronic disease and pain syndromes. A questionnaire-based survey of the database of the Interstitial Cystitis Association (ICA) received a 35% response rate [72]. The respondent individuals with interstitial cystitis were 100 times more likely to have inflammatory bowel disease and 30 times more likely to have systemic lupus erythematosus than the general population. A study by Leppilahti et. al [27] reported that the age-standardized prevalence of possible and probable interstitial cystitis-like symptoms was greater among Sjögren's syndrome patients than controls, corresponding with prevalence rate ratios of 5.3 for possible IC and 15 for probable IC. This suggests a shared susceptibility or etiology of the two disorders. Weissman et. al 73] using genetic linkage studies, has demonstrated a syndrome which includes interstitial cystitis, thyroid disorders, panic disorder , severe headaches, and other disorders of possible autonomic or neuromuscular control. In an earlier study this syndrome was mapped to specific genes on chromosome 13q [74].

7. A Broader Symptom-Based Definition for Epidemiological Studies

There is increasing evidence that the definition of interstitial cystitis needs to be expanded beyond that established by the NIH / NIDDK in 1988 [75]. These guidelines are too restrictive and non-specific for epidemiologic studies. *Until specific diagnostic markers are verified and/or a set of agreed upon diagnostic criteria based on well-designed published data are established, it might be more appropriate to use a more inclusive, symptom specific*

definition of the IC symptom complex to permit a more accurate assessment of the population burden. This recommendation is supported by studies that have demonstrated the restrictiveness of the NIDDK criteria. For example, among participants of the Interstitial Cystitis Data Base study, of those who were entered into the study with less stringent criteria than the NIDDK criteria, 90% were considered by experienced clinicians to have clinical IC [60]. In contrast, if the NIDDK criteria were strictly applied to the cohort studied, >60% clinically diagnosed with IC by experts would have been misdiagnosed and not classified as IC. There is evidence reported that the cystoscopic presence of glomerulations, one of the few objective NIDDK criteria, can be observed with equal frequency in asymptomatic women and women clinically diagnosed with IC [76].

One alternative to the restrictive definition of IC is to expand it to a symptom based definition of chronic pelvic pain predominantly localized to the bladder, or PBS. This does present an additional challenge because there are many diverse causes of chronic pelvic pain that are not related to the bladder. Parsons et al studied 244 patients with pelvic pain, including those diagnosed with endometriosis, vulvodynia and other pelvic disorders. Only 1.6% of the patients had received an initial diagnosis of IC. 81% of these pelvic pain patients had a positive potassium test [77]. The test, although non-specific, may demonstrate that there is some common dysfunction among this disparate group of pelvic pain patients. Clemons et. al [78] used the O'Leary Sant symptom index to define IC in a cohort of patients presenting with chronic pelvic pain. Each person was hydrodistended and cystoscoped. The diagnosis of IC was made if the patient had pain, frequency, urgency and positive cystoscopic findings. 38% were diagnosed with IC using these criteria. A score of 5 or more on the Symptom Index had 94% sensitivity and 93% negative predictive value in diagnosing IC. This demonstrates that IC is quite prevalent and undiagnosed in women presenting with chronic pelvic pain, and that a well designed and validated symptom based questionnaire such as the O'Leary Sant or the Wisconsin interstitial cystitis scale[79,80] should be further studied to determine utility for diagnosing IC.

• Conclusion:

The study of the epidemiology of painful bladder syndrome / interstitial cystitis has been hampered by many obstacles. The most obvious of these is a vali-

dated diagnostic marker and the lack of an evidence based symptom specific definition of the disease. Although the NIDDK criteria have served their purpose in making clinical research studies comparable, they are too restrictive and exclude many persons from inclusion in epidemiologic studies. They tend to prevent persons with the disease from receiving an accurate diagnosis and supportive clinical care. The lack of well-defined diagnostic criteria may also be responsible for the perceived low rate of PBS/IC diagnosed in men. *Reliable and adequate epidemiological studies are necessary to evaluate risk factors for the disease and for the development of effective treatment strategies*

IV. INTERSTITIAL CYSTITIS/ PAINFUL BLADDER - PATHOLOGY

A review of the published literature on interstitial cystitis and pathology generated over 250 references but many of these did not relate to the histopathology of IC. The references reviewed and discussed below are those relating to human data including light microscopy findings, electron microscopy studies and immunohistochemical studies of series of patients with interstitial cystitis or painful bladder defined in a number of ways and often compared to control subjects. There were also studies using animal models that have given added insight into pathophysiology.

There are many differences among papers that address PBS/IC pathology, including the definition of what constitutes IC, how and where bladder biopsy is taken, how the biopsy is treated in terms of fixation and staining, which histological criteria are analyzed, differences in the inclusion of control subjects and the type of control subject. There is large international variation in the practice of bladder biopsy in PBS/IC, with Europe and Japan commonly performing biopsy. On the other hand, in the United States the IC database study had an overall biopsy rate of 33% (range 9 to 64%) [81] . *The potential reasons to perform a biopsy in IC would be to confirm the diagnosis of IC, to exclude other conditions, if there were a prognostic or therapeutic value, and for research purposes. The potential benefit of these indications would have to be balanced against complication and cost.*

Most of the literature describes light microscopy findings in bladder biopsies taken after hydrodistension

by cold-cup forceps or transurethral resection, which are , formalin fixed, routinely processed and stained with hematoxylin and eosin. stained. Some specialized stains or immunohistochemical techniques are described, in particular when demonstrating mast cells (toluidine blue, tryptase), fibrosis (trichrome, Van Gieson) or nerve cells (S-100). There are numerous papers investigating the pathogenesis of IC which employ immunohistochemical methods to report, for example, comparative levels of cytokines [48] , leucocyte antigens [82], immunohistocompatibility antigens [83], neuropeptides [37], estrogen receptor status [84], microvasculature [85] or collagen staining [86] in IC versus control subjects.

An overview of the literature allows us to view the original clinical and pathological description of IC which was then broadened by the 1978 paper ofby Messing and Stamey [87]. In the United States this was followed by the NIDDK criteria to establish a research definition of IC which did not include biopsy or pathology findings [59]. A further broadening of the definition of IC was evidenced by papers such as those produced by the IC database study which included patients who were diagnosed as having IC by an experienced clinician and may have had a normal cystoscopy [81]. Glomerulations were no longer conceived to bewere not specific to IC [88] and were demonstrable after bladder over-distention in asymptomatic patients [76]. However in Europe there continued to be a more stringent clinical definition of IC with a strong emphasis on bladder biopsy. Detrusor mastocytosis >28 cells/mm^2 was used as one of the criteria for defining IC [89]. More recently European studies have strongly supported the contribution the histopathology makes to the distinction between early and classic disease [90].

1. HISTORICAL REVIEW

One of the best known historical descriptions of interstitial cystitis was the elegant paper by Guy Hunner in 1918 of 18 case histories including pathology of "a rare type of bladder ulcer" seen over 17 years of his gynecological practice [91]. The pathological description was that of a loss of epithelium with the underlying mucosa showing granulation tissue, increased capillaries, oedema and chronic inflammatory cells, also involving the muscle coat and thickened peritoneum over a diseased area. Bumpus in 1921 described the pathology of submucous ulcer in the male and the main features were "marked submucous lymphocytic infiltration, extravasation of blood and markedly thinned epithelium"

[92]. John Hand in 1949 reported on 223 patients with IC (204 women and 19 men) he had observed over the previous 17 years [93]. He commented that the biopsies taken showed similar changes to a cystectomy specimen with a very vascular stroma, edema and fibrosis between muscle bundles. Venules were dilated and there was an abundance of nerve tissue with extensive leucocytic infiltration.

A retrospective review of the files of the Armed Forces Institute of Pathology which had been designated as chronic edematous pancystitis with mast cell infiltrate and a poor therapeutic response was reported by Smith and Dehner in 1972 [94]. Microscopically all 28 lesions showed ulceration with oedema and inflammatory infiltrate in the submucosa and increased mast cells. The muscularis layer was also affected to a greater or lesser extent and fibrosis occurred in cases of long duration. However these cases may not all have had interstitial cystitis as 12 of the 14 patients with urine cultures showed infection. In addition the study is of limited value as the inclusion criteria were histological changes rather than clinical symptoms and cystoscopic findings.

In 1978 Messing and Stamey reviewed 52 patients who were diagnosed with interstitial cystitis over the previous 12 years. Thirty-eight had biopsies; 19 of these had classic disease defined as reduced anesthetic bladder capacity and Hunner's ulcer, and 19 had early disease defined as glomerulations on second bladder distention. They described non-specific mucosal ulceration or denudement in 70 % of classic but 35% of early cases. Submucosal oedema and vasodilatation was the main finding in both classic and early cases, and chronic inflammatory infiltrate in a third of both early and classic IC patients. Submucosal and muscle layer fibrosis was seen rarely [87,94]. This is an important paper that for the first time made the distinction between 2 subgroups of IC, classic and early. Mattila (1982) found normal bladder biopsy histology in 20 of 47 (43 %) IC patients with 18/47 (38%) showing lymphocytic and plasma cell infiltrate and 9 /47 (19%) showing thickened telangiectatic vessels [95].

Fall, Johansson and Vahlne in 1985 reported a series of 37 women and 4 men with chronic interstitial cystitis who all had ulceration which was described as "patches of reddened mucosa with small vessels to a central pale scar which ruptures during bladder filling". They had a control group of 14 that included patients with irritative symptoms and often glomerulations on second overdistention, as well as 5 stress incontinent women with normal cystoscopy. The IC group with ulceration had histology showing areas of mucosal ulceration and detachment, edematous lamina propria, a range between mild to severe chronic inflammatory infiltrate which was often perineural or perivascular in a focal rather than diffuse pattern. The authors made the point that the perineural or perivascular infiltrates were seen only in transurethral resection specimens and not forceps biopsy specimens. Biopsies from the "symptomatic control group" showed non-specific cystitis in 10, glandular or squamous metaplasia in 3 and carcinoma in situ in 1. Biopsies from the stress incontinent control group had normal pathology [6]. In an additional study from 1987 Fall, Johansson, and Aldenborg studied 28 patients with IC and 14 healthy controls. Sixteen of the patients (15 females and 1 male) had classic or ulcerative disease and 12 (11 females and 1 male) had non-ulcerative or early IC.The authors concluded that the differences between the two variants (mean age at diagnosis, mast cell distribution, cystoscopic appearance and histopathological findings) warranted separation of the two entities in clinical studies [10].

Holm-Bentzen and colleagues in 1987 published their series of 115 patients with painful bladder symptoms, at least 79 (70 %) of whom satisfied NIDDK criteria [96]. They performed "deep biopsies" and defined IC as greater than 28 detrusor mast cells/mm^2 and found that this group of 43 patients all had disrupted epithelium, mononuclear inflammation, lamina propria edema and fibrosis, and detrusor inter and intrafascicular fibrosis. The remaining 72 were described as showing normal epithelium, inflammatory cells, oedema and collagen deposits in lamina propria, and interfascicular collagen (43), bladder wall fibrosis (12) or presumed detrusor myopathy, referring to focal changes of the detrusor cells such as hydropic cytoplasm (12). Bladder biopsy was normal in 4 (3%). Gillespie and colleagueset al, (1990) in their assessment of 339 IC patients (95 % met NIDDK criteria) and 5 controls found that the IC histology showed greatly decreased or absent mucous layer with epithelial ulceration. Marked edema, vascular ectasia and hemorrhage was seen in both late (defined as capacity <400ml, terminal hematuria, glomerulations and in two thirds ulceration or fissuring) and early (capacity >400ml and 90% with glomerulations) groups [97].

2. RECENT SERIES

In recent series authors have attempted to use semi-

quantitatve methods in the analysis of the pathological changes rather than the largely descriptive methods reported previously. Lynes and colleagues [98] described the pathology of (mainly) forceps biopsies from 22 IC (all but 2 met NIDDK criteria) and 10 control subjects. They found 4 IC cases with ulceration, an increase in denuded epithelium (7 IC and 0 controls) and prominent submucosal lymphocytic inflammation (10 IC and 1 control). These abnormalities occurred only in the group with small capacity bladder or culture negative pyura. They found no difference in the degree of submucosal oedema and vascular ectasia, with marked changes occurring in both IC and controls after bladder hydrodistention. Submucosal and muscle fibrosis was not identified. Twelve of the 22 (55%) IC patients had no histological abnormality.

Johansson and Fall (1990) described 64 subjects with "classic" (ulcer) IC, 44 with non-ulcer IC and 20 control subjects who had *transurethral resection* biopsies [15]. The classic IC group had mucosal ulceration, often wedge-shaped, extending into the lamina propria (100%) and mucosal haemorrhage (89%), granulation tissue (95%) and mild to severe mononuclear infiltrate (100%). Denudation of neighboring mucosa was common. Of the early IC subjects 67% had mucosal ruptures or tears and 91% had focal submucosal haemorrhages with mild to moderate inflammatory infiltrate in only 20%. Biopsies from normal-appearing mucosa in the non-ulcer group were normal apart from slight oedema. Inflammatory infiltrate was limited to the lamina propria usually and consisted of lymphocytes, plasma cells, neutrophils, eosinophils, and mast cells. Eighty per cent of the classic group had perineural infiltrate. Mucosal mast cells were seen in all but 2 of the classic disease only. Lamina propria and detrusor mast cells were significantly increased only in the classic group. Fibrosis was seen in only 5 of the most severe "classic" IC patients. In 5 classic and 4 non-ulcer patients there was some diagnostic doubt cystoscopically, and the biopsy was used for differentiation. In terms of differential diagnosis the authors comment that carcinoma in situ can mimic IC in terms of symptoms and cystoscopy findings but has different cytology and histology. They also commented that Ttuberculous cystitis could have similar symptoms and pathology findings as IC becauseas granulomas are not always seen.

Denson and colleagues in 2000 analysed forceps biopsies from 65 females and 4 males with IC symptoms [99]. It is not reported exactly how many fit NIDDK crtiteria but at least 9 % did not. They found <10 % specimens showed vasodilatation or submucosal oedema. Inflammation was not seen in 30 %; was mild in 41% and moderate to severe inflammatory infiltrate was found in 29 %. There was poor correlation between inflammation and severity of cystoscopic changes. However, they found more severe cystoscopic changes along with more severe inflammatory changes in the population >60 years.

Hanus et.al in 2001 presented a series of 84 biopsies from 112 IC patients [100]. They reported a linear relationship between the mean bladder capacity under anesthesia and severity of glomerulations. They did not find that the most prominent and extensive histologic features were in biopsies from areas of glomerulations. There were no specific ultrastructural changes of granules of mast cells in most patients with clinical diagnosis of IC. There was increased S-100 nerve ending staining of muscular and lamina propria layers in those with a longstanding IC. They did not find a correlation between severity of symptoms and histopathological changes observed by light or electron microscopy.

The most extensive histological study in IC is the preliminary report by the IC database [81]. The ICDB cohort study enrolled 637 patients who had symptoms of urgency, frequency or pain/discomfort for the previous 6 months and included patients who had been previously diagnosed as IC by experienced clinicians. In other words this was a broader group than those meeting NIDDK criteria. Of this group 226 elected to undergo cystoscopy and 211 biopsies were obtained (11% normal cystoscopy, 83 % had mild to severe glomerulations and 6 % or 12 patients had Hunner's ulcer). However 15 % or 31 of 203 patients had granulation tissue in the submucosa, which means that they had classic IC since granulation tissue is not seen in non-ulcer (early) IC. The protocol included 2 forceps biopsies in the area of a Hunner's ulcer if present or in the area of glomerulations. Two random biopsies were taken if the bladder was cystoscopically normal and a further trigonal biopsy as internal control was also taken in each case. Numerous clinical features such as pain, urgency, 24-hour frequency and nighttime frequency in addition to 39 histological criteria were analysed. Multivariate analysis was performed and showed an association between nocturnal frequency and complete urothelial denudation, lamina propria granulation tissue and vascular density, and lamina propria mast cell count (by tryptase stain only and not in 5 other types and locations of mast cell count). Urgen-

cy and submucosal granulation tissue were associated, as was urinary pain with urothelial denudation and submucosal hemorrhage. The association between submucosal hemorrhage and urinary pain is not clear, as the trend does not appear to be consistent. The IC database is a very exhaustive study of which only the preliminary findings of the association between histology and symptoms have been published to date. A possible drawback is the wide criteria for inclusion and a possible lack of rigor in efforts to identify or separate classic and early disease.

The results of a histological study comparing bladder forceps biopsies from 35 control and 34 IC subjects, 6 of whom were classified as severe with cystoscopic capacities < 400 mL, were presented by Rosamilia and colleagues at the International IC Consensus meeting in Kyoto, Japan 2003 [101]. Only light microscopy was utilized and six histological characteristics were graded. The bladder epithelium was described as intact, partly or completely denuded. The appearance of submucosal edema, congestion and ectasia, inflammatory infiltrate, hemorrhage, and fibrosis was graded 0 (none) to 3 (severe). Fibrosis was not evident in any of these hematoxylin and eosin stained forceps biopsy specimens. Epithelial denudation, submucosal edema, congestion and ectasia and inflammatory infiltrate were increased in the IC group. No difference was seen in the degree of submucosal hemorrhage. Completely denuded epithelium never occurred in controls but was present in 14% of early ICand IC and 50% of severe IC. Submucosal edema of a moderate degree (score of 2) was found in only 3% (1) of controls, 13% of early IC, and 50% of severe IC subjects. Moderate or marked submucosal congestion and/or ectasia (scores of 2 or 3) was present in only 3% (1) control subject, 10% of early IC and 50% of severe IC subjects. Moderate to severe (scores 2 and 3) submucosal inflammatory infiltrate of predominantly mononuclear cells was found in 6% (2) of controls, 13% of early IC, and 50% of severe IC subjects. Submucosal hemorrhage was found to occur in 67% of all IC, whether early or severe, and 54% of control subjects.

An abnormal composite submucosal histology score was arbitrarily defined as the sum of the individual submucosal scores and was increased in the IC subjects. Scores of 4 or greater for the composite histology score were obtained in 44% of the IC group compared with 1 (3%) of the control subjects who was later found to have recurrent urinary infection. A composite submucosal histology score of 4 or greater had a sensitivity of only 44% to detect IC (67%

for severe IC) and a specificity of 97%. The positive predictive value for a composite submucosal score of 4 or greater to predict IC was 94%. Conversely, in this series the histological parameters studied were normal and indistinguishable from control subjects in more than half (55%) of IC subjects. The pattern of abnormal histology when it occurred supported a theory of pathogenesis involving epithelial dysfunction and leakage resulting inallowing submucosal edema and ectasia. Increased edema may have also been the explanation for a study by the same authors who found a decrease in subepithelial microvascular density in IC [85]. In support of this, a trend to increased edema was seen in 13 IC biopsies taken after as compared with before hydrodistention, which contrasted with 13 control biopsies where no such change occurred [49].

The case for pathological confirmation of IC is strongest for the classic disease as defined by either a Hunner's ulcer or low anesthetic capacity. The most commonly reported histological changes in classic IC include epithelial ulceration or denudation, submucosal inflammation, granulation tissue formation, edema, congestion, hemorrhage; detrusor fibrosis (and myopathy), increased epithelial, submucosal and detrusor mast cell number and activation and increased neuronal staining. Early IC is generally characterised by normal or near normal bladder capacity under anesthesia and the presence of glomerulations. Light microscopy findings range from mucosal ruptures, submucosal hemorrhage and mild inflammation in transurethral resection biopsies [15] to normal histology in forceps biopsies approximately half the time [95,98,101]. This may represent a sampling difference. In other words in the clinical setting of early IC, bladder forceps biopsy pathology may be normal and is not therefore useful as a confirmatory test.

3. MAST CELLS

The literature on mast cell density and mast cell activation was thoroughly reviewed by Theoharides et.al in 2001 [102]. Increased detrusor mast cell density was reported by Larsen et. al [103] and Feltis et. al [104]who also found increased submucosal mast cell density. Aldenborg et. al [105] found an increased number of mast cells per mm^2 in the mucosa and lamina propria (180 vs 100 vs 95) as well as the detrusor (120 vs 65 vs 40) of ulcerative IC versus non-ulcer IC and controls. Lynes et. al [106] found increased mast cell density and degranulation in the

detrusor but not the submucosa. Johansson and Fall (whose series could have included the subjects of Aldenborg et al.) reported increased lamina propria (164 vs 93 vs 88) and detrusor (99 vs 46 vs 36) mast cells in ulcerative vs non-ulcer vs controls. Christmas and Rode found that the epithelium and submucosa of biopsies from 22 IC subjects had 146 mast cells per 10 high power field (HPF) versus 51 for controls and correspondingly, 170 versus 46 in the detrusor muscle [107]. Immunocytochemical techniques have confirmed that mast cells are more consistently increased in ulcerative IC up to 6 to 10-fold with a greater abundance of epithelial mast cells while in non-ulcer IC the increase is two-fold [8]. Electron microscopy studies in IC confirm mast cell intragranular activation [12,108,109].

Peeker and Fall in 2002 evaluated 130 patients with classic and 101 with non ulcer IC retrospectively and reported differences such as younger age at diagnosis and higher anesthetic bladder capacity in the nonulcer group [110]. They summarized their findings as "classic" IC biopsies showing mucosal ulceration, hemorrhage, granulation tissue, inflammatory infiltrate, high mast cell counts, and perineural infiltrates. Biopsies from patients with non-ulcer disease had relatively normal mucosa with sparse inflammation but multiple small mucosal ruptures and suburothelial hemorrhages. In classic IC mast cell growth factors were expressed in the epithelium. The authors distinguished between classic and non-ulcer IC by epithelial mast cell recruitment and high bladder wall mast cell density. They reported an overall increase in mast cell density especially in the epithelium that is 6 to 10 fold in ulcerative and 2 fold in early IC with evidence of mast cell intragranular activation.

4. NEURONAL STUDIES

Neuronal studies in IC include the immunohistochemical study by Christmas and colleagues in 1990 that reported increased nerve fibre density in the suburothelium and detrusor layer of 18 chronic IC versus 12 controls [36]. Pang and colleagues in 1995 found increased number of substance P positive nerve fibres only in the submucosa of 8 IC (ulcerative status unknown) patients as compared with 5 control subjects [111]. Bladder biopsies from 6 patients with classic IC and 7 with nonulcer IC showed increased density and number of nerve fibers immunoreactive for tyrosine hydroxylase compared with 6 control subjects. There was a difference between classic and nonulcer disease in overall nerve density, being greater in the classic group [43].

Hohenfellner et. al in 1992 found increased numbers of neurons positive for vasoactive intestinal polypeptide and neuropeptide Y in 10 IC patient biopsies versus 10 control subjects whereas the number of neurons positive for substance P and calcitonin-gene-related peptide was not significantly different. This was thought to represent an increase of sympathetic but not cholinergic neurons [37]. Hofmeister and colleagues in 1997 attempted to develop a diagnostic algorithm based on the alteration of mast cell and nerve fiber observed in IC bladder tissue [9]. Non-IC samples from 6 control groups (N = 10, 10, 13, 2, 11, and 3, respectively) and nonulcerative IC (NC-IC, N = 20) were stained with Giemsa stain in order to calculate the detrusor to mucosa mast cell ratio (DMMCR) using quantitative image analysis and morphometry (QIAM). Immunohistochemical staining for S-100 protein was also performed to quantify nerve fiber proliferation in the detrusor muscle of the bladder. The average DMMCR of NC-IC was 1.19. The corresponding figure in patients with , Bacille Calmette-Guerin (BCG) cystitis was 0.84 and in patients with microscopically normal bladder tissue from patients with bladder or prostate cancer it was 0.45. No case of IC had a DMMCR < 0.5. The number and percentage area of nerve fibers in the detrusor in IC were increased compared to controls and BCG (IC, 2.01%; BCG, 0.95%; control, 1.3%). They concluded that a diagnostic algorithm for IC based on the findings include the following: 1) if the DMMCR > 0.75, then IC is present; 2) if the DMMCR < 0.5, then IC is negative; and 3) if the DMMCR is between 0.5 and 0.75, a quantitative S-100 protein staining analysis be employed to evaluate nerve fiber proliferation to detect those marginal cases of non ulcer NC-IC. There is an increase in nerve fibre density in IC.

5. INFLAMMATORY CELLS

Erickson and colleagues in 1994 studied 16 IC (NIDDK criteria) subjects and found that 5 had severe inflammation (greater than 100 mononuclear cells/ high power field in submucosa and detrusor) and 11 mild inflammation (less than 100 mononuclear cells/ high power field and submucosa only). The groups differed in that the patients with severe inflammation experienced better symptom relief after bladder distention. There was a trend for those with severe inflammation to be older, have a longer duration of symptoms and smaller anesthetic bladder capacity [113].

Harrington and colleagues in 1990 compared lymphocyte subpopulations and found 10 control subject

biopsies with no ulcers, few lymphoid cells (predominately T-helper cells), rare T cell nodules and no B cells. The 9Nine nonulcer patient biopsies had rare mucosal ruptures but no ulcers, slightly increased lymphoid cells (predominately T-helper), occasional T cell aggregates, no B cell nodules and rare plasma cells. No statistically significant difference between control and nonulcer IC was seen. In contrast, the classic IC group had ulcers, intense inflammation with focal sheets of plasma cells, aggregates of T cells, B cell nodules including germinal centers, a decreased or normal helper-to-suppressor cell ratio and suppressor cytotoxic cells in germinal centers [31]. Al HadithiTincello and colleagues found bladder biopsies had leukocyte populations with increased CD20+ as assessed by immunohistochemistry in patients with IC (9 meeting NIDDK criteria) as compared with 31 with idiopathic reduced bladder storage (sensory urgency) and 20 controls [82]. Christmas in 1994 identified lymphocyte sub-populations and found increased numbers of CD4+, CD8+ and gamma delta T cells as well as IgA+, IgG+ and IgM+ plasma cells within the urothelium and submucosa in patients with IC [114].

There is an increase in lymphocytic infiltration especially in classic IC.

6. RISK OF CANCER/ OTHER PATHOLOGY

In the literature there have been concerns raised regarding the possible differential diagnosis of malignancy, especially carcinoma in situ. Utz and Zincke in 1974 reported follow up ranging from 6 months to 33 years for 224 women and 53 men originally diagnosed with interstitial cystitis [115]. Bladder cancer, usually carcinoma in situ, was subsequently identified in 3 (1.3 %) women and 12 (23 %) men. They summarized by commenting that the diagnosis of IC can never be established in men without a bladder biopsy and negative urine cytology. Hamm et. al in 1997 reported the development of a verrucous carcinoma of the urinary bladder in a 66-year-old woman who had been suffering from interstitial cystitis with Hunner's ulcer for 10 years [116]. It was described as an uncommon event as only 7 cases of verrucous carcinoma of the urinary bladder unassociated with bilharzial cystitis had been reported. The chronic irritation of the bladder was thought to be the most important etiologic factor for the malignant transformation.

Peters and colleagues reviewed 600 patients referred for investigation and management of IC between 1998 and 2002 and of these 6 (1%) were subsequently diagnosed with transitional cell carcinoma. Four of the six did not have haematuria and 3 were nonsmokers [117]. A combined clinical series of approximately 100 female IC subjects all of whom had a bladder biopsy was reviewed: two cases of eosinophilic cystitis and no case of carcinoma in situ were diagnosed [Rosamilia, Dwyer and Scurry; unpubl. series]. Isolated cases of amyloidosis have been reported.

The risk of carcinoma developing from IC is very low particularly in women. The possibility of either misdiagnosis or later onset of carcinoma or carcinoma-in-situ is more common in men. In all circumstances the combination of urine cytology and cystoscopy would exclude carcinoma. Biopsy is mandatory if there are any suspicious lesions.

7. PROGNOSTIC VALUE

MacDermott and colleagues in 1991 retrospectively compared clinical and pathological features with outcome in 39 women [118]. They all had non-ulcer IC and were divided into a severe outcome group (10 with radical surgery) and conservatively treated group of 29. Thirty-seven biopsies were available and the degree of inflammation, fibrosis (trichrome stain) and detrusor mast cell count (Giemsa or toluidine blue stain) was assessed on each. The clinical features of age, duration of symptoms, frequency, nocturia, pain and bladder capacity was noted. Severe lamina propria fibrosis was evident in 2 (25 %) of the surgical versus 2 (7%) of the conservative outcome group. Severe inflammation was seen in 4 (50%) of surgical group versus 4 (14%) of conservative group. Two (29%) of the surgical group versus 4 (18%) of the conservative group had severe muscle fibrosis and 50 % of the surgical group had high mast cell counts (>30 cells/ mm^2) compared with 32 % of the conservative therapy group. Of the 10 patients with cystectomy, 6 had initial biopsy available for comparison and only detrusor fibrosis had changed, having worsened in 5. The authors concluded that there appeared to be no statistical correlation between the severity of histological findings at initial diagnosis and the eventual outcome of the disease, although the study may not be sufficiently powered to provide a result as only 8 surgical outcome biopsies were available and there appears to be at least a trend for the surgical group to more commonly have fibrosis and inflammation.

Christmas et. al in 1996 attempted to determine whether any histological characteristics of the detrusor muscle in early IC predicted the subsequent develop-

ment of severe symptoms due to bladder contracture. Bladder biopsies from 21 patients with IC were examined in sections stained with haematoxylin and eosin. The detrusor appeared normal in 13 patients; in 8 there was evidence of detrusor myopathy. Patients with biopsies confirming detrusor myopathy were significantly more likely to have hypocompliant bladders than those with normal detrusor muscle histology (P < 0.02). Over the following 3 years, six of the eight patients with detrusor myopathy developed progressively severe symptoms and required subtotal cystectomy whereas none of the 13 patients without detrusor myopathy required bladder substitution [119].

McDougald and Landon analyzed the first 100 of approximately 200 cystoscopies performed over a 5 year period in a UK urogynaecology department and found 1 transitional cell carcinoma and one benign tumour. Clinical outcome was correlated with histology to the extent that 2/3rds with normal histology were discharged from the clinic at 2 years compared with 1/3rd with chronic inflammation. If histology revealed mast cells, more severe pathology was seen, and none of these patients had been discharged at 2 years. In no case would failure to biopsy have resulted in failure to diagnose a malignant lesion as these were cystoscopically visible [120].

Nordling and colleagues of the Copenhagen IC study group presented a large series which correlated six different diagnostic criteria with clinical outcome in 357 patients (339 women and 18 men) with a median follow up time of 2 years [121]. The criteria were pain, nocturia, petechiae or ulcer, small bladder capacity, detrusor mast cell count (naphthol esterase stain), and intrafascicular fibrosis (van Gieson stain). The outcome was classified ranging from 1 to 8, with 1 being symptom free after hydrodistention to 8 as requiring surgery or in severe persistent pain. There was a significant correlation between the number of positive criteria and the poorer the outcome. The group with mild symptom outcome had a significantly lower detrusor mast cell count (threefold) and percentage intrafascicular fibrosis (twofold) than the severe symptom group. Poorer outcome was most strongly correlated with detrusor mast cell density, anesthetic bladder capacity, glomerulations, fibrosis and nocturia in that order.

There may be a trend for histological features such as high mast cell count, fibrosis and severe inflammation to be associated with surgical rather than conservative outcome.

8. ELECTRON MICROSCOPY

Electron microscopy (EM) studies have included that of Collan and colleagues who reported a series of 50 IC and 9 controls and found that in half of the IC samples there was an increase in large swollen epithelial cells with decreased lateral processes (cell junctions) in addition to inflammatory mucosal changes [122]. On the other hand, Dixon and colleagues in 1986 found no difference in the EM appearance of the glycocalyx or urothelial cells between 10 IC and 10 control subjects [89]. Anderstrom and colleagues in 1989 reported scanning EM on 13 classic IC and found they had a larger area with disrupted or absent mucinous layer, marked cell size variability, round and pleomorphic microvilli and focally impaired cell to cell contact compared with the 9 control subjects. These changes were not specific to IC, also occurring in tumours and infection, and probably represented increased cell turnover [17].

Elbadawi and Light in 1996 described the EM appearance of forceps biopsies taken after hydrodistention from glomerulations and normal-appearing bladder in 5 nonulcer IC patients [42]. Control tissue was from two normal adult bladders and 8 elderly women. It is not clear if these biopsies were also taken after similar hydrodistention. Marked edema was found in the IC glomerulation specimens, including the urothelium and the detrusor muscle cells giving an oak leaf appearance. In the urothelium there was focal separation of triple junctions between umbrella cells with some becoming detached and the absence of the asymmetric unit membrane of normal umbrella cells. The suburothelium had changes such as engorged or collapsed capillaries, edema, lymphocytes and mostly activated mast cells and edematous Schwann cells. These changes were seen to occur focally and in mild form in the normal-appearing bladder biopsies from IC patients. Horn and colleagues in 1998 reported an EM study of detrusor muscle cells in bladder biopsies from 13 patients (8 interstitial cystitis (IC) and 5 controls). In all IC-patients and in one control a varying number of smooth muscle cells revealed a characteristic oak leaf pattern with protrusions of the sarcolemma [123].

The electron microscopy changes described in association with IC include variable disruption to the mucin layer, edema and loss of contact between urothelial cells, submucosal changes including mast cells, lymphocytes, edema and an oak leaf pattern of the detrusor smooth muscle cells.

9. Pathologic Studies in Animal Models

Westropp and Buffington in 2002 reviewed the literature with regard to the role of animal models of interstitial cystitis [124]. They evaluated 16 models and classified them as bladder inflammation induced by intravesical administration of an irritant or immune stimulant, systemic and environmentally induced inflammation, and a naturally occurring model of IC in cats. Noxious intravesical stimuli such as acetone in rats resulted in inflammation as well as decreased bladder strip contractility. Electron microscopy changes of neutrophil accumulation and edema was observed in rabbit bladder exposed to acid infusion. Immunological stimulants induced the release of inflammatory mediators and neuropeptides with histological changes of intense vasodilatation and leucocyte migration. The experimental autoimmune model in female Lewis rats is an example of a systemic noxious stimulus and results in edema amd vascular congestion without inflammatory infiltrate. Noxious environmental stimuli including acute cold stress in rats result in bladder mucosal edema, leucocyte infiltration and mast cell degranulation. These induced models of injury provide some insight into the response of the bladder to injury but they have limitations in modeling the process occurring in IC. The naturally occurring feline interstitial cystitis which follows a similar clinical pattern to IC in humans, largely meets the NIDDK criteria and also demonstrates some of the increased neuropeptide and norepinephrine levels seen in human IC, provides a better model than that of injury in healthy animals.

10. Conclusion

Whether the clinician uses NIDDK criteria or less stringent criteria, the diagnosis of interstitial cystitis or painful bladder syndrome is one that requires exclusion of other causes of irritative bladder symptoms such as infection, malignancy, radiation or drugs. There is disagreement between practitioners in Europe and those in the United States regarding the role of bladder biopsy in IC. The difference in opinion relates to a basic one regarding definition of IC or painful bladder syndrome. On one extreme there are clinicians, for example in the United Sstates, who would diagnose IC in a patient who has a 3 month history of urinary urgency and frequency with a negative urine culture and maybe cytology (if there are risk factors for cancer) and possibly an IC questionnaire and voiding diary. On the other hand there is a strong European opinion that this presentation should be investigated with cystoscopy and hydrodistention under anesthesia and diagnosed as IC only if there are cystoscopic changes and preferably histological changes also.

In terms of exclusion of other conditions, the differential diagnoses for the symptoms of urinary urgency, frequency and pain include those listed in the NIDDK criteria (genital or urinary tract tumour, infection, diverticulum, radiation or drug cystitis). The differential diagnosis includes transitional urothelialcell carcinoma and carcinoma in situ (CIS). Urothelial carcinoma is generally evident clinically on cystoscopy and CIS is usually but not universally accompanied by malignant urine cytology. suggestive of malignancy. These two conditions are extremely raredo not occur in women less than forty. Benign causes of these symptoms include eosinophilic cystitis, amyloidosis, lupus cystitis and tuberculosis. Bladder biopsy is likely towould diagnose these rare conditions. Vesical endometriosis is an uncommon condition, presenting with cyclic haematuria rather irritative symptoms and is evident on cystoscopy and often on imaging.

The question of prognostic value of bladder biopsy has been addressed by only very few authors and all retrospectively. Overall there is some correlation between symptoms and some pathology findings [81] and pathology and prognostic outcome [121]. The combination of severe clinical features (for example, low anesthetic capacity) and abnormal pathology has been associated with a poor prognosis such as the need for radical surgery. However the finding of fibrosis is the histological corollary of low anesthetic capacity and represents the same process: it therefore may not confer any added prognostic value. In addition it is possible in a retrospective study that bias is present, for example, IC patients having a biopsy showing a high detrusor mast cell count may have been offered radical surgery more readily than those without. It is not known whether abnormal histology has any influence on determining along with other criteria such as symptoms and bladder capacity the advice given to patients or the treatments offered. The IC database[81] represents a unique opportunity to follow the enrolled patients longitudinally and correlate pathological findings with outcome.

There are two ways in which biopsy could have therapeutic value: 1) excision by transurethral resection or fulguration of abnormal bladder mucosa and submucosa eg: Hunner's ulcer with symptom resolution has been described, but the disease process is usually widespread and symptom recurrence is very common; 2), if biopsy and pathological findings were able to better direct treatment such as the use of anti-

inflammatories in the subset with significant inflammation. This is a potential benefit, which has not been tested.

The role of bladder biopsy in IC as a research tool is obvious, but even then there are significant limitations. By necessity, only a small often superficial area of the bladder is obtained with the cold-cup forceps for assessment and there may be significant sampling errors.

The complication of bladder biopsy is that of bladder perforation which Messing and Stamey suggest occurs in up to 10 % of cases in transurethral resected biopsies [87]. Johansson and Fall reported the need for cystoscopic irrigation for bleeding in 7, retroperitoneal perforation in 5 with indwelling catheter for 3 to 5 days and laparotomy in 1 of 64 classic, 44 nonulcer and 20 control subjects undergoing transurethral resection biopsies [15]. These risks are far less with forceps biopsies, and the latter have not generally been included in publications.

The cost of cystoscopy under anesthesia and biopsy in addition to a generally broader clinical definition with correspondingly fewer abnormal pathology findings may be one of the reasons for the lower rate of biopsy in the United States compared with Europe. Biopsy pathology can be useful in confirming interstitial cystitis but usually in the clinical setting of severe disease. Urine cytology should be mandatory in the population at risk of malignancy but this would not include women younger than 40 years. There is also the possibility of false negative cytology so that biopsy has an important role if malignancy is suspected. There are the rare occasions where other diagnoses such as eosinophilic cystitis are made. Biopsy remains an optional test in the diagnostic work up of IC.

SPECIFIC RECOMMENDATIONS INCLUDE:

Standardization of biopsy techniques is essential if conclusions are to be drawn as to the value of biopsy.

International consensus on what constitutes the minimum pathological criteria to be analysed.

Including a tryptase mast cell stain as the most appropriate stain for mast cells and epithelial, lamina propria and detrusor count.

Continued longitudinal follow up correlating pathology findings with outcome and treatment response

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V. DIAGNOSIS

Much work has been put into the attempt to define objective diagnostic criteria based on, among others factors, cystoscopy under local or general anaesthesia, bladder distension with registration of bladder capacity and/or possible presence of glomerulations and Hunner's ulcer, 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 might be 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 the disease.*

1. DEVELOPMENT OF NIDDK CRITERIAL

The most successful attempt to define a clinical useful definition of IC was the NIDDK inclusion and exclusion criteria established at a workshop in 1987 [59].

INCLUSION CRITERIA

Hunner's ulcer – automatic inclusion or

Pain on bladder filling relieved by emptying

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

Glomerulations on endoscopy

Decreased bladder compliance on cystometrogram
- 2 pos. factors necessary for inclusion

EXCLUSION CRITERIA

<18 years old

Benign or malignant bladder tumors

Radiation cystitis

Tuberculous cystitis

Bacterial cystitis

Vaginitis

Cyclophosphamide cystitis

Symptomatic urethral diverticulum

Uterine, cervical, vaginal or urethral Ca

Active herpes

Bladder or lower ureteral calculi

Waking frequency <5 times in 12 hrs.

Nocturia <2 times

Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (for example phenazopyridine hydrochloride)

Duration <12mos.

Involuntary bladder contractions (urodynamics)

Capacity >400cc, absence of sensory urgency

These criteria were revised after a workshop in 1988 and published in a book [125]:

INCLUSION CRITERIA

Either glomerulations on cystoscopic examination or a classic Hunner's ulcer

Either pain associated with the bladder or urinary urgency

EXCLUSION CRITERIA

Bladder capacity of greater than 350 ml on awake cystometry using either gas or liquid as a filling medium

Absence of an intense urge to void with the bladder filled to 100 ml of gas or 150 ml of water during cystometry, using a fill rate of 30 – 100ml/min

The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described above

Duration of symptoms less than 9 months

Absence of nocturia

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

A frequency of urination, while awake, of less than eight times per day

A diagnosis of bacterial cystitis or prostatitis within a 3-month period

Bladder or lower ureteral calculi

Active genital herpes

Uterine, cervical, vaginal or urethral cancer

Urethral diverticulum

Cyclophosphamide or any type of chemical cystitis Tuberculous cystitis

Radiation cystitis

Benign or malignant bladder tumors

Vaginitis Age less than 18 years

The presence of two sets of NIDDK criteria with the latest only published in a book has not helped clarify the area. The objective of these criteria was to establish a uniformity in patients entering a clinical trial, making comparisons between trials possible. This goal was very successfully reached, but the NIDDK criteria were at the same time by many considered as diagnostic criteria for IC, which was never intended. This was clearly demonstrated by Hanno et. al [60] showing, that only 32% of patients considered by researchers as definitely or very likely to have IC actually met the NIDDK criteria.

3. DIFFERENTIAL DIAGNOSIS

- Cystitis (bacterial, virus (herpes), TB, irradiation, chemical)
- Vaginitis
- Tumor of the bladder, urethra, uterus, cervix, vagina
- Urethral diverticulum
- Stone in the bladder or lower ureter
- Prostatitis
- Musculoskeletal pain (myosis, arthrosis, spondylosis)
- Neurogenic (prolapsed intervertebral disc)

4. SYMPTOMS

Although as mentioned the diagnosis of IC/PBS is clinical based on symptoms of frequency, urgency, and pain, there is no definition or guideline delineating the quantification of these symptoms in order to establish a diagnosis. Normal number of voidings is normally set at 7 or 8 times per 24 hours, but is influenced by drinking habits and perspiration. A definite number is therefore not very meaningful. Analysing frequency into diurnal and nocturnal frequencies might be useful but needs further evaluation. Urgency is difficult to quantify, although a VAS score might be useful.

• Pain is an essential component of IC/PBS.

Traditionally pain is described as increasing pain on bladder filling relieved by bladder emptying. It is today recognised, that pain might present as bladder pain, urethral pain, vaginal pain, pelvic pain, or rectal pain. Pain might be suprapubic, urethral, perineal or a combination. There are no criteria for the location of the pain, the severity of the pain or the character of the pain except, that it must be chronic in nature and have no other obvious cause.

Porru et. Al rported that of 30 female patients with IC according to NIDDK criteria, 18 presented with bacterial cystitis (culture positive). No patients had simultaneous onset of urgency/frequency, nocturia and pain. Seventy per cent of patients had only one symptom at onset, and 11 months was the mean time from the onset of first symptom to all symptoms were present. Initial diagnosis was urgency/frequency in 27% of patients and pain in 13% of patients [126].

The diagnosis of IC/PBS is a clinical one, based on symptomatology and exclusion. There is no evidence to qualify or quantify the symptoms of IC/PBS to include or exclude patients from the diagnosis of IC/PBS.

5. CYSTOSCOPY

The classic cystoscopic picture of IC 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 [127]. Since then glomerulations, described as punctate petechial hemorrhages and observed after hydrodistension to70 – 80 cm of water for 1 – 3 minutes, have become the primary cystoscopic feature of IC [87]. But not all patients with symptoms of IC/PBS have glomerulations [88;99;60] and not all patients with glomerulations have symptoms of IC/PBS [128;76,129]. *Neither presence nor severity of glomerulations correlate with any of the primary symptoms of IC/PBS [81], although, the presence of a Hunner's ulcer is significantly associated with bodily pain and urinary urgency [128].* Even more frustrating is the fact, that the finding of a Hunner's ulcer or glomerulations seems very subjective. No clear definition exists of these entities. Some researchers find a Hunner's ulcer in 50% of their IC patients, while others hardly ever see it [130]. Attempts have been made to score the cystoscopic images of glomerulations and bleeding seen during cystoscopy [76]

0 representing no glomerulations or only those in regions that could be induced by scope trauma, 1+ = fewer than 3 to 5 glomerulations per cystoscopic field with the scope held approximately 1 cm. From the bladder wall in focal areas only, 2+ = more diffusely distributed glomerulations of this intensity or focally distributed collections of greater number of glomerulations, 3+ = more densely dispersed [over 5 glomerulations per cystoscopic field] involving most of the bladder [128] or 5 grades: 0 = normal mucosa, I = petechiae in at least two quadrants, II =

*large submocasal bleeding (ecchymosis), III = diffuse global mucosal bleeding, IV = mucosal disruption, with or without bleeding/oedema [*2].

One might assume that such different classification systems might reflect huge differences in reported findings of the presence or absence of glomerulations during cystoscopy. No inter- or intra-individual variation in cystoscopic classification of these findings has ever been reported. Bladder capacity during hydrodistension has not drawn much attention although it is strongly associated with increased urgency [128].

Cystoscopic findings of Hunner's ulcer and glomerulations are not well described and classified. Both might be found in patients without IC/PBS, and be absent in patients classified by experienced researchers as having IC/PBS . Diagnostic sensitivity and specificity cannot be given since no clear definition of the disease exists. The fact that cystoscopic findings are not diagnostic for IC/PBS does not necessarily mean that stratification of patients according to cystoscopic findings might not be important for effect of treatment and disease prognosis. Research into this is strongly needed.

6. PATHOLOGY

Pathological changes in light microscopic and electron microscopic features in patients with IC 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 pathognomic findings on biopsy in terms of diagnosis [81].

7. POTASSIUM TEST

Christopher Payne recently reviewed this test for the 2003 National Institutes of Health / Interstitial Cystitis Association meeting in Washington.

The potassium sensitivity test (PST) was introduced by Parsons et. al [131] and has been examined clinically in a number of papers by Parsons and other investigators. The test is an office-based examination in which solutions of sterile water and 0.4N KCl are sequentially instilled into the bladder and the subject asked to rate the degree of urge and pain produced by the instillation. Water is used as a control to help

account for those patients with extreme volume sensitivity. For the purposes of this literature review Parsons' paper from Techniques in Urology [132] will be taken as the "correct" procedure for performing and interpreting the test, although not all papers followed this exactly. The technique elicits responses to 40cc of plain water or 40cc of potassium chloride solution (40mEq per 100cc of water). The subjects are asked to rate their subjective responses on a scale of 0-5 (0=no change from baseline, 5= severe pain or urgency) 3-5 minutes after instillation of each solution and told to compare the two. A test is considered to be negative when neither water nor potassium provokes any symptoms. A test is considered positive if the individual has no response to water (volume sensitivity) and a 2 or greater response to the potassium for pain **or** urgency. If the patient is extremely volume sensitive to water but recognizes a substantial difference when the potassium is instilled, this is considered a positive test. If such a patient does not recognize a difference between the two solutions then the test is indeterminate, not negative. The hypothesis is that the potassium ions may be abnormally absorbed through the IC urothelium. The potassium will then stimulate sensory nerves in the submucosa producing painful urgency. This might be used to identify IC as the cause of pelvic pain and to direct therapy toward the urothelium. It is attractive because, in the absence of a biologic marker, it is simple and inexpensive, especially when compared to other proposed diagnostic tools (urodynamics and cystoscopy/bladder distension/biopsy). Because of this, the PST is in fairly common use in the United States as a primary diagnostic tool for IC. *However, it must be clear that what is actually being assessed is sensitivity, not permeability. Increased sensitivity could be due to increased permeability or to increased responsiveness at the nerve terminals (a positive PST may turn out to be a generalized marker for hyperesthesia).* In addition, the simple effect of a second fill with water could be significant. It has been shown that repetitive distension of bowel in Irritable Bowel Syndrome (IBS) patients becomes progressively more painful [133]. To date this differentiation between sensitivity to a second distension and the potassium solution itself has not been investigated.

• PST in the Diagnosis of IC—

Only one relatively small study has prospectively examined using the PST in a group of undiagnosed patients [134]. The entry criteria are not defined other than "39 consecutive patients attending our cli-

nic . . . who had symptoms consistent with IC". The test was not performed exactly as described by Parsons; the scale used to rate pain was symmetrical and allowed for the possibility that pain would be decreased by an instillation. All patients then underwent bladder distension under anaesthesia, which was considered to be the gold standard. In the population as a whole the probability of IC being diagnosed by cystoscopy was 59%. The probability of a positive cystoscopy increased to only 66% after a positive potassium test. Conversely, a negative PST in patients suspected of having IC clinically only reduced the probability of a diagnosis of IC from 59% to 46%. The authors conclude that a positive PST "added no useful information" and a negative PST "would not be useful in making clinical decisions". This type of study would be very useful if a larger number of patients were enrolled and followed for a longer period of time in order to determine the ultimate diagnosis and outcome of the patients as there is no true "gold standard" in the diagnosis of IC at this time. A retrospective study of this type has been reported including 189 patients [135]. These authors used the PST along with urodynamics, cystoscopy and biopsy and correlated the test results with response to therapy. The authors found that PST did not correlate with symptoms or cystoscopic findings. The power of the study is limited by its retrospective nature and the fact that not all patients had all tests. Similarly, Chen [136] did not find a correlation in a prospective assessment of PST comparing symptomatology, cystoscopy and biopsy in the diagnosis of IC. In fact, they found higher pain scores with PST to be associated with a greater maximum bladder capacity. Although this suggests that PST does not predict results of bladder distension, it is not adequate to conclude that PST is not a good diagnostic test for IC.

A diagnostic test need not be perfectly accurate to be useful; however, in order to recommend a test be used in the diagnosis (as opposed to screening) for a condition it should:

• have a high enough sensitivity so that patients can be effectively screened for the presence of disease

and

• have a high positive predictive value so that even if some patients are not identified by the test the clinician can have confidence that those identified actually have the disease in question

At this time the committee concludes that there is inadequate data to recommend using the PST for

diagnosis as neither of these criteria is established. There is a large body of data that is beginning to define how the test performs in different populations of patients. Many investigators have examined the PST in patients diagnosed with IC, usually by strict NIDDK criteria (**Table 1**). Approximately 75-80% of these IC patients test positive. This is not an encouraging figure since the NIDDK criteria are widely criticized as being too strict so one would hope that a new test would do a better job of identifying these classic patients. Several authors have studied the PST in asymptomatic controls (**Table 2)** and these subjects rarely have any response. Comparing results between NIDDK diagnosed patients and normal controls is not clinically helpful and cannot be used to predict a similar positive predictive value when the test is used in a broad spectrum of patients with symptoms including pelvic pain and/or urinary frequency [137].

The critical issue in defining the utility of the PST is determining how it performs in patients with lower urinary tract symptoms and/or pelvic pain that are not due to interstitial cystitis. Studies that report results of PST in patients with other conditions are summarized in **Table 3**. The PST seems to be appropriately negative in many other urologic conditions but there is a significant rate of positive results in conditions that could be confounding in the diagnosis of IC including overactive bladder and urinary infections. Of more concern, 85% of gynaecologic patients with pelvic pain [138,139] and 84% of prostatitis patients tested positive with the PST [140]. While it is certainly possible that many of these subjects actually had undiagnosed IC, an alternative explanation is that any chronic pain syndrome can increase pain response in other areas in the body. The fact that the PST tends to be positive in painful pelvic conditions may be a sign of central sensitisation of pelvic sensory pathways. In any case, these data suggest that the specificity of the PST may be rather low, precluding use of the test in diagnosis.

It should be noted that the PST is not an intrinsically physiologic test; the concentration of potassium employed (400meq/l) far exceeds typical urinary potassium concentrations of 40-80meq/l depending upon dietary intake [141].

1. **The PST assesses sensitivity to intravesical instillation of potassium. The concentration used is pharmacological, not physiological. A positive test may indicate increased permeability of the urothelium to potassium, increased acuity of response of the bladder nerves, or a combination of the two. The simple effect of a second instillation has not been studied.**

2. **Efforts to use the PST in the diagnosis of IC, although methodologically flawed, have been unsuccessful to date. The PST cannot be recommended for general use as a diagnostic tool for IC at this time as neither a high sensitivity or specificity has been established.**

8. URODYNAMICS

The NIDDK criteria excluded patients with detrusor overactivity at filling cystometry in order not to confuse the picture in clinical trials. This does however not mean, that detrusor hyperactivity does not co-exist with IC/PBS. *In the Interstitial Cystitis database approximately 14% of IC/PBS patients had overactive detrusors [4]*. Whether these patients respond better to anticholinergics than IC/PBS patients with stable bladders has never been investigated, which otherwise would be the rationale to do a filling cystometry in these patients. In males infravesical obstruction might be a differential diagnosis and it is recommended to do flowmetry in all males and pressure-flow studies in men with a peak flow rate below 20 ml/s[2]. There are no data to support this recommendation.

There are no data to support or refute the use of urodynamics in patients with IC/PBS.

Studies should be undertaken to see if the presence of detrusor hyperactivity makes a clinical difference, and in males to find the prevalence of bladder outlet obstruction (BOO) in male patients with symptoms of IC/PBS and the influence of treating BOO on these symptoms.

Table 1. PST in IC Patients

Author	Year	Condition	# Tested	# Positive	% Positive
Chambers	1999 [134]	IC	231	173	75
Chambers	1999 [142]	IC^	39	24	62
Daha	2003 [143]	IC, 0.4M KCl	40	39	98
		IC, 0.2M KCL (mild-mod pain)	40	7	18
Forrest	2001 [144]	IC, all men	8	7	88
Gregoire	2002 [135]	IC, 173F & 16M	127	105	83
Kuo	2001 [145]	IC, all female	40	40	100
		IC after intravesical heparin instillation	40	20*	50
Kuo	2003 [146]	IC with >350cc bladder capacity	196	138	70
Parsons	1994 [147]	IC	33	23	70
Parsons	1998 [148]	IC	231	174	75
Parsons	2001 [149]	IC (women & men)	466	362	78
Parsons	2001 [77,138]	IC	4	4	100
Parsons	2002 [139]	IC	213	172	81
Parsons	2002 [150]	IC, Enrolled in PPS trial^	377	302	80
Payne	1996 [151]	IC	20	18	90
Payne	2001 [152]	IC, all women	16	11	69
Teichman	1997 [153]	IC, Bladder Related Pain (BRP)	17	16	94
		IC, Non Bladder Related Pain	13	6	46
		IC, BRP after lidocaine			22
		IC, NBRP after lidocaine			9
Teichman	1999 [154]	IC	38	23	61

BRP=bladder related pain, NBRP=non bladder related pain 7positive & 13 improved
^ PST not performed as described by Parsons, 1994

Table 2. PST in Controls

Author	Year	Population	# Tested	# Positive	% Positive
Chambers	1999 [134]	Normal Subjects	41	2	5
Daha	2003 [143]	No SUI or Sxs of IC 33F, 5M	38	0	0
Parsons	1994 [131]	Paid Volunteers, No GU Hx	22	3	14
Parsons	1998 [148]	Normal Subjects	41	2	5
Parsons	2001 [149]	Normal Females, No GU Sxs	42	0	0
Parsons	2002c [139]	Gynecologic Pts, No GU Sxs	48	0	0
Parsons	2002 [77]	Gynecologic Pts, No GU Sxs	47	0	0
Teichman	1997 [153]	Stress Incontinent Females	13	2	15
		SUI Females after Lidocaine		1	9

Table 3. PST in Patients with Other Conditions

Author	Year	Condition	# Tested	# Positive	% Positive
Bernie	2001 [155]	LUTS526M, 25F w/ urgency, frequency or incont	551	89	16
Parsons	1994 [147]	Radiation Cystitis	4	4	100
		IC, in remission	11	2	18
Parsons	1998 [148]	BPH	29	1	3
		Chronic UTI	5	0	0
		Acute UTI	4	4	100
		Detrusor Instability	16	4	25
		Normal Controls before Protamine	19	3	16
		Normal Controls after Protamine	19	19	100
		Normal Controls after Heparin Reversal	19	10	53
Parsons	2001 [149]	Urethral Syndrome (early IC?)	116	64	55
Parsons	2002 [77]	Gyn Pts with Pelvic Pain (includes all initial dx below)	244(134)	197(114)	81(85)
		~Pelvic Pain	93(50)	71(41)	76(82)
		~Vulvar vestibulitis/vulvodynia	45(33)	37(26)	82(79)
		~Endometriosis	22(14)	19(12)	86(86)
		~Yeast vaginitis	7(6)	6(5)	86(83)
		~Dyspareunia	28(11)	25(10)	89(91)
		~Recurrent UTI (UTI)	15(10)	12(9)	80(90)
		~Urgency-frequency syndrome	24	18	75
		~Other*	6	5	83
Parsons	2002 [140]	Prostatitis/Chronic Pelvic Pain Syndrome	44	37	84
Parsons	2002 [139]	Pelvic Pain	121	91	75
Yilmaz	2004 [137]	Prostatitis/Chronic Pelvic Pain syndrome	40	20	50

' 110 Pts added to 2001 study & 47 controls*other=urethral syndrome, detrusor instability, pelvic floor dysfunction, urinary incontinence, urgency-frequency syndrome included in 2001 study only

9. BIOMARKERS OF INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME

a) Introduction:

The lack of universally accepted clinical diagnostic criteria for IC/PBS 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, etc., 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 is essential for the establishment of reproducible diagnostic criteria for IC/PBS and also for monitoring the effects of treatment.

b) Criteria for Biomarker Selection

A biomarker for any disease needs to demonstrate high sensitivity (i.e. present in a high percentage of patients with the disease) and high specificity (i.e. not highly present in patients who do not have the disease). In addition, the marker assay needs to be reproducible in many labs and ideally; the marker assay should be suitable for use in a clinical diagnostic laboratory.

c) Candidate Biomarkers

Almost all of the published studies on biomarkers for IC have been on biomarkers isolated from urine. Erickson et. al [156] has published an excellent review of the current state of knowledge of urine markers for IC. The most thoroughly investigated marker is known as antiproliferative factor (APF). This factor has been identified and characterized by Dr. Susan Keay and her colleagues at the University of Maryland [157, 158]. Control subjects for this study included patients with bacterial cystitis, asymptomatic, and vulvovaginitis. Further studies

demonstrated that APF is found in urine from the bladder and not from the renal pelvis [159]. Treatment of symptomatic IC by either hydrodistenstion or neurostimulation normalized the APF levels concurrent with symptom relief [160,161]. It is not known if other forms of treatment will affect APF levels. Preliminary studies in 58 women with documented IC demonstrated a sensitivity value of 91.4% and a sensitivity of 90.6% [162]. A later study with 219 symptomatic IC patients and 325 controls with and without other urological disorders documented the sensitivity as 94% and the specificity at 95% [163].APF has been isolated from urine and found to be a heat-stable, low molecular weight , trypsin-sensitive protein that inhibits bladder cell proliferation [157]. Keay et al have suggested that APF might inhibit cell proliferation by the downregulation of genes that stimulate cell proliferation along with the upregulation of genes that inhibit cell growth [19]. *APF appears to be an ideal candidate for a biomarker for symptomatic IC.* There need to be additional studies to determine if can serve as an IC marker for IC patients in symptom remission and for those who have not yet become symptomatic. The findings on symptomatic patients need to be replicated in other laboratories and the assay has to be developed for use in a clinical laboratory before it becomes a standard clinical biomarker.

GP-51 is a glycoprotein present in the both the transitional epithelium and urine of humans and other mammals. Moskowitz et. al [164]has shown that bladder biopsies of IC patients had decreased staining for GP-51. The same laboratory also demonstrated that although GP-51 demonstrates a high specificity for IC it is not as sensitive as APF [165] (i.e., there are many IC patients who do not demonstrate the presence of the marker). This suggests that it is not as accurate a biomarker for IC as APF. This could be due to the small sample population tested. There would need to be further studies in a larger patient population before this could be validated as a potential biomarker for IC.

There have also been many published studies on heparin-binding epidermal growth factor-like growth factor (HB-EGF) [18,160,161,163,166]. 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 solely as a biomarker for IC.

There are other potential biomarkers for IC which have not been well characterized and for which the sensitivity / specificity values for IC have not been studied [167]. Additional studies are needed to determine their specificity as an IC marker.

d) Conclusion

Antiproliferative Factor is emerging as the best candidate for a biomarker for symptomatic IC. The findings, however, need to be replicated in numerous independent laboratories worldwide.

VI. CLINICAL SYMPTOM SCALES

Symptom scales have potential utility in interstitial cystitis / painful bladder syndrome. They may eventually be developed in such a way that they may aid in the diagnosis of the syndrome. Ideally, a brief questionnaire that reliably segregated IC/PBS from other urologic disorders would not only make diagnosis inexpensive and readily available to all health care providers, but would also aid in epidemiologic studies in determination of the true incidence, prevalence, and natural history of the disease. Questionnaires and symptom scales can also be utilized to measure treatment outcome using a tool that can be utilized in developing new treatment strategies and therapies for IC patients. A recent "expert opinion" level review concluded that further study of all questionnaires is indicated and that no firm conclusions about any of these goals can be made at the present time [168].

There are only three published IC symptom questionnaires: the University of Wisconsin IC Scale, the O'Leary-Sant IC Symptom Index and IC Problem Index, and the Pelvic Pain and Urgency/Frequency (PUF) Scale.

The University of Wisconsin IC Scale [79,80] has not been published in intact form for a reader to use, nor has evidence-based data been collected to demonstrate its validity in identifying and diagnosing IC patients. A version has been posted on the internet and is shown in **table 4** [169]. Unlike the other two symptom questionnaires, the Wisconsin scale addresses some quality-of-life issues, and this makes its utility promising, especially when the study being undertaken wishes to address these issues. The most attractive features of the UW-IC Scale are its clinically apparent face validity, and its ease of implementation [80].

The O'Leary-Sant indexes (**Tables 5 and 6**) are a validated questionnaire that was originally developed by focus groups, subjected to test-retest reliabi-

Table 4. The University of Wisconsin IC Scale

data	enter								Citations with documentation. 14.29.01	
									Sriram & Svirbely 2000	
Are you evaluating a woman with interstitial cystitis? (Y or N)	Y :-):-):-)									
enter an "x" in the appropriate column for each symptom based how much you have experienced it today (give only 1 answer per row)										
		not at all	minimally	a little	some	a fair amount	quite a bit	a lot		
bladder pain		not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
bladder discomfort		not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
getting up at night to go to the bathroom		not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5

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	not at all	minimally	a little	some	a fair amount	quite a bit	a lot	Yes	5
going to the bathroom frequently during the day	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
urgency to urinate	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
difficulty sleeping because of bladder problems	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
burning sensation in the bladder	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
general pelvic discomfort	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
headache	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
backache	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
dizziness	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
feelings of suffocation	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5
chest pain	not at all	minimally	a little	some	a fair amount	x	a lot	Yes	5

	not at all	minimally	a little	some	a fair amount	quite a bit	a lot	Yes	5
	not at all	minimally	a little	some	a fair amount	quite a bit	a lot		
ringing in the ears	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
aches in the joints	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
swollen ankles	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
nasal congestion	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
flu symptoms	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
abdominal cramps	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
tingling in the fingers and toes	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
nausea	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
blind spots or blurred vision	not at all	minimally	a little	some	a fair amount	quite a bit / x	a lot	Yes	5
heart pounding									

	not at all	minimally	a little	some	a fair amount	quite a bit	a lot		
sore throat						x		Yes	5
coughing						x		Yes	5
calculate	**result**								
data complete?	Yes								
evaluation appropriate?	Yes	:-):-)							
UW-IC scale of cystitis symptoms	35	out of 42							
average response on cystitis scale	5.0	which is	quite a bit						
number of high-end cystitis responses	7	out of 7							
score for reference symptoms	90	out of 108							
average responses for reference symptoms	5.0	out of 6							
number of high-end reference responses	18	out of 18							

Table 5. Interstial Cystitis 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:___

Table 6. Interstitial Cystitis 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: ___

Table 7. Pelvic pain and urgency/frequency

PATIENT SYMPTOM SCALE

Patient's Name:_____   Today's date: _____

Please circle the answer that best describes how you feel for each question.

		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	Are you currently sexually active. YES _____ NO_____							
4	a. **IF YOU ARE SEXUALLY ACTIVE,** do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always			
	b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes or scrotum)?	Never	Occasionally	Usually	Always			
6	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
7	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
8	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			

SYMPTOM SCORE (1, 2a, 4a, 5, 6a, 7, 8a)	
BOTHER SCORE (2b, 4b, 6b, 8b)	
TOTAL SCORE (Symptom Score + Bother Score) = Total score ranges are from 1 to 35.	

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lity analysis, and validated via administration to IC patients and asymptomatic controls [65,66]. The questionnaire centers on three questions focused primarily on the symptoms of urgency/frequency and one on bladder-associated pain. It does not address generalized pelvic pain or symptomatology associated with sexual activity. However, this is not because these topics were not considered in 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 [170].

The questionnaire published most recently and studied in a large population of both urologic and gynecologic pelvic pain patients is the PUF questionnaire (**Table 7**) [139]. The PUF questionnaire 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 urgency, a symptom that is separate from frequency. One-third of the PUF 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 IC [139]. This makes many wary as to the utility and face-validity of the PUF [168]. A total score of 10-14 = 74% likelihood of positive PST; 15-19 = 76%; 20+ = 91% Potassium Positive. To the extent that the reliability of the potassium test is suspect, the PUF data become even less reliable.

As yet, none of the questionnaires has been shown to be of value in terms of diagnosis [171]. They are often used to follow the course of the disorder and responses to treatment, and may have value in terms of the individual patient response.

Prospective therapeutic trials of IC/PBS have used a subjective "global response" as primary endpoint. The "Patient's Overall Rating of Improvement of Symptoms" (PORIS) scale (**table 8**) was used as the primary treatment outcome measure in two early clinical trials [172,173]. A modified "Global Response Assessment" (GRA), has been used in subsequent trials sponsored by the National Institute of Diabetes, Digestive, and Kidney Diseases, and is favored because it is balanced at 0 (**table 9**) [174].

Table 8. Patient Overall Rating of Improvement of Symptoms (PORIS)

Please check the category that **BEST** describes your condition **TODAY** in **COMPARISON** to your condition **BEFORE** you started therapy.

1. Please check the category that best describes the **OVERALL CHANGE** in **PAIN** associated with your bladder since the start of therapy. (Check one)

[　　　　] Worse

[　　　　] No better (0% improvement)

[　　　　] Slightly improved (25% improvement)

[　　　　] Moderately improved (50% improvement)

[　　　　] Greatly improved (75% improvement)

[　　　　] Symptoms gone (100% improvement)

2. Please check the category below that best describes the **OVERALL CHANGE** in **URGENCY** or pressure to urinate associated with your interstitial cystitis since the start of therapy. (Check one)

[　　　　] Worse

[　　　　] No better (0% improvement)

[　　　　] Slightly improved (25% improvement)

[　　　　] Moderately improved (50% improvement)

[　　　　] Greatly improved (75% improvement)

[　　　　] Symptoms gone (100% improvement)

3. Considering your responses to items 1 and 2, please check the category below that best describes the **OVERALL CHANGE** in your interstitial cystitis **COMPARED TO BEFORE YOU STARTED** therapy. (Check one)

[　　　　] Worse

[　　　　] No better (0% improvement)

[　　　　] Slightly improved (25% improvement)

[　　　　] Moderately improved (50% improvement)

[　　　　] Greatly improved (75% improvement)

[　　　　] Symptoms gone (100% improvement)

Table 9. Global Response Assessment (GRA) [174]

-3: MARKEDLY WORSE

-2: MODERATELY WORSE

-1: SLIGHTLY WORSE

0: NO CHANGE

+1: SLIGHTLY IMPROVED

+2: MODERATELY IMPROVED

+3: MARKEDLY IMPROVED

VII. ASSESSING OUTCOMES

Tools for assessing treatment results in patients with Interstitial Cystitis

There is a complex overlap between data collection as a part of a research project and data collection for monitoring a patient's condition.

Clinical trials in Interstitial Cystitis (IC)

Designing clinical trials for IC can be a particular challenge. There is so little that is well understood about IC, that even defining the condition can be controversial. However, we should not let this challenge defeat us and when assessing the effects of a treatment, we must strive to the highest standard of research tools available to us – namely, a double blind, placebo controlled, randomised trial.

Evidenced Based Medicine in clinical practice.

Where possible the results of randomized controlled studies should be used in our decision making for the management of our IC patients and we should endeavor towards placebo controlled, double blind studies as our benchmark. Unfortunately, there are very few studies of IC that fall into that level 1 evidence category.

Propert et. al [175] in their review emphasize the risk of interpreting data from case series studies, which account for the majority of the information about treatment and IC published. They highlight the risks of selection bias, the problems of not having a placebo control and the importance of considering variability of symptoms over time. Clinically, it is also important to appreciate that even when randomised trials do reach significance, we can talk only about the 'probability of a 'percentage' response. That is, not every patient will respond and even if the patient does, the patient may only obtain a percentage improvement. Under such circumstances one has to use the best available evidence, taking into account the risk benefit ratio. Number needed to treat and number needed to harm data may be particularly helpful [176].

1. Outcome measures in research and for monitoring the clinical status

Interstitial Cystitis is a pain syndrome and as such may be assessed and monitored using standard pain medicine psychophysical assessments as well as tools aimed at the symptoms and pathological findings specifically associated with the IC syndrome. As the condition is poorly understood subjective assessments may be as useful as objective assessments (which in fact are lacking), and tools using purely descriptive components that are not rated may have a role, particularly for the individual patient.

In research dealing with a poorly defined condition such as IC, care has to be exercised when using statistical analysis to interpret the data as the data may not be a true reflection of the disease process but represent a coincidental associated finding; having said that, non-disease process data may be especially relevant to the patient [177]. Assessment of individual patients requires covering those areas the individual patient considers relevant. For instance, frequency of urination is a symptom often associated with IC. Whether, frequency is directly related to the severity of the disease process is not clear. As well as the disease process other factors unique to individual patients may play a role in determining urinary frequency. Thus, for an individual patient urinary frequency may be a relevant symptom to inquire about, but when it comes to understanding the effect of a treatment upon the disease process urinary frequency may be less relevant. This presents special challenges for those involved in IC research.

• Primary outcome measures and factors that may confound outcome

When making decisions on assessment it is important to choose early on what will be the primary outcome measure and what secondary measures will be evaluated. Expected changes in the primary outcome measure need to be known from previous studies or a pilot study. Those expected changes will form the basis for calculations on the number of patients required in both the active and placebo controlled limbs to make the paper statistically sound.

Currently the lack of universally accepted outcome measures for IC compounds the problems for resear-

ch in this area. Other factors that complicate research in this area are: a lack of agreement on duration of treatment and follow-up, carry over effects, concurrent therapy, and co-incidental medical conditions (which may be associated with IC, such as fibromyalgia). **Failure to follow an intent-to-treat model may also be an issue that results in biased results**.

2. Selection of patients for IC clinical trials.

Defining IC for clinical trials and hence selecting patients for IC clinical trials is one of the most difficult problems we face. Similarly it can be very difficult to know how to classify a patient presenting in the clinic. The NIDDK [59] inclusion criteria only demonstrated a 32% sensitivity but a 91% specificity when the data from the Interstitial Cystitis Data Base (ICDB) study was analysed [60. The taxonomy of these conditions is being reviewed [178]. Currently, for any study proposed, the most important way forward is to clearly define the inclusion and exclusion criteria

3. Placebo

It is important that placebo controls are used to separate out, where possible, the psychological aspects of any treatment from those that are truly affecting the pain syndrome. A placebo is defined as any therapy (or that component of any therapy) that is deliberately used for its non-specific psychologic or psychophysiologic effect, or that is used for its presumed specific effect on a patient, symptom, or illness, but which, unknown to patient and therapist, is without specific activity for the condition being treated [179]. The placebo effect can be very powerful, the quoted percentage of placebo responders in the population varies between 0-100% [180]. The mechanism of action of a true placebo is complex and more than one mechanism probably exists, therefore any placebo arm of treatment must be identical to the active arm and the best way to account for the placebo effect is by means of a double blind placebo trial. To be meaningful all IC clinical trials should have a placebo arm [175].

4. Regression to the mean.

Over time severe symptoms may appear to improve, a condition known as regression to the mean. This is a statistical phenomenon. In the Cystitis Data Base study [60,69,181] patients with severe pain tended to see a reduction in symptoms whilst patients with mild symptoms tended to become worse. Randomized controlled studies can reduce these phenomena.

5. Criteria for Pain Measurement.

The following criteria were published by Donald Price in 1999 [182] and should form the basis of any tool used for the measurement of pain where statistical analysis is planned.

1. Have ratio scale properties

2. Be relatively free of biases inherent in different psychophysical methods

3. Provide immediate information about the accuracy and reliability of the subjects' performance of the scaling responses

4. Be useful for both experimental and clinical pain and allow for reliable comparison between both types of Pain.

5. Be reliable and generalizable

6. Be sensitive to changes in pain intensity

7. Be simple to use for pain patients and non-pain patients in both the clinical and research settings

8. Separately assess the sensory-intensive and affective dimensions of pain.

Not every tool used for assessment in pain management fulfils the above criteria and as a consequence a number of different tools may be required. Advice about specific tools for a specific condition or research project will require input from a psychologist and statistician who should be involved early on in any project design.

a) Core outcome domains for chronic pain clinical trials: IMMPACT recommendations.

The IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) 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 are:

1. Pain

2.Physical functioning

3. Emotional functioning

4.Participant ratings of improvement and satisfaction with treatment

5. Symptoms and adverse effects, participant dispo-

sition.

b) Standard Pain Medicine Psychophysical Tools.

Standard psychophysical tools investigate the domains. Within each domain there will be a series of subset domains that may be investigated. Examples include:

- *PAIN — SEVERITY, E.G.*

  i. Current

  ii. Past week as an average

  iii. Pain score when pain is at a maximum

  iv. Pain score on average

  v. Pain score at a minimum

  vi. Pain Quality, e.g.

  vii. Measures of duration

  viii. Site and referral

  ix. Sensory perception qualities – burning, ache, shooting

  x. Threshold

  xi. Tolerance

- *PHYSICAL FUNCTIONING – behavioural e.g.*

  xii. Disability

  xiii. Solicitation

  xiv. Health care usage

- *EMOTIONAL functioning - psychosocial, e.g.*

  i. Mood / emotional affect

  ii Cognitive

  iii Coping skills

  iv Pain beliefs

- *Formats:*

The information about the various domains and subdomains can be collected from a number of sources using a number of formats. Examples include:

1. Clinical interviews
   a. Structured
   b. Unstructured
2. Self report questionnaires/scales
3. Significant other reports
4. Measures of health service usage
5. Structured observer ratings

- *Tools:*

By using the above formats a number of tools have been devised to assess the above domains.

c) Visual analog scale (VAS):

Domain: Pain

Format: Self report scale

Visual analog scales have been used in many studies and have been identified as being robust scales to use. They are easy to administer and to interpret. It is important that the anchor points are robust and clear. Anchor points that may be used are: no pain at one extreme of the scale and worst pain imaginable at the other extreme. The scale is usually a standard 10cm length, this allows direct statistical comparisons to be easily made by measurement and recording a numerical value. No other marks should appear on the scale. VAS scales may be used for least, average, current or maximum pain experienced. They are most robust when measured at the time of the experience and not when relying on memory; pain diaries incorporating VASs scales and other points of information, such as drug usage, are valuable tools. The patient should not be able to compare to previous VASs that they have completed. A number of tools exist to facilitate collecting data using VASs and include electronic scales and sliding rule scales.

VASs may be used for domains other than pain, such as mood and coping. Suitable anchor points such as no distress and severe distress would be used. Verification is less clear for such domains but they are still considered useful tools. There is also evidence that VASs can be used to consider normal sensory functions as well as pain. Three anchor points may be used in such cases, e.g., bladder feels empty … Bladder feels full, no pain … severe bladder pain [183].

Providing the anchor words are appropriate, VAS scores are theoretically continuous and have ratio scale properties. Parametric analysis can thus be undertaken 184,185]. The major disadvantage of the VAS is its assumption that pain is a unidimensional experience [186].

d) Numerical rating scales (NRS):

Domian: Pain

Format: Self report scale

This is an example of an ordinal rating scale. Patients are asked to score their pain as a number. For instance, 0-10, where 0 is no pain and 10 is the worst imaginable pain. Appropriate anchors must be used. Ordinal rating scales are easy to use. However they

are often misused. For example on the above 0-10 scale, a fall in pain score from 8 to 4 does not necessarily equate to a 50 percent reduction in pain! Equal numerical intervals are assumed but this may not be the case. The numbers are in fact showing a rank order and not a true pain score as the data is not continuous and data should be analysed with nonparametric statistics.

e) A 0-10 (11 point NRS) is as sensitive and reliable in detecting clinically significant differences as a 0-100 VAS [187].

• VERBAL RATING SCALES:

Domain: Pain

Format: self report scale

Several such scores exist. Mild, moderate severe are terms commonly used. They have little to commend their use. Melzack and Torgerson introduced the five category PPI (Present Pain Intensity) scale of Mild, discomforting, distressing, horrible and excruciating. These terms represent 'equal scale intervals and thereby provide anchors for the specification of the overall pain intensity.' The data is nonparametric[188].

f) McGill Pain Questionnaire (MPG):

Domain: Pain severity and quality, physical and emotional functioning

Format: Structured self report questionnaire

The MPQ[186] is a tool that has been much used and reviewed over the years[189].

The questionnaire consists of 78 words describing pain in sensory, affective and evaluative terms (the subclass'). Within each subclass the words are arranged in groups with similar qualities but different rankings. For instance tugging, pulling, and wrenching fall into one group. The patient should only choose one word in each group but as many words as they feel appropriate in each subclass. The questionnaire also includes the PPI and a list of sensory adjectives. The ranking of the words is such that the first word in each group scores 1 and the next 2 and so forth. Wrenching would thus score a 3. Totals for each of the subclass' and the total score can be calculated.

The MPQ is a well-validated and tested questionnaire and has been used as a standard tool for some 30 years. If the affective scores are high more formal psychological assessments of mood need to be undertaken. The MPQ not only assesses the quality of the pain but has diagnostic properties. The main disadvantage is that it is slow to administer and evaluate.

g) Short-form McGill Pain Questionnaire (SF-MPG):

Domain: Pain severity and quality, physical and emotional functioning

Format: Structured self report questionnaire

This was introduced in 1987.This questionnaire has 15 words divided into sensory and affective. Each word is ranked as: none, mild, moderate, severe. The SF-MPQ correlates well with other major pain rating indices and is sensitive[190].

h) Beck Depression Inventory (BDI):

Domain: Mood - depression

Format: Structured self report questionnaire

This is a highly sensitive self report questionnaire for depression. However, the questionnaire was normalized within the psychiatric population. Many of the symptoms within the depressed patient can also occur within the non-depressed pain patient, for instance interrupted sleep. Thus the cut-off point for the diagnosis of depression is different for chronic pain patients, 21 as opposed to 10 has been suggested [191].

i) Hospital anxiety and Depression Scale (HADS):

Domain: Mood - depression

Format: Structured self report questionnaire

This scale lacks some of the problems of the BDI [192].

j) Modified Zung Depression Inventory:

Domain: Mood - depression

Format: Structured self report questionnaire

This questionnaire takes into account the somatic symptoms found both in physically ill patients and those that are depressed and as a result is a good questionnaire for the chronic pain patient [193].

k) Pain Anxiety Symptoms Scale:

Domain: Mood – anxiety, cognition

Format: Structured self report questionnaire

Specifically designed for pain patients and covers anxieties related to the pain. The test has been shown to be valid and consistent [194].

l) Fear of Pain Questionnaire:

Domain: Mood – fear

Format: Structured self report questionnaire

This reliable questionnaire looks at fear of severe, minor and medical pain [195].

m) Coping Strategies Questionnaire:

Domain: Mood, cognition

Format: Structured self report questionnaire

The catastrophizing subscale of this questionnaire has been demonstrated to be very useful in helping predict who will do poorly in treatment. Those that catastrophize predictably do badly [196,197].

n) Short form 36 of Medical Outcomes Study (SF36):

Domain: Physical functioning, psychosocial

Format: Structured self report questionnaire

This questionnaire covers physical functioning as well as mental health, emotional and social functioning. There are age sex normal references[198].

o) Sickness Impact Profile (SIP):

Domain: Physical functioning, psychosocial

Format: Structured self report questionnaire

Questions include: ambulation, bodily care, mobility, eating and work as well as emotion, alertness, social interaction, recreation, communication[199].

p) Multidimensional Pain Inventory (MPI):

Domain: Physical functioning, psychosocial

Format: Structured self report questionnaire

This looks more at how the pain interferes with activity and the control the patient has. It also looks at spouse response [200].

q) Pain Disability Index (PDI):

Domain: Physical functioning, psychosocial

Format: Structured self report questionnaire

Looks at self-care, home responsibilities, recreation, social activity, occupation, sexual activity [201].

r) Brief Pain Inventory (BPI):

Domain: Physical functioning, psychosocial

Format: Structured self report questionnaire

Amongst other things this questionnaire looks at pain, activity, mood and relationships [202].

IC SPECIFIC PSYCHOPHYSICAL TOOLS.

These structured self-report questionairres include the O'Leary Sant, University of Wisconsin, and PUF metrics cited above.

IC SPECIFIC TOOLS ASSESSING PATHOPHYSIOLOGY.

Unfortunately there are currently no markers for IC that correlates with the disease process[203] Similarly there are no biomarkers of pain [204]

s) Cystoscopy and urodynamics:

Bladder compliance in patients with IC is normal, but hypersensitivity to filling is present[203]. Glomerulations are non specific for IC[76,129]. The bladder was normal in 8.7% of patients undergoing cystoscopy with hydrodistension entered into the IC database[203]. Therefore, where as cystoscopy and urodynamics may be abnormal they are of little use for the assessment of progress.

SUMMARY

Currently for IC there is very little in the way of disease markers that can be used for the assessment of response to therapy. The best markers of progress are subjective questionnaires. There are at least two disease specific questionnaires that are well validated. However, the IMMPACT recommendations suggest that as well as symptom scores any future study on a pain syndrome must involve more general assessments of psycho-physical functioning. There are a number of such measures available that are well validated for chronic pain. However, there is limited experience of the use of these measures for Interstitial Cystitis. All future studies of IC must fulfil the highest standards available and should be of the placebo controlled, randomised double blind format. In view of the difficulty in defining IC, inclusion and exclusion criteria should be clearly described.

VIII. CONSERVATIVE THERAPY OF INTERSTITIAL CYSTITIS / PAINFUL BLADDER DISEASE

Once a diagnosis of painful bladder disease has been made, the next decision is whether to institute therapy or consider a course of "watchful waiting". This is a decision for which there is little data upon which to make a decision. *The natural history of this disorder, especially in patients with a recent onset of symptoms, is very poorly described, and the percentage of patients who will spontaneously improve and whose symptoms will ultimately resolve in a matter of weeks or months has not been studied or reported to date.* This question is currently being looked at in the National Institutes of Health NIDDK Interstitial Cystitis Clinical Research Network trials ongoing in the United States and Canada (UO1; DK-03-003). It was the focus of a recent epidemiology meeting [205] and will be a part of a new National Institutes of Health research study (RFA DK-04-009).

If the patient's symptoms are tolerable, and do not significantly impact quality of life, a policy of withholding treatment is reasonable. Data that treatment affects the natural history or course of the disease is lacking at this time, and an argument for the early institution of therapy cannot be supported on the basis of epidemiologic data or clinical trials to date. Patients who awaken once a night to void and have daytime frequency every 2-3 hours with minimal pain might fall into this category. Patients must be educated about the disease and understand that no treatment is likely to make them "perfect", and that any therapy is a tradeoff between the inconvenience, chronicity, and side effects associated with that treatment modality and the benefits. As with any decision in medicine, "excellence is the enemy of good".

Patient education and empowerment is an important initial step in therapy [206]. On-line databases, interactive computer programs, electronic mail lists for disabled persons, telephone hotlines, educational videos, health magazines, and public libraries enable patients to make health choices they can feel comfortable with [207]. Patients can be reassured learning that their symptoms are a part of a well-described syndrome affecting many persons, and that they do not have a life-threatening disease, or one that is likely to inevitably progress [56,57]. The Interstitial Cystitis Association [208] and its affiliated international organizations have been an important resource for patients as well as a clearing house for ideas and funding for researchers and clinicians.

1. BEHAVIORAL MODIFICATION

A voiding diary can give the patient and clinician important information with regard to disease severity, and is important if behavioral therapy is entertained. A one day voiding chart is probably as reliable an indicator of frequency as a three day voiding diary [209].

Barbalias looked at a type of bladder training as an adjunct to treatment with intravesical oxybutynin in patients with interstitial cystitis [210]. In this unblinded, randomized inpatient study, patients were catheterized and filled with gradually increasing volumes of saline (control group) or oxybutynin solution in a continuous manner while awake daily for one week, weekly for 6 weeks, and then monthly for 3 months. At the conclusion of treatment there was a modest decrease in frequency in the oxybutynin group of 15-13 voids per day vs 14.7 to 13.7 voids per day in the control group. There was a modest improvement in O'Leary-Sant symptom and problem scores in both groups at six months, and both groups had statistically significant improvement of all evaluated parameters.

Chaiken et. al [211] reported short-term behavioral therapy in 42 women consisting of diary keeping, timed voiding, controlled fluid intake, and pelvic floor muscle training. Voids per day dropped dramatically from 17 to 8, functional bladder capacity increased from 92-165cc, and 50% of patients' self-reported marked improvement. This was a highly selected and motivated group comprised of patients with primarily frequency rather than pain symptoms, who were subjected to an intense 12-week regimen of therapy with a skilled therapist. Patients who experience pain more than frequency would be unlikely to tolerate such a program, and the results are hardly generalizable.

From the above studies, one might infer that behavioral modification may have modest benefit for some IC patients, but one cannot consider the specific methodology of these studies to be generally applicable to IC/painful bladder patients, nor are the methods particularly conservative. In a simpler approach, Parsons reported success in 15 of 21 patients who had primarily frequency rather than pain, by gradually encouraging longer voiding intervals over time through voiding diary techniques

[212]. A similar study with 15 patients concluded that although average voided volume increased by 65cc after a month, the persistent sense of bladder fullness did not change from pre-intervention volumes [213].

2. Physical Therapy

Pelvic floor physical therapy is cited as effective in the management of functional urogenital and anorectal disorders [214], however there are no randomized, controlled trials in the literature attesting to its efficacy. Biofeedback and soft tissue massage may aid in muscle relaxation of the pelvic floor [213,215] A non-peer-reviewed abstract [216] reported success in 16 patients with interstitial cystitis, "high-tone pelvic floor dysfunction", and sacroiliac dysfunction treated with direct myofascial release, joint mobilization, and a home exercise program. All patients had dyspareunia, and 9 of 16 were able to resume intercourse. Frequency and suprapubic pain responded to a greater degree than urgency and nocturia in this small series. The same group had success in 9 of 10 women using transvaginal Theile massage [217]. Moldwin had 69% success rate in 16 patients treated with electromyographic biofeedback, but treatment response did not correlate to changes in muscle identification, and the placebo effect may have been considerable [213].

3. Stress Reduction

While there is no conclusive literature to show it, common sense dictates, and clinicians believe, that stress reduction, exercise, warm tub baths, and efforts by the patient to maintain a normal lifestyle all contribute to overall quality of life [218]. In a controlled study of 45 IC patients and 31 healthy controls, higher levels of stress were related to greater pain and urgency in patients with IC but not in the control group [219]. Maladaptive strategies for coping with stress may impact adversely on symptoms [220].

4. Dietary Manipulation

A majority of interstitial cystitis patients seem to have symptom exacerbation related to the intake of specific foods and beverages [70,221]. Most often, "acidic" beverages, coffee, spicy foods, and alcoholic beverages are sited. However, different patients seem to be affected to different degrees by specific foods and beverages, and it would seem prudent to advise the patient to avoid only those foods and beverages that they find make their symptoms worse. The so-called "interstitial cystitis diets" or list of "foods to avoid" **(table 10)** that are noted in articles [218] and on patient-directed web sites (ICHELP.ORG) have never been subjected to controlled clinical trials and have no scientific basis. In addition, they are largely unpalatable, and may even diminish overall quality of life.

Table 10. Interstitial cystitis association dietary recommendations Foods to Avoid

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WWW.ICHELP.ORG

Milk / Dairy Products
    Aged cheeses
    Sour cream
    Yogurt
    Chocolate

Vegetables
    Fava beans
    Lima beans
    Onions
    Tofu
    Soybeans
    Tomatoes

Fruits
    Apples
    Apricots
    Avocados
    Bananas
    Cantaloupes,
    Citrus fruits
    Cranberries
    Grapes
    Nectarines
    Peaches
    Pineapples,
    Plums
    Pomegranates
    Rhubarb
    Strawberries
    Juices from above fruits

Carbohydrates and grains
    Rye bread
    Sourdough bread

Meats and fish
    Aged, canned, cured processed, smoked meats and fish
    Anchovies
    Caviar
    Chicken livers
    Corned beef
    Meats containing nitrates or nitrites

Nuts
    Avoid most nuts

Beverages
    Alcoholic beverages including beer and wine

Carbonated drinks
Coffee
Tea
Fruit juices

Seasonings
Mayonnaise
Ketchup
Mustard
Salsa
Spicy foods (Chinese, Indian, Mexican, Thai)
Soy sauce
Miso
Salad dressing
Vinegar

Preservatives and additives
Benzol alcohol
Citric acid
Monosodium glutamate
Artificial sweeteners
Preservatives
Artificial ingredients
Food coloring

Miscellaneous
Tobacco
Caffeine
Diet pills
Junk foods
Recreational drugs
Allergy medications with ephedrine or pseudoephedrine
Certain vitamins

A small, placebo-controlled dietary study [222] never published or printed in a peer review journal failed to demonstrate a relationship between diet and symptoms. Bade et. al studied the dietary habits of IC patients in The Netherlands, and found that patients tended to have a healthier daily diet than the general population and consumed less coffee, but no other general dietary or fluid intake changes were found [223]. Nguan et. al [224] studied the effects of altering intravesical pH on the symptoms of IC in a prospective, double blind, randomized cross over study, placing either acidic saline solution (pH 5.0) and a neutral buffered saline solution (pH 7.5) in the bladder by catheter. There was no change in pain or other symptom parameters. The fact that many patients avoid orange and grapefruit juices, despite the fact that they actually tend to increase urine pH [225], attests to either the influence of the IC diet recommendations or the likelihood that an effect other than that on pH is responsible for their effect on symptoms.

IX. ORAL THERAPY OF INTERSTITIAL CYSTITIS / PAINFUL BLADDER DISEASE

The number of therapies (encompassing oral, intravesical, behavioral, parenteral, and surgical modalities) that have been used in an attempt to alleviate the symptoms of interstitial cystitis / painful bladder syndrome almost defies enumeration. **(see tables 11 and 12 for listing and Oxford levels)** Many have been announced with great fanfare and incredible success rates, yet relatively few are in common use today. What is the problem that has led to this virtual cornucopia of discarded, promising-looking treatments?

Interstitial cystitis / painful bladder syndrome is an extremely difficult condition in which to follow results of therapy. The disease tends to wax and wane in severity over time, and up to 50% of patients may experience temporary remissions unrelated to therapy for an average duration of 8 months [57]. As primarily a symptom complex with as yet no diagnostic marker or pathognomonic feature, the diagnosis depends on the patient's perception of their symptoms, the ability of the patient to communicate this to their physician, and the proper interpretation of the physician.

There are several concepts one must be aware of when interpreting clinical trials of this syndrome. Do the entry criteria tend to select for the more severe cases? While the NIDDK criteria have been successful in selecting out a well-defined group of patients that all researchers can agree have IC [60], by definition they select out patients with symptom duration greater than 9 months and with symptoms severe enough to warrant invasive testing. ***Thus, the concept of "regression to the mean" becomes important in analyzing results of even well constructed, randomized clinical trials [226].*** Small, statistically significant improvements might reflect nothing more than the tendency for severe patients to note symptomatic improvement, as their symptom severity tends to regress to the mean. Patients with low levels of symptoms who would tend to get worse are not included in the study.

Bias is another, often hidden factor in trials. Unconscious bias can occur, either in the assignment of patients to a particular treatment group or in the assessment of responses [227]. Randomized prospective double-blind studies virtually eliminate this

Table 11. Some of the oral medications that have been used for treatment of interstitial cystitis [203,300]

Drug	RCT	% Success
Amitriptyline; tricyclic antidepressants [253,301 254,255]	yes	42%
Antibiotic regimens [279,281,302]	yes	48%
Anticholinergics and antispasmodics [181,269,303,304]	no	anecdotal
Azathioprine [305]	no	50%
Benzydamine [306,307]	yes	0%
Chloroquine derivatives [305]	no	50%
Cimetidine [267,269-271]	yes	65%
Cortisone308 and other steroids [304,309,309]	no	80%
Cyclosporine [286, 287]	no	90%
Doxycycline [280]	no	71%
Gapapentin [310,311]	no	anecdotal
Hormones [309,312]	no	anecdotal
Hydroxyzine [174,264]	yes	31%
L-Arginine [275,276]	yes	not effective
Methotrexate [282,313]	no	50%
Misoprostgil [285]	no	48%
Montellukast [283]	no	90%
Nalmefene [235]	yes	not effective
Narcotic analgesics [297,314,315]	no	anecdotal
Nifedipine [316]	no	87%
phenazopyridine [181]	no	anecdotal
Quercetin [278]	no	92%
Sodium pentosanpolysulfate	yes	33%
Suplatast tosilate [277,317]	no	86%
Vitamin E [318]	no	anecdotal

Table 12. Conservative Management and Oral Medications Used In the Treatment Of Interstitial Cystitis: Assessments according to the Oxford System

	Level of Evidence	Grade of Recommendation
Behavioral Modification	5	D
Dietary Manipulation	5	D
Sodium Pentosanpolysulfate	1	**-C**
Amitriptyline	2	B
Hydroxyzine	1	D
Cimetidine	4	D
L-Arginine	**-1**	**-A**
IPD-1151T	4	not available, testing pending
Quercetin	4	D
Antibiotics	4	**- C**
Methotrexate	4	D
Montelukast	4	D
Nifedipine	4	D
Misoprostol	4	D
Cyclosporine	4	C
Analgesics	5	C

potential problem, and in those that are not, individuals other than those who assigned the patients must do assessments [228]. Another bias occurs when the author has a financial interest in the company or its competitors. At times, the full extent of such an interest is not made clear. With more and more randomized trials funded by pharmaceutical companies, knowledge of this "built-in" bias is critical for those interpreting the results [229].

Is there a placebo control? *High rates of unsustainable good outcomes can be related to a combination of the natural history of the disease, regression to the mean, and the placebo effect.* The powerful force exerted when a physician and patient both believe a treatment is effective cannot be underestimated. In a pain syndrome, nonspecific effects of treatment tend to be underestimated, and patient improvement is likely regardless of treatment. It cannot be assumed that a treatment whose response rate is more than one third is better than placebo [230]. This is not to denigrate the positive benefits of the placebo-effect, also termed "remembered wellness" [231]. The placebo effect is crucial in the treatment of pain, having a physiologic counterpart in decreasing brain activity in pain-sensitive brain regions

including the thalamus, insula, and anterior cingulate cortex [232]. The placebo effect is virtually free, requiring only the time investment of the physician and patient. One would not want to use an agent with its accompanying expense and potential risk of adverse events, in the absence of knowledge that the effect is in addition to any placebo effect and not masked by it.

If we had an agreed-upon, effective treatment for IC, that would be the standard against which to measure new treatments. Lacking that, it would seem that placebo controlled trials are not only ethical, but also mandatory in making clinical judgments on the value of new therapies. Recent decisions by pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for IC [233,234] like low concentration hyaluronic acid (Bioniche, Canada), a high concentration hyaluronic acid (SKK, Tokyo), resiniferatoxin (ICOS, Bothell, Washington USA), as well as the oral treatment Nalmefene [235] (IVAX, Miami, Florida USA) illustrate the need to confirm efficacy with placebo-controlled randomized trials. As will be evident, 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 Institutes of Health [175,175].

1. SODIUM PENTOSANPOLYSULFATE

Parson's suggestion that a defect in the epithelial permeability barrier, the glycosaminoglycan (GAG) layer, contributes to the pathogenesis of IC [236] has lead to an attempt to correct such a defect with the synthetic sulfated polysaccharide sodium pentosanpolysulfate [237](PPS), a heparin analogue available in an oral formulation, 3-6% of which is excreted into the urine. It is sold under the trade name Elmiron®. The approved dosage is 100mg three times daily. Oral bioavailability in serum of a 1500mg dose in healthy male volunteers looking at primary and secondary effect parameters was negligible [238]. It's mechanism of action in interstitial cystitis has been attributed not only to correction of a putative defect in the naturally occurring GAG layer, but also its ability to inhibit histamine release from connective tissue and mucosal mast cells [239], 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 [240].

PPS is without a doubt the most intensively studied treatment ever proposed for interstitial cystitis. It is the only medication approved by the Food and Administration for the pain of interstitial cystitis [241]. Parsons initially administered the drug at a dosage of 50mg 4 times daily or 150mg twice daily in an open trial involving 24 patients [242]. 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 75 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. Patients who improved showed improvement in 5-10 weeks.

Fritjofsson et. al studied 87 patients in an open, controlled, multicenter trial at a dose of 400mg twice daily for 6 months [243]. Fifty-eight per cent of patients responded favorably with diminution of pain within only 4 weeks. Bladder capacity was not altered by treatment. There was a 25% decrease in frequency in the non-ulcer group only.

Holm-bentzen et. al [245] reported a very elegant multicenter double-blind placebo controlled trial in 1987 looking at 115 patients with painful bladder disease. 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 [172]. A total of 110 patients in 5 medical centers were studied for 3 months on a dosage of 100mg three times daily. *This was the first study where overall subjective global improvement as determined by the patient was a primary criteria of efficacy.* 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 [173]. In a multi-center, 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 [174]. 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 nonsignificant 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. A subsequent industry-sponsored trial [245]showed no dose-related efficacy response in the range of 300mg to 900mg daily, however adverse events *were* dose-related.

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 [246]. 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. A study by Jepson et. al [247] on the compassionate use population reported a response rate of between 6.2% and 18.7% in 97 patients who enrolled in the program between 1987 and 1995.

Elmiron® appears to be a very well-tolerated medication [246] 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 interstitial cystitis should be regarded with caution.

2. AMITRIPTYLINE AND THE TRICYCLIC ANTIDEPRESSANTS

A report of an anecdotal case [248]in which a psychiatric patient placed on amitriptyline for depression experienced resolution of her symptoms of interstitial cystitis encouraged physicians to try this medication for the relief of interstitial cystitis symptoms. It quickly became one of the most commonly used, though least studied, treatments for the disease [181]. 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 [249], 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 side effects. Kirkemo et. al [250] treated 30 patients and 90% had subjective improvement in 8 weeks. Pranikoff and Constantino [251] 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. Desipramine and doxepin have also been used with success [252,253].

The only prospective, double-blind, placebo-controlled RCT was reported in 2004 at the American Urological Association meeting [254,255]. Fifty patients were randomized to placebo or a titrated dose of amitriptyline up to 100mg daily. One patient from each group dropped out do to side effects. 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.

It is well known that amitriptyline has proven analgesic efficacy with a median preferred dose of 75mg in a range of 25-150mg daily [256-258]. This range is lower than the 150-300mg traditionally used for depression. The mechanism of action for pain relief is unknown, but does not appear to be related to changes in mood [259]. Analgesia may be related to inhibition of synaptic re-uptake of serotonin or norepinephrine, thus inhibiting nociception by actions at the spinal cord, brain stem, or thalamic sites. As the strongest H_1 receptor antagonist of the tricyclic class, amitriptyline may help in stabilizing mast cells and inhibiting mediator stimulated vascular leakage. Its nighttime sedation can be therapeutic in the IC population as well as its purported beta receptor stimulation in the bladder which can increase bladder capacity [260].

While *amitriptyline seems to be very useful for the symptoms of interstitial cystitis,* it has never been appropriately studied in a large, multicenter RCT. It is unlikely that a pharmaceutical company would undertake this expensive task for a generic drug. Thus, there is a great need for a government-sponsored trial to ascertain the true efficacy of amitriptyline in this difficult to study disorder, and its proper place in the treatment algorithm.

3. HYDROXYZINE

The ability of hydroxyzine, an H-1 receptor antagonist, to inhibit bladder mast cell activation by neurogenic stimuli, along with its anticholinergic, angiolytic, and analgesic have made it a reasonable candidate for use as a therapeutic agent for interstitial cystitis [261]. Simmons first proposed use of antihistamines in 1955 [262]. His findings of mast cells in the wall of a normal bladder and the edema and increa-

sed 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 [263].

Theoharides popularized the use of hydroxyzine at a dose of 50mg before bed with or without 25mg in the afternoon. He reported on 13 patients and stated that "most" had a 75% decrease in frequency and nocturia, increased sleep, and significant reduction in burning and pain [264]. A subsequent study of 40 patients showed benefit in 37 in virtually all parameters studied [265]. A third open label study of 140 patients included 65% who returned case-report forms. Of these, there was a 40% reduction in symptom scores, but the true response rate is difficult to discern [266]. Such optimistic reports led to inclusion of hydroxyzine in the NIDDK trial with PPS mentioned previously [174]. 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 reached statistical significance.

Hydroxyzine may have a beneficial effect in a small proportion of IC patients, but larger trials would be necessary to determine whether this effect is real. At this point its use rests on theoretical benefits and anecdotal reports.

4. CIMETIDINE

The H2 histamine receptor antagonist cimetidine has been explored for use in interstitial cystitis. In a pilot study [267], 9 patients were treated with a dose of 300mg orally twice daily for one month. At followup 26 to 42 months later, 4 patients had complete relief of frequency, dysuria, nocturia, and suprapubic pain. Lewi [268] 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 [269] 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 400mg twice daily or placebo [270]. Median suprapubic pain and frequency scores improved significantly, but the publication does not state exactly how many patients in each group improved. No histologic changes in bladder biopsies were apparent in responders as compared to the placebo group. A cli-

nical-pathological study in 8 cimetidine responders could find no antihistaminic effect on patients with painful bladder syndrome and concluded that the presence of excess histamine in the form of increased mast cell numbers does not explain the beneficial effects of cimetidine [271].

These initial studies on cimetidine are encouraging, but a large RCT is needed to determine whether the efficacy suggested is real. The lack of any histopathological correlation with improvement or compelling theory to explain its benefits is puzzling. In addition, the drug has not found wide acceptance in the IC population despite its being widely available over-the-counter in most countries.

5. L-ARGININE

Foster and Weiss were the original proponents of L-arginine in the therapy of interstitial cystitis [272]. Nitric oxide synthase (NOS) activity is elevated in patients with urinary infection and thought to play a role in the bladder's response to infection and in the inflammatory response that follows infection. They measured urinary NOS activity in 14 IC patients and 22 non-infected asymptomatic female controls. NOS activity was significantly reduced in the IC patients, and cyclic GMP levels paralleled the NOS activity in both IC patients and controls. Eight patients with IC were given 500mg of L-arginine 3 times daily. After one month, urinary NOS 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 [273].

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 [274]. A placebo-controlled RCT of 53 IC patients could find no difference on an intention to treat analysis between drug and placebo-treated patients [275]. 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 [276].

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

6. IPD-1151T

Suplatast Tosilate (IPD-1151T) is a new 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 [277]. 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. Eight of the 14 patients had associated allergic conditions, which might explain some of the findings. Further tests are planned including a larger, multicenter RCT.

7. QUERCETIN

Quercetin, a bioflavenoid available in many over-the-counter products, may have the antiinflammatory effects of other members of this class of compounds found in fruits, vegetables, and some spices. Katske et. al [278] administered 500mg twice daily to 22 IC 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.

8. ANTIBIOTICS

Warren et. al [279] 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 interstitial cystitis 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 is reported.

Burkhard et. al [280] 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 painful bladder syndrome we are focusing on. Nevertheless, he recommended empiric doxycycline in this group. The overwhelming majority of PBS 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 interstitial cystitis in the absence of a culture-documented infection*. [281]

9. METHOTREXATE

Low dose oral methotrexate significantly improved bladder pain in 4 of 9 women with interstitial cystitis, but did not change urinary frequency, maximum voided volume, or mean voided volume [282]. No placebo-controlled, RCT has been done with this agent.

10. MONTELUKAST

Mast cell triggering releases 2 types of proinflammatory mediators, including granule stored pre-formed types such as heparin and histamine, and newly synthesized 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 [283], 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.

11. NIFEDIPINE

The calcium channel antagonist nifedipine inhibits smooth muscle contraction and cell-mediated immunity. In a pilot study [284], 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.

12. MISOPROSTOL

The oral prostaglandin analogue misoprostol was studied in 25 patients at a dose of 600 micrograms daily [285]. At 3 months 14 patients were signifi-

cantly improved, and at 6 months 12 patients still had a response. A cytoprotective action in the urinary bladder was postulated.

13. Cyclosporine

Cyclosporine, a widely used immunosuppressive drug in organ transplantation, was the subject of one interstitial cystitis trial [286]. Eleven patients received cyclosporine for 3-6 months at an initial dose of 2.5-5mg/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, uncontrolled follow-up study, 20 of 23 refractory IC patients on low-dose therapy followed for a mean of 60.8 months (range 14-123) 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 [287]. An anecdotal response in an 8 year old child has also been noted [288].

14. Analgesics

The long-term, appropriate use of pain medications forms an integral part of the treatment of a chronic pain condition like interstitial cystitis. Most patients can be helped markedly with medical management using pain medications commonly used for chronic neuropathic pain syndromes including antidepressants, anticonvulsants, and opioids [289]. Many nonopioid analgesics including acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDS) and even antispasmodic agents [290] have a place in therapy along with agents designed to specifically treat the disorder itself. The advent of the cyclo-oxygenase-2 inhibitors may allow for safer long-term anti-inflammatory/analgesic treatment [291], but efficacy for chronic pain may be no better than that of standard NSAIDS. Unlike opiates, with increasing doses, acetaminophen aspirin, and the other NSAIDs all reach a ceiling for their maximum analgesic effect [292]. Gabapentin, introduced in 1994 as an anticonvulsant, has found efficacy in neuropathic pain disorders including diabetic neuropathy [293] and post herpetic neuralgia [294]. No studies in IC have been reported.

With the results of major surgery anything but certain, the use of long-term opioid therapy in the rare patient who has failed all forms of conservative therapy over many years may be considered. Opiates are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analgesics have failed [295,296]. As this is a difficult decision, and involves a major commitment on the part of both the patient and physician, involvement of a pain specialist is helpful. A single practitioner has to take responsibility for pain treatment and write all prescriptions for pain medications [297]. Opioids are effective for most forms of moderate and severe pain and have no ceiling effect other than that imposed by adverse events. The common side effects 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 major impediment to the proper use of these drugs when they are prescribed for long-term nonmalignant pain is the fear of addiction. Studies suggest the risk is low [298]. The long-acting narcotic formulations that result in steady levels of drug over many hours are preferable.

No studies on the long-term use of narcotics for the symptoms of interstitial cystitis have been reported to date. Nevertheless, it is important to include them in any discussion of therapy for interstitial cystitis. Chronic opioid therapy can be considered as a last resort in selected patients. It is most safely administered in the setting of a pain clinic, requiring frequent reassessment by both patient and physician [299].

X. INTRAVESICAL THERAPY

BACKGROUND

Today several drugs are available in many parts of the world for intravesical therapy for interstitial cystitis. These include dimethyl sulfoxide (DMSO), chlorpactin, hyaluronic acid, heparin, and pentosanpolysulphate (PPS). The latter three are purported to restore the glycosaminoglycan (GAG) layer.

Drugs that have been proposed for intravesical administration in interstitial cystitis, their reported efficacy, and their Oxford levels are listed in **tables 13 and 14**.

1. Resiniferatoxin (RTX)

Lazzeri´ et al. demonstrated that the prolonged intravesical instillation by in situ drug delivery system supports the efficacy of RTX in the treatment of

Table 13. Some of the intravesical medications that have been used for treatment of IC/PBS

DRUG	RCT %	SUCCESS
Silver Nitrate [312,358-360]	No	60%
Clorpactin WCS-90 [87,355,356,361]	No	60%
DMSO [341,343,345,346,348,362,363]	Yes	70%
BCG [336-338,364]	Yes	Conflicting RCT data as to efficacy
RTX [319,320,365]	Yes	No proven efficacy
Hyaluronic Acid [234,320-324,366]	Yes	No proven efficacy
Heparin [145,326]	No	60%
Chondroitin Sulfate [327]	No	33%
Lidocaine [328-331,333,334]	No	65%
Capsaicin [335]	No	No demonstrated efficacy
Oxybutinin [210,367]	No	Efficacy suggested
Doxorubicin [350]	No	Anecdotal efficacy
PPS [349]	Yes	Suggestion of possible efficacy 40%

Table 14. Intravesical therapy for IC Assessments according to the Oxford System

	Level of Evidence	Grade of Recommendation
DMSO	2	B
Hyaluronic Acid	1	D
RTX	1	-A
Heparin	3	C
Lidocaine	3	C
BCG	1	C-
Oxybutinin	2	C
PPS	2	C
BTX-A	3	not recommended pending further clinical trials
Chondroitin sulfate	3	C
Clorpactin WCS 90	3	C+
Doxorubicin	4	D

interstitial cystitis patients [319]. The dosage and the treatment schedule are unknown. Further studies are necessary to confirm these results. ***Recently an unpublished phase 2 safety and proof of concept multicenter, placebo-controlled trial conducted by ICOS Corporation of Bothell, WA found no significant efficacy of RTX compared with placebo, although no safety issues were identified [320].***

3. HYALURONIC ACID/SODIUM HYALURONATE

Intravesical hyaluronic acid has been used as an epithelial coating in joints. An intravesical instillation of 40 mg weekly for 4- 6 weeks has been approved in Europe and Canada as a treatment for IC. Though several clinical studies have shown efficacy for interstitial cystitis [234,321-323] no randomized controlled study has been published.

However, in the summer of 2003 Bioniche Life Science Inc. [324] and in the spring of 2004 (Seikagaku Corporation) [325] reported double blind, placebo-controlled, multicenter clinical studies of their respective hyaluronic acid preparations (40mg or 200mg per cc), and found no significant efficacy of sodium hyaluronate compared to placebo. Neither preparation has been approved for use for IC in the United States.

4. HEPARIN

Two clinical studies of intravesical heparin in patients with interstitial cystitis have been reported [145,326]. These trials suggested that intravesical heparin can relieve bladder symptoms in most patients. However, no adequately designed controlled studies of heparin have been published, and further randomized controlled trials (RCTs) are necessary to confirm efficacy and safety

5. INTRAVESICAL CHONDROITIN SULFATE

Chondroitin sulfate demonstrated a 33% response rate (intent to treat) in 18 patients in an open label trial for interstitial cystitis. A further study is necessary to confirm accuracy of the only reported trial [327].

6. LIDOCAINE

Several clinical studies of this drug in patients with interstitial cystitis have been reported [328-334]. All involved electromotive drug administration (EMDA), which utilizes an electric current to facilitate the active transport of ionized drugs. While short-term efficacy was demonstrated, randomized controlled studies are needed to determine its place in the treatment of interstitial cystitis. Two case reports suggested lidocaine is safe and efficacious [329,330]. Both articles demonstrated that repeated intravesical instillations of lidocaine in the urinary bladder relieved pain. A pharmacokinetic study of lidocaine shows that the decrease in pain scores in the interstitial cystitis group is related to concentration of local anesthetic within the bladder wall. It blocks the sensory neurons within the submucosal plexus [328].

7. CAPSAICIN

A detailed description of intravesical capsaicin, a C-fiber afferent neurotoxin, for treatment of interstitial cystitis can be seen in a recently published article by Fagerli et. al [335]. Further attempts for the treatment of interstitial cystitis should be performed to evaluate this drug in terms of efficacy, tolerability and safety. Its clinical usage is limited by pain occurring with intravesical administration and lack of proven efficacy.

8. BACILLUS CALMETTE-GUERIN (BCG)

In 1994 Zeidman et. al reported the use of intravesical BCG in the treatment of interstitial cystitis [336]. Subsequently, Peters et. al conducted a randomized, prospective, double-blind, placebo controlled trial [337]. Improvement of the symptoms was observed in 60% (9 of 15 patients) in the BCG-group compared to 27% (4 of 15 patients) in the placebo group. Of the BCG responders 8 of 9 (89%) continued to have an excellent response in all parameters measured at a mean of 27 months [338]. Levels of symptoms correlated with cytokine levels in the urine [339].

Peeker et. al performed a prospective, randomized double-blind study with a crossover design between BCG and dimethyl sulfoxide (DMSO) in interstitial cystitis [340]. BCG was not found to be efficacious. However, after DMSO therapy, a significant reduction in urinary frequency was noted, but only in the ulcerative form of interstitial cystitis. A substantial pain decrease was noted in patients with ulcerative and nonulcer interstitial cystitis.

A large, double blind, multicenter, placebo-controlled trial conducted by the National Institutes of Health (NIDDK) is complete, and will be reported in the fall of 2004. This should provide a definitive answer on BCG safety and efficacy, and its place, if any, in the treatment of the painful bladder.

9. DIMETHYL SULFOXIDE (DMSO)

Dimethyl sulfoxide (DMSO) remains the basis of intravesical therapy for interstitial cystitis. This drug has various effects but the way it acts on interstitial cystitis is not fully understood. As mentioned above, in a randomized double-blind controlled study with crossover design recently performed, it was reported that DMSO resulted in significant reduction of pain and also reduction of urinary frequency in patients with classic interstitial cystitis whereas no effect could be shown in patients with nonulcer interstitial cystitis [340]. Perez-Marrero et. al conducted a controlled crossover trial in 33 patients [341]. Several other clinical studies or case reports of this drug in patients with interstitial cystitis have been reported [342,343] [344-348].

10. OXYBUTYNIN

Barbalias showed that bladder training alone produced a satisfactory result by gradually expanding the bladder, and an additional statistically significant improvement was evident with intravesical oxybutynin [210]. No adequately designed controlled trials of this drug for treating interstitial cystitis patients have been published.

11. PENTSANPOLYSULPHATE (PPS)

Only 1 small double-blind placebo controlled study with intravesical PPS instillation has been conducted [349]. Four of 10 patients treated with PPS showed improvement versus 2 of 10 on placebo. Further randomized controlled trials (RCTs) are necessary to determine its place in the treatment of interstitial cystitis.

12. DOXORUBICIN

In one clinical trial [350] of three patients, intravesical doxorubicin seemed to have some beneficial effects in the treatment of interstitial cystitis.

13. BOTULINUM TOXIN TYPE A (BTX-A)

The therapeutic value of BTX-A stems partially from its ability to temporarily inhibit acetylcholine release and cause flaccid paralysis in a dose related manner. It can correct focal dystonia when injected into a muscle. In recent years there has been increasing evidence that BTX-A might also have analgesic properties [351].

Initially this was thought to be due to relief of muscle spasm. However, botulinum has been shown to reduce peripheral sensitization by inhibiting the release of several neuronal signaling markers, including glutamate and substance P, and reducing c-fos gene expression.

It may affect the sensory feedback loop to the central nervous system by decreased input from the muscle tissue, possibly by inhibiting acetylcholine release from gamma motor neurones innervating intrafusal fibers of the muscle spindle [352].

Botulinum toxin type A (BTX-A) has been used effectively for years in different conditions with muscular hypercontractions. A recent study has demonstrated that intravesical BTX administration blocked the acetic acid-induced bladder pain responses and inhibited CGRP release from afferent nerve terminals in the bladder mucosal layer in rats. These results support clinical trials of BTX-A for the treatment of interstitial cystitis and other types of visceral pain [353].

A multi-institutional case series was recently presented that examined the effect of intravesical Botox or Dysport on 13 patients with refractory interstitial cystitis [354]. Overall, 9 of 13 patients (69%) noticed subjective improvement from BTX-A treatment. Improvements in symptoms lasted a mean of 3.72 months (range 1 to 8). No systemic complications such as respiratory depression, muscle weakness or fatigue were observed. However, 2 patients treated with intravesical Botox injection noticed a decrease in the force of urinary stream with some need to strain to void.

Botox cannot be recommended for clinical use outside of carefully controlled studies.

14. CLORPACTIN WCS 90 (HYPOCHLOROUS ACID)

Clorpactin is a trade name for closely related, highly reactive solutions having a modified derivative of hypochlorous acid (oxychlorosene) in a buffered base. It has oxidizing and detergent effects. Wishard et. al [355] reported on 20 patients treated with 0.2% Clorpactin gently lavaged in the bladder for 3-5 minutes without anesthesia; 14 had subjective improvement. Murnaghan et. al [356] noted improvement in 14 of 17 patients, though 10 required further treatment during the average 2 year follow-up (level 3). Messing [87] used a 0.4% solution under anesthesia administered at 10cm water pressure. Success rate was 72%. Reflux is a contraindication, as ureteral fibrosis has been reported [357].

XI. SURGERY FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) is a chronic and debilitating disease. Surgical options should be considered, however, 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. SURGERY ON NERVOUS SYSTEM

a) Sacral nerve neuromodulation consists of temporary percutaneous sacral S3 or S4 root stimulation and permanent implant for those who respond well to a temporary one. Zerman et. al reported significant improvement in a 60-year-old woman treated for severe interstitial cystitis 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 [368](Level 4). Maher et. al showed that temporary stimulation was effective in 73% of 15 women with refractory IC/PBS [369]. 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 (Level 3). Zermann et. al reported that percutaneous S3 nerve root neurostimulation improves not only symptoms but normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis [370] (Level 3). Comiter et. al reported a series of 25 patients with a mean age of 47 years and refractory interstitial cystitis who were prospectively evaluated with temporary sacral nerve stimulation. Seventeen patients who demonstrated 50% improvement in frequency, nocturia, voided volume and average pain received a permanent sacral nerve stimulator implant. 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 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 [371] (Level 2).

Sacral Nerve Modulation is a promising surgical treatment for IC/PBS. It still should be considered investigational.

b) Cystolysis- peripheral denervation. Hunner [127] simply dissected bladder from surrounding tissue. Initial results were encouraging however after 3 years of follow-up symptoms reoccured (Level 4). Worth and Turner-Warwick [372] attempted to do more formal cystolysis and were more successful in regard to symptoms (Level 4). Worth [373] followed patients up to 7 years and found bladder areflexia a significant complication of this procedure , . Patients had to use Crede technique or even be on self intermittent catheterisation (Level 4). Albers & Geyer [374] reported recurrence after 4 years in most of the patients (Level 4).

- Cystolysis – peripheral denervation is not indicated for IC/PBS

c) Sympathetic denervation. Visceral pain is transmitted in most of the cases by sympathetic nervous system. Gino Pieri [375] applied this principle to the bladder pathology and suggested resection of superior hypogastric plexus (presacral nerves), paravertebral sympathetic chain and gray rami from S1-3 ganglia (Level 4). This was repeated by Douglass [376] a few years later. Immediate results were very good; however Nesbit [377] showed that the long term results were short lived , (Level 4).

- Sympathetic denervation is not indicated for IC/PBS

c) Parasympathetic denervation. Based on presumption that S2-S4 segments contribute to bladder innervation Moulder and Meirowsky [378] used S3 neurectomy in 3 patients (Level 5) with good long term follow-up (Level 4). A larger series was reported by Milner [379] and Mason [380] (Level 3) but results after five years were not encouraging (Level 3). To improve results selective dorsal sacral roots neurectomy, unilateral or bilateral, was introduced by Bohm and Franksson [381] . The outcomes of this procedure were unclear (Level 4).

- Parasympathetic denervation is not indicated for IC/PBS

2. BOWEL SURGERY

a) Bladder augmentation- cystoplasty. This procedure has been commonly used for refractory IC/PBS for years. First reports of ileocystoplasty from 1958 were very satisfactory [382](Level 4). Later publications were less clear with good results varying from up to 100% [383,384] to 25% [309,385] (Level 4). Cystoplasty is usually done with or without bladder resection.

Cystoplasty alone was reported as early as 1967 by Turner-Warwick and Ashken [3867]advocating augmentation with removal of the diseased tissue (Level 4). Several subsequent studies indicated that cystoplasty with subtrigonal cystectomy offers better results than without subtrigonal cystectomy [384,387-389] (Level 4). 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 segment are used to enlarge bladder. It is the general consensus that the intestine segment used for bladder augmentation should be detubularized [390] (Level 5). Different bowel segments have been used for augmentation:

- Ileum [309;384;389;391;383;392;393;394;395] (Level 4)

- ileocecum [360;384;385;396;387;397] (Level 4)

- cecum [383;398] (Level 4)

- right colon [309,384,399] (Level 4)

- sigmoid colon [392;389;396;387] (Level 4)

- gastric segments [400;401] (Level 4)

There is no significant different between different bowels segments in regard to outcome except for gastric tissue substitution which contributes more to 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 [383] described excellent results in eight of 13 patients with a follow-up of 12-72 months (Level 4). Bruce et. al [389] reported satisfactory relief of IC symptoms by ileocystoplasty and colocystoplasty in eight patients (Level 4). Dounis and Gow [402] reported improvement in pain and frequency in seven IC patients after supratrigonal cystectomy with ileocecal augmentation (Level 4). Kontturi et. al [387] used segments of colon and sigmoid colon in 12 cases38 (Level 4) with 100%

symptoms 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 [403] followed six IC patients for 30 months, and reported that all were symptom-free and voided spontaneously (Level 4). Nielsen et. al [385] report was less favorable. Six out of eight patient (Level 4). Van Ophoven et. al [404]reported the long-term (mean 5 years) results of orthotopic substitution enteroplasty in 18 women with IC, using ileocecal (n = 10) or ileal (n = 8) segments with only two failures. In the group [405] augmented with ileum, three patients required self-catheterization and one a suprapubic catheter (Level 3). Peeker et. al [406] found that patients with end-stage classic IC had excellent results following ileocystoplasty but not the patients with non-ulcer disease. Patients with low cystoscopic capacity (<200 ml) under general anaesthetic achieved better results [87,93,407,408] (Level 3-4).

There is some weak evidence that cystoplasty with supratrigonal resection may benefit some selected patients.

c) Cystoplasty with subtrigonal cystectomy — orthotopic continent bladder augmentation (i.e. with trigone removal but preservation of the bladder neck) in the management of IC has been reported less often [405,409-411] . Because of need of ureteral reimplantation, it is associated with some risks of urine leakage, urethral stricture and reflux. Nurse et. al [412] blamed 50% (13 0ut 0f 25) surgical failures rate on the trigone left in place 54 (Level 4).

Linn et. al [403] had three failures in 17 patients and half of the patients with good symptomatic response required self catherization 46 (Level 4). Nielsen et. al [385] had better results following orthotopic substitution with low bladder capacity (200 mL versus 525 mL, respectively) (Level 4). *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.

There is no evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy but is associated with more complications and poorer functional bladder rehabilitation.

3. 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 IC/PBS[413]. Initially, diversion can be done without cystectomy and only when bladder pain is persistent, cystectomy may be considered. Bladder de-functionalization alone produced symptoms relief in several reports [414;309;93;87;415;414,] (Level 3-4). Very often diversion is performed as a next step after unsuccessful bladder augmentation. To prevent further bowel resection, a bowel segment used for cystoplasty can be often converted to a conduit [416] . In some patients chronic inflammatory changes have been seen in the cystoplasty pouch resembling interstitial cystitis [87,309,417,418] (Level 4), 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 IC urine [419] (Level 4). Relatively good response to diversion with or without cystectomy have been reported in small series [385,420] (Level 4).

CONTINENT URINARY DIVERSION

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 IC in the pouch is a real possibility.

Better outcome with surgical procedures can be achieved by;

1. using detubularized intestinal segment,

2. performing supratrigonal bladder resection

3. selecting patients with low cystoscopic bladder capacity

XII. FUTURE DIRECTIONS IN RESEARCH: INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME

The average delay in diagnosis of interstitial cystitis/painful bladder syndrome in the United States is 5-7 years [57,63]. There are many reasons for this delay. They include the lack of a clinically available specific test for IC/PBS, the lack of awareness of the condition among health care professionals, as well as the public, and the lack of uniformly effective treatments - making IC a challenging condition to treat. In addition, research has been impeded by the lack of epidemiologic data and a poor understanding of the etiology and pathogenesis of IC/PBS, as well as the lack of financial support when compared with well known and better understood diseases [421].

There are eight recommendations for future directions in research on IC/PBS that the committee believes will lead to a greater understanding of the pathophysiology of the condition and will have a major impact on its clinical treatment[421].

a) Investigate the cause and development of IC/PBS through studies that will:

- Identify urinary, epithelial, inflammatory, vascular, and neurologic abnormalities, as well as hormonal influences

- Identify specific markers associated with pathogenesis, risk, disease activity, prognosis, response to therapy, and remission

- Identify genetic predisposition and patterns of familial inheritance

- Classify subgroups of people based on abnormalities and markers

b) Conduct epidemiologic research, including population and case-control studies of incidence, prevalence, and natural history. Identify risk factors for the development of IC/PBS, and formulate preventive strategies.

c) Develop a simple, non-invasive diagnostic test for IC/PBS. This will most likely involve urinary markers [156,167,422-424]. Urinary markers may help to subclassify various types of IC. This test will determine the diagnosis of IC/PBS 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 IC/PBS [422.] This test will also differentiate patients with urinary incontinence/overactive bladder syndrome from those patients with IC/PBS.

Determining if the potassium sensitivity test (PST) is actually correlated to urothelial permeability; if not, development of a practical test to measure urothelial permeability in humans.

d) Investigate IC/PBS and co-morbid conditions such as vulvodynia, irritable bowel syndrome (IBS), fibromyalgia, inflammatory bowel disease

(Crohn's disease and ulcerative colitis), chronic fatigue syndrome, and other autoimmune diseases such as lupus erythematosus and Sjogren's syndrome. Is IC an end-organ disease of the bladder or a systemic condition? Are there common underlying factors linking these conditions to IC/PBS [72,203]?

e) Pathogenesis and treatment of pain in IC/PBS patients: The committee recommends a review of the literature on visceral pain as well as collaboration with the IASP (International Association for the Study of Pain) and other organizations that focus on the etiology, pathogenesis and treatment of visceral pain. It is essential that IC/PBS patients be provided with adequate pain management, particularly in view of the paucity of uniformly effective treatments for IC/PBS currently available. Suicides occur each year in this patient population due to ineffective pain management.

f) Conduct clinical trials of novel therapies, including pain medications, for the treatment of visceral pain. Avoid undue pharmaceutical industry influence as well as promotion of various prescription medications and over-the-counter products that provide personal financial gain to researchers. Complete financial disclosure by researchers is imperative in order to avoid conflicts of interest.

g) Develop new, uniform diagnostic criteria for IC/PBS so that research can be conducted internationally in a comparable manner, until such time as a definitive test for IC/PBS is commercially available. (see # 3)

h) Encourage standardization of biopsy techniques to enable formation of valid conclusions as to contributions of biopsy with regard to clinical and basic research questions.

i) Resolve nomenclature of PBS/IC and its various subtypes in order to facilitate communication and research in the international community. Establish the place of PBS/IC in the spectrum of chronic pelvic pain syndromes.

A reasonable diagnostic and treatment algorithm based upon the current state of knowledge of PBS/IC is depicted in the **figure 2** that follows.
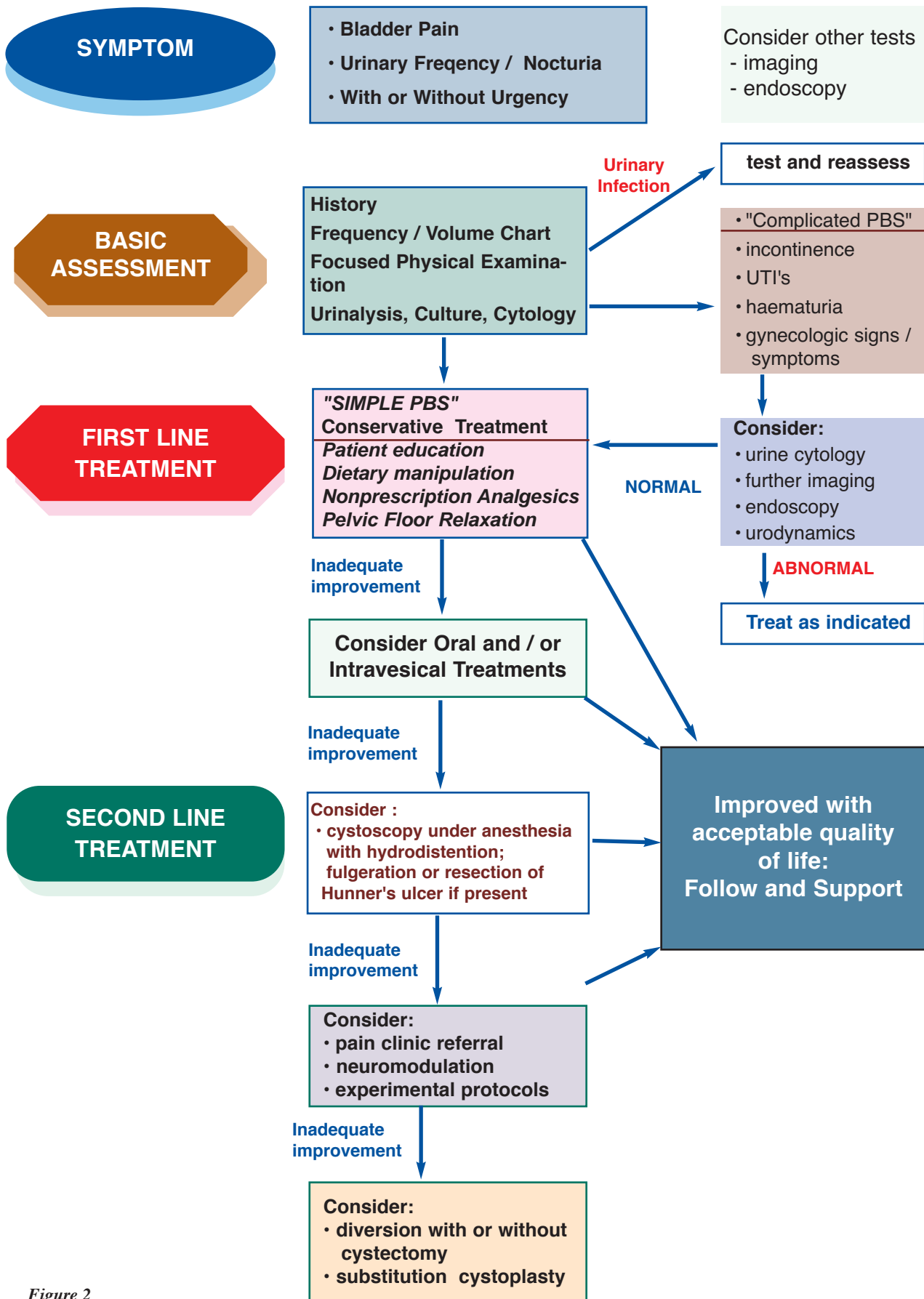
PAINFUL BLADDER SYNDROME

SYMPTOM

- Bladder Pain
- Urinary Freqency / Nocturia
- With or Without Urgency

Consider other tests
- imaging
- endoscopy

BASIC ASSESSMENT

History
Frequency / Volume Chart
Focused Physical Examination
Urinalysis, Culture, Cytology

Urinary Infection → test and reassess

- "Complicated PBS"
- incontinence
- UTI's
- haematuria
- gynecologic signs / symptoms

FIRST LINE TREATMENT

"SIMPLE PBS"
Conservative Treatment
Patient education
Dietary manipulation
Nonprescription Analgesics
Pelvic Floor Relaxation

Consider:
- urine cytology
- further imaging
- endoscopy
- urodynamics

NORMAL

ABNORMAL → Treat as indicated

Inadequate improvement

Consider Oral and / or Intravesical Treatments

Inadequate improvement

SECOND LINE TREATMENT

Consider :
- cystoscopy under anesthesia with hydrodistention; fulgeration or resection of Hunner's ulcer if present

Inadequate improvement

Consider:
- pain clinic referral
- neuromodulation
- experimental protocols

Inadequate improvement

Consider:
- diversion with or without cystectomy
- substitution cystoplasty

Improved with acceptable quality of life: Follow and Support

Figure 2

1510

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