Expert Opinion

Interstitial cystitis: bladder pain and beyond

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Background: Interstitial cystitis is characterized by over 6 months of chronic pain, pressure and discomfort felt in the lower pelvis or bladder. It is often relieved with voiding, along with daytime frequency and nocturia in the absence of a urinary tract infection. Interstitial cystitis occurs primarily in females including adolescents and its diagnosis is still one of exclusion. It is now recognized as a serious medical condition associated with significant disability. *Objective*: The aim of this paper was to review the pathogenesis and treatment of interstitial cystitis with emphasis on new pathogenetic trends and therapeutic modalities. *Methods*: About 713 mostly original papers were reviewed in Medline from 1990 to August. 2008. All authors independently reviewed the literature. Large, double-blind, placebo-controlled, clinical trials were few and the medical histories of the patients used varied considerably making conclusions difficult. Promising pilot trials turned out mostly negative on follow-up. *Results*: Increasing evidence of co-morbid diseases, neurogenic inflammation and the effect of stress are promising as new targets for pathophysiology. No new effective treatments have emerged. Oral pentosanpolysulfate, amitriptyline, hydroxyzine and quercetin, as well as intravesical heparin/bicarbonate/lidocaine solutions, are still used with variable success. Some pilot open-label trials presented encouraging findings. *Conclusion*: Interstitial cystitis contributes substantially to chronic pelvic pain and to poor quality of life. Oral or intravesical administration of solutions containing sodium hyaluronate, chondroitin sulfate and quercetin to both reduce bladder inflammation and 'replenish' the glycosaminoglycan layer should be tried. There is a clear need for therapeutic modalities. New potential translational research areas are suggested.

Keywords: amitriptyline, bladder, hydroxyzine, inflammation, mast cells, pain, pentosan polysulfate, quercetin, treatment

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1. Introduction

Interstitial cystitis is a disorder with urinary bladder pain and irritative symptoms being the main manifestation [1]. Interstitial cystitis occurs mostly in young and middle-aged women (median age 40 years) [1], with no known etiology or cure [2-5]. Interstitial cystitis is an important disorder that can contribute to chronic pelvic pain (CPP) and poor quality of life [6]. The constellation of interstitial cystitis symptoms has been given different names. The International Continence Society named the disease interstitial cystitis/painful bladder syndrome (IC/PBS) [7], while the Multinational Interstitial Cystitis Association called it painful bladder syndrome/interstitial cystitis (PBS/IC) [8]. The European Society for the Study of Interstitial Cystitis proposed it be named 'bladder pain syndrome', in keeping with 'pelvic pain syndrome' and to avoid the confusion generated by

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the fact that interstitial cystitis may have different meanings for different urologists, centers or countries [9]. It was further decided that the term 'bladder pain syndrome (BPS)/interstitial cystitis' be used in the interim. Here, the term interstitial cystitis was used alone since it appeared in all but five of the publications surveyed and because of the added confusion between the terms 'interstitial cystitis/PBS', PBS/interstitial cystitis and 'BPS/interstitial cystitis'.

2. Methods

The study reviewed the pathophysiology and treatment of interstitial cystitis by searching English-language publications in Medline and references from relevant articles published between 1990 and 2008. About 713 publications were reviewed. Most of the clinical studies were small (< 20 patients), open label and used different ways of evaluating symptoms. Articles were selected on the basis of their quality, relevance to the illness and importance in illustrating a proposed pathophysiology or on the basis of whether clinical trials were randomized and placebo controlled or whether they were multicenter; only open-label studies that included at least 20 patients were included. Case reports were excluded unless they made a unique point that contributed to our understanding of the disease. All the authors independently reviewed the selected publications and contributed comments as necessary. A group consensus had to be reached for any study to be included in this review.

The main search terms were allergy, amitriptyline, animal models, antidepressants, antiproliferative factor (APF), anxiety, biopsy, bladder, bladder pain, botulinum toxin, capsaicin, chronic cystitis, chronic fatigue syndrome, CPP, co-morbid diseases, corticotropin-releasing hormone, cure, cystoscopy, detrusor instability, dimethyl sulfoxide (DMSO), eosinophilic cystitis, epidemiology, cytokines, endometriosis, etiology, flavonoids, fibromyalgia, glomerulations, glycosaminoglycans, growth factors, Hunner's ulcers, hydroxyzine, infection, inflammation, interstitial cystitis, irritable bowel syndrome (IBS), mast cells, mechanisms, neuromodulation, neuropathic pain, neuropeptides, overactive bladder, pain threshold, pathogenesis, pathophysiology, pelvic floor muscles, pentosan polysulfate (PPS), phantom pain, reflex sympathetic dystrophy, sensory nerves, sensory urgency, stress, treatment, therapies, trigger points, twins, urgency, urodynamics, urothelial damage and vulvodynia.

3. Presentation

Interstitial cystitis is a symptomatic diagnosis by exclusion based on 3 – 6 months of pain, pressure or discomfort felt over the lower pelvic area or the bladder along with frequency of urination in the absence of a urinary tract infection or other identifiable causes for the symptoms [1,4]. Interstitial cystitis pain is regional, chronic and diffuse over the lower pelvic/suprapubic area and in many aspects mimics neuropathic pain as in 'chronic regional pain syndrome' [10]. Even though the pain presentation is consistent with bladder pain, it does not prove the bladder is the origin of the pain as patients with vulvodynia or urethral syndrome often present similarly [11]. In fact, interstitial cystitis patients may experience pain differently than controls, possibly through a lower pain threshold as is often reported for fibromyalgia and IBS patients [12]. The pain most often worsens on bladder filling and may be relieved by voiding. Of the 629 interstitial cystitis patients (mean age 45 years) in the Interstitial Cystitis Database (ICDB), 94% reported pain or discomfort, in whom 80% was abdominal, 74% urethral and 65% low back pain [10]. In another retrospective study of 68 interstitial cystitis patients (mean age 41 years), of those 47 who had undergone hydrodistention, 61% reported bladder pain, 62% vaginal pain and 67% dyspareunia [13].

The National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK) has established stringent clinical research criteria for interstitial cystitis (see [1] for a list of the criteria and a discussion), but over 60% of patients diagnosed with interstitial cystitis failed these criteria, thereby prompting an expansion of the interstitial cystitis definition [14,15]. Frequency of urination is less common in men, who comprise ~ 10 – 15% of interstitial cystitis patients and who may also be diagnosed as having chronic prostatitis [16]. The urgency felt by interstitial cystitis patients tends to be excluded for definition purposes because it is more due to pain, rather than the impeding loss of control typical of an overactive bladder [1]. Moreover, there was no association between urgency and any histological findings [17]. Nevertheless, a study of 138 female patients with a recent (12 months) diagnosis of interstitial cystitis concluded that the severity of the persistent need to void may be more appropriate for evaluation in interstitial cystitis patients than its sudden nature [18].

One study showed that interstitial cystitis symptoms can worsen with stress [19]. Spicy or 'acid' foods and smoking may also exacerbate the symptoms [20]. However, a prospective, double-blind, randomized, crossover study raising the urine pH of interstitial cystitis patients had no effect on their pain [21]. The results from the Events Preceding IC Study reported recently that the pain in 151 out of 156 patients (97%) worsened with certain foods and drinks: this value was compared to 262 out of 270 (97%) in the ICDB [22].

Interstitial cystitis symptoms are often confused with or may overlap those of sensory urgency and an overactive bladder. One study suggested that the prevalence of interstitial cystitis may be higher in women with detrusor instability who do not respond to anticholinergics [23]. Interstitial cystitis patients also have a higher incidence of other co-morbid diseases (**Table 1**) [24-29] including allergies (40 – 60% of interstitial cystitis patients), with allergic complications reported in 86% of young patients [1,30,31], fibromyalgia [29], IBS (35% of interstitial cystitis patients) [32], vulvodynia (20% to as high as 51.4% [33]) [31] and inflammatory bowel disease (IBD) (over 30 times higher in those patients with

Table 1. Co-morbid conditions.

Diseases	%*	Ref.
Allergies/Asthma	47 – 60	[24,27,30]
Atopic dermatitis‡	40	[24]
Endometriosis	30	[26,31]
Fibromyalgia	25	[26,29]
IBD§	2.3	[25,27]
IBS	40	[25,32]
Migraines	20	[81]
Panic disorder	30	[37,48]
Rheumatoid arthritis	13	[27]
SLE¶	2	[25,27]
Vulvodynia and VVS	20 – 50	[26,48]

*Approximate percentage of PBS/interstitial cystitis patients with the disease shown on the left.
‡Many patients describe 'sensitive' skin in the absence of any allergic diathesis.
§This prevalence of IBD in PBS/interstitial cystitis patients with 'classic' interstitial cystitis with Hunner's ulcers was 33 times higher than that seen in the general population [27].
¶PBS/interstitial cystitis patients were reported to be 100 times more likely to have IBD and 30 times more likely to have SLE than the general population [25].
IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; SLE: Systemic lupus erythematosus; VVS: Vulvar vestibulitis syndrome.

Hummer's ulcers) [25,27]. Investigation of 127 twin pairs showed that interstitial cystitis was more common in the twin who had chronic fatigue syndrome [34]. One study reported that there was an increased incidence of interstitial cystitis, endometriosis and vulvar pain in women with CPP [31]. Results from a database of ~ 2 million beneficiaries also indicated that patients with symptoms consistent with interstitial cystitis often had a higher diagnostic prevalence of endometriosis, vulvodynia and CPP [35]. A case – control study of mental health diagnoses in patients with interstitial cystitis and CPP concluded that depression and panic disorder were present in 23% more interstitial cystitis patients than female controls ($p < 0.0001$) [36]. Moreover, a family linkage study identified a high correlation of interstitial cystitis with panic disorder [37].

3.1 Epidemiology

The prevalence of interstitial cystitis was originally estimated to be between 18 and 67 in every 100 000 women. However, 95% of those participants were White professionals, suggesting that patients with limited access to healthcare may have been missed [1]. Recent studies have reported higher rates [38], with a population-based study in Finland estimating an interstitial cystitis prevalence of 230 in every 100 000 women [39]. A study of urban females in Vienna gave an estimate of 464 in every 100 000 women [40], an office survey in the USA indicated 575 in every 100 000 women [41] and a study of self-reported adult interstitial cystitis cases in an urban community estimated a prevalence of 4% [42].

Children and adolescents can also have interstitial cystitis [43]: in fact, interstitial cystitis patients appear to have had 10 times more bladder problems as children than the general population [1].

3.2 Diagnosis

Interstitial cystitis remains a diagnosis of exclusion [1,44,45]. The most common presumed initial 'diagnosis' in interstitial cystitis patients is urinary tract infection, in spite of negative urine cultures or repeated courses of antibiotics. A medical history should include suprapubic pain/pressure/discomfort related to bladder filling and an increased daytime and night-time frequency and any pelvic surgery or spinal cord trauma, as well as allergic, gastrointestinal, gynecological and musculoskeletal diseases [1]. Questions on possible abuse should be included as it is more common in females, especially with CPP [46]. Moreover, it was recently reported that 49% of 76 interstitial cystitis women evaluated had a history of abuse, with more than 50% of them mentioning sexual abuse [47], often in more than one life stage [48].

Interstitial cystitis symptoms can be evaluated using a number of validated questionnaires, which are not designed for diagnosing interstitial cystitis but measuring the extent of symptom severity. These include the one-page O'Leary – Sant Symptom and Problem Index [49], which correlates well with the University of Wisconsin Symptom Instrument [50] and with the Global Response Assessment (GRA). A change of 1.2 points on the O'Leary – Sant Symptom and Problem Index correlated with a 3.1 point change on the University of Wisconsin Symptom Instrument and a one-category change in the GRA: all changes were responsive over time [51]. The Pelvic Pain, Urgency and Frequency Index [52] is often used for screening purposes but has not been sufficiently validated yet, especially since urgency is excluded for an interstitial cystitis diagnosis as mentioned above.

3.2.1 Non-invasive

There are no specific blood or urine markers available for interstitial cystitis diagnosis [53,54]. However, combination of specific urine markers may prove helpful, possibly for subsets of patients. The histamine metabolite methylhistamine [55] and the unique mast cell protease tryptase [56] were increased in the 24-h urine of interstitial cystitis patients who met NIDDK criteria, but the sample was too small for calculating the specificity or sensitivity. A small number of newly diagnosed interstitial cystitis patients have elevated levels of IL-6 [53,57,58], which appears to be associated with their age at symptom onset and the severity of bladder inflammation [59]. The urine histamine metabolite 1,4-methyl imidazole acetic acid and eosinophil cationic protein have been shown to be increased and correlated with bladder mast cell density in interstitial cystitis [53]. Antiproliferative factor, as determined by its ability to decrease *in vitro* proliferation of bladder

epithelial cells, is increased in interstitial cystitis urine [53,60] and was identified as a frizzled-8 surface sialoglycopeptide [61]. Antiproliferative factor and heparin-binding epidermal growth factor (HB-EGF) and insulin-like growth factor binding protein-3 were also increased in 24 h urine [53]. Urine APF and glycoprotein-51 levels clearly separate interstitial cystitis patients from controls [53,62]. Antiproliferative factor could distinguish interstitial cystitis from other urologic disorders [60], but still needs to be validated and reproduced independently. A recent study comparing 40 women with interstitial cystitis to 29 healthy controls showed that 24-h urine IL-6 and histamine, normalized to urine creatinine, were significantly elevated: there was 70% sensitivity and 72.4% specificity, with a positive predictive value of 77.8% and a negative value of 63.6% [63]. Increased urinary levels of chondroitin sulfate and hyaluronic acid have been reported in some PBS/interstitial cystitis patients [64,65], along with decreased mucosal glycoprotein GP1 [66]. In another study, urine urate and sulfated glycosaminoglycans normalized to creatinine were compared between 37 interstitial cystitis patients who fulfilled the NIDDK criteria (except for glomerulations) and 14 normal controls: there was 80 and 88% sensitivity and 92.3 and 69.2% specificity, respectively, for detecting the severity of interstitial cystitis symptoms [67]. The key regulator of inflammatory genes, NF-κB, was also activated in the bladder of interstitial cystitis patients [68]. Interestingly, urine markers taken before and 1 month after bladder hydrodistention in 33 newly diagnosed interstitial cystitis patients with no prior treatment showed some statistical improvement for APF and HB-EGF, but these changes were not associated with the mild decrease in symptom scores [69]. A recent study of 72 interstitial cystitis patients showed that the only statistically significant correlation was between spot urine IL-8 levels and the number of mast cells in the lamina propria, irrespective of the presence of Hunner's ulcers [70]. Classic interstitial cystitis may be differentiated from non-ulcer interstitial cystitis by decreased urine nitric oxide levels in patients with classic interstitial cystitis who responded to treatment [71]. A reduced urine level of nitric oxide synthase activity was also found in common interstitial cystitis [72], but higher nitric oxide synthase activity was reported in interstitial cystitis bladder biopsies [73].

3.2.2 *Invasive*

Intravesical administration of concentrated (0.4 M) KCl, known as the potassium sensitivity test, is used by some physicians to help determine whether the bladder is the source of pain in women with CPP and whose histories and physical examination results are unclear [52]. However, even though the use of the potassium sensitivity test may be helpful for eliciting bladder pain of unknown origin, it is not appropriate for diagnosis because of its low prognostic value (75% sensitivity and specificity) [74].

Cystoscopy and 'hydrodistension' under general or spinal anesthesia is mandated by the NIDDK criteria and commonly performed in interstitial cystitis patients, especially in Europe [1,7,44]. This procedure should be performed (preferably with isotonic saline or glycine) in order to avoid hypotonic urothelial cell damage due to water (hydro) that may also result in non-specific histological and urine marker findings. This procedure can identify bladder ulcers ('Hunner's ulcers') [75]: this is often referred to as 'classic' interstitial cystitis and could vary considerably (still < 10%) among urologists [76]. Classic interstitial cystitis might be differentiated from non-ulcer disease by elevated urine nitric oxide [71]. In a recent study of 38 Chinese interstitial cystitis patients with Hunner's ulcers (26 without, 10 normal controls, 10 with bacterial cystitis and 10 with bladder cancer) APF was higher and HB-EGF was lower ($p < 0.0001$) in interstitial cystitis, but the classic form could not be distinguished from the common type [62]. Cystoscopy with bladder distension could also document urothelial petechiae (glomerulations) [1]. However, glomerulations may be noted even in non-interstitial cystitis bladders and are not diagnostic by themselves [77]. For instance, in a retrospective study of 68 women and 16 men with interstitial cystitis (mean age 41 years), cystoscopy with hydrodistension did not provide useful information over that of their history and physical examination [13]. Moreover, when interstitial cystitis patients were compared using cystoscopic appearance, bladder biopsy, urine markers and the University of Wisconsin Symptom Instrument 1 month after bladder hydrodistension under anesthesia, the only positive correlation was between those interstitial cystitis patients meeting the cystoscopic NIDDK criteria and worse frequency [45]. Another study of 12 newly diagnosed and untreated interstitial cystitis patients did show a positive correlation between pain on bladder filling and inflammation ($p = 0.011$), as well as nocturia ($p = 0.001$) but not daytime frequency [17]. Urodynamic studies remain controversial in interstitial cystitis, but may be useful for identifying those patients with sensory urgency and detrusor overactivity, as well as patients with atypical symptoms, especially voiding difficulty.

Bladder biopsies may be necessary for excluding other pathologies. An analysis of bladder biopsies in the ICDB identified subgroups, the bladder histopathology of which correlated with an increased 24-h frequency ($p < 0.001$) [78]. When the biopsy features were analyzed individually instead of in clusters, multivariant analysis revealed several associations between biopsy features and symptom severity. Nocturia was associated with an increased number of mast cells in the lamina propria ($p = 0.048$), complete loss of urothelium and granulation tissue and vascular density in the lamina propria [79,80]. In fact, a count of > 28 mast cells/mm^2 tryptase-positive bladder mast cells in the detrusor was recommended by the European Society for defining a subtype of interstitial cystitis [9].

3.3 Pathogenesis

There is no known pathogenesis. However, increasing evidence, including the existence of co-morbid diseases discussed

earlier and the effect of stress, suggests that interstitial cystitis may actually be a systemic disorder with bladder symptoms being the main manifestation [81,82].

There may be some genetic predisposition, since the interstitial cystitis prevalence was reported to be 17 times more common in first-degree relatives than the general population [83]. Moreover, five out of eight monozygotic twins had either probable or confirmed interstitial cystitis, as compared with none out of eight in dizygotic twins [84].

No infectious etiology has been identified to date, including *Helicobacter pylori*, *Gardnerella vaginalis* and *Chlamydia trachomatis*, as well as adenovirus, cytomegalovirus, herpes simplex I and II and all types of papillomavirus [85]. One report of a 16S rRNA fragment from some unknown Gram-negative bacteria in the bladder of 29% of interstitial cystitis patients is considered a sampling artefact. However, frequent clinical or subclinical infections could lead to neuroimmune activation through activation of toll-like receptors [86].

There are a number of non-mutually exclusive theories that may help explain some of the objective findings and symptoms in interstitial cystitis (**Table 2**). Neurogenic inflammation could explain the pain and some histological aspects of interstitial cystitis, even though bladder inflammation is variable [59]. In one study of 12 newly diagnosed, untreated female patients with interstitial cystitis, bladder inflammation only correlated positively ($p = 0.011$) with pain [63]. Interstitial cystitis bladder nerve endings are increased and correlate positively with the number of mast cells [87]. In particular, there was an increased number of nerve endings positive for the pro-inflammatory neuropeptide substance P and these were associated with mast cells, which are also increased in interstitial cystitis bladders [88]. An increased number of activated bladder mast cells in interstitial cystitis has been repeatedly reported [89]. There are two times more urothelial and 10 times more detrusor mast cells in ulcerative interstitial cystitis than controls [90], but only 50% of patients in the ICDB had high lamina propria mast cell counts [79]. One paper reported similar lamina propria mast cell counts between non-ulcer interstitial cystitis patients and controls [90], but this study did not use either appropriate staining methods or controls (cancer) [91]. The most critical point generally missed is the high degree of activation and not simply the number of mast cells in interstitial cystitis [91]. These mast cells may be recruited by stem cell factor or monocyte chemoattractant protein-1, which is produced by human detrusor muscle cells [92] and is chemotactic for mast cells [93]. Bladder biopsies from interstitial cystitis patients have shown stem cell factor to be increased [90,94]. Mast cells have been implicated in immunity and inflammatory disorders [82] by secreting many vasoactive, inflammatory and nociceptive mediators [82]: histamine, kinins and proteases, such as tryptase, as well as cytokines, leukotrienes, prostaglandins and nitric oxide, including vascular endothelial growth factor [95], which is over-expressed in 58% of interstitial cystitis bladders [96]. In addition to histamine, IL-6 and IL-8 are also secreted, as discussed earlier. Tryptase could cause microvascular leakage [97] and stimulate protease-activated receptors, leading to widespread inflammation and neuronal hyperexcitability. Mast cell-derived tumor necrosis factor-α (TNF-α) could also mediate urothelial inflammation [98].

There may also be some bladder lining damage in interstitial cystitis. A layer made primarily of the glycosaminoglycans chondroitin sulfate and hyaluronate sodium, as well as other glycoproteins and mucins, protects the bladder [1]. Some studies have shown that there was increased epithelial permeability, as determined by urea absorption in interstitial cystitis [99], but a subsequent permeability study using ^{99m}technetium failed to confirm this [100]. Nevertheless, the apparent ability of concentrated KCl to elicit pain in suspected interstitial cystitis cases [101] may indicate glycosaminoglycan/urothelial damage. Increased urinary hyaluronic acid levels normalized to creatinine were significantly higher in untreated interstitial cystitis patients ($n = 17$) who met the NIDDK criteria [65], regardless of the presence of glomerulations as compared to interstitial cystitis patients with mild symptoms ($n = 12$) and normal controls ($n = 14$) ($p < 0.001$) [67]. One study ($n = 32$) reported no change in interstitial cystitis urine chondroitin sulfates and total sulfated glycosaminoglycans normalized to creatinine when compared to 16 controls [102], but a more recent prospective study showed that total sulfated glycosaminoglycans normalized to urine creatinine were elevated ($n = 25$) in moderate-to-severe cases [67]. However, it is difficult to determine whether this was due to elevated production rather than glycosaminoglycan damage. Moreover, the discrepancies among studies could be due to symptom severity, with mild cases showing no difference.

3.4 New trends

Functional neuroimmune networks in the bladder may explain the sensory neuronal hyper-reactivity leading to neuropathic pain in interstitial cystitis [103]. Antidromic stimulation of the lumbosacral dorsal roots induced vascular permeability in the rat urinary bladder, an effect reduced after capsaicin administration, thereby implicating sensory neuropeptides [104]. Moreover, rat CNS-induced neurogenic cystitis was associated with bladder mast cell degranulation [105].

Mast cells are located peri-vascularly close to nerve endings, especially those containing substance P [88]: they communicate with neuronal processes [106] and are involved in antigen-induced cystitis [107].

Restraint stress in rodents induced bladder mast cell activation, increased urine histamine and IL-6 [108] and also resulted in loosening of urothelial tight junctions [109]. Corticotropin-releasing hormone (CRH) released under stress from sacral spinal cord projections [110] could have pro-inflammatory actions [82], apparently through activation of mast cells [111]. Interestingly, the vasodilatory effect of CRH on human skin was greater in female subjects [112]. Intravesical administration of CRH led to increased vascular endothelial growth factor release from mouse bladder

Table 2. Potential mechanisms involved in the pathogenesis of interstitial cystitis*.

Mechanism	Pathophysiologic effect	Ref.
Bladder lining abnormalities	Damage to the bladder protective glycosaminoglycan (glycosaminoglycan) layer	[99,102]
Abnormalities of descending inhibitory pain pathways	Dysfunction in brain centers (or the pathways from these centers) that normally downregulate pain signaling in the spinal cord	[67,103,104]
Neurogenic inflammation	Increased bladder neuropeptide containing nerve endings juxtaposed to increased and activated mast cells, increased urine IL-6	[88,107]
Neurohormonal dysregulation	Dysfunction in the hypothalamic-pituitary-adrenal axis, including higher bladder expression of corticotropin-releasing hormone (CRH)	[19,108-110,114]
Decreased urothelial repair	Increased secretion of antiproliferative factor (APF) shown to inhibit urothelial cell growth *in vitro*	[60,61]
Comorbid conditions	Increased rate of psychiatric comorbid conditions, including depression, anxiety, post-traumatic stress, and somatization, as well as allergies, chronic fatigue syndrome, endometriosis, fibromyalgia, IBS, and IBD	See **Table 1**

*These could vary for individual patients.

explants [113]. Corticotropin-releasing hormone was also reported to lower the micturition threshold *in vitro* [114]. Finally, cats with feline interstitial cystitis also had elevated plasma CRH, which may characterize a subset of interstitial cystitis patients with other co-morbid conditions [115].

3.5 Oral treatment

There is no curative therapy for interstitial cystitis [2,3,5]. Behavioral, physical, dietary, oral and intravesical interventions are used, often together, based on the symptoms [5,116]. The most common interventions for interstitial cystitis compiled by the ICDB were bladder hydrodistention, intravesical heparin and oral amitriptyline [117].

Frequently prescribed oral products include PPS, amitriptyline, hydroxyzine and quercetin-containing formulations (**Table 3**). A major problem of the clinical studies reported to date has been the inclusion of patients with a widely varied duration and severity of symptoms, making both comparisons and the likelihood of significant findings difficult. Moreover, most of the studies used different methods for evaluating any 'efficacy' (e.g., questionnaires, visual scales, global assessment, response rates, percentages of patients with symptom reduction at particular stages, i.e., 25% response, etc.), thereby precluding any reasonable analysis. Consequently, any 'evidence-based' single treatment for all interstitial cystitis patients cannot be recommended.

A recent systematic review of randomized controlled clinical trials reported that only PPS was 'modestly beneficial' [118]. Pentosan polysulfate is a polysaccharide originally synthesized as a 'small molecular weight heparin substitute'. It is promoted as 'replenishing' the glycosaminoglycan layer and is the only oral drug approved for interstitial cystitis (under the Orphan Disease Act) in the USA (**Table 2**) [119]. Two early randomized, double-blind, placebo-controlled, multicenter studies of 110 and I48 interstitial cystitis patients each on PPS (300 mg/day for 3 months) showed 25% ($p = 0.03$) [119] and 32% ($p = 0.04$) [120] symptom reductions, but the control group's response rate was unusually low at 18%. A meta-analysis of four studies showed that there was only a 16% benefit in pain and frequency [121]. A more recent randomized, double-blind, placebo-controlled multicenter clinical trial funded by the NIH of 121 interstitial cystitis refractory interstitial cystitis patients meeting the NIDDK criteria showed that PPS (300 mg/day for 3 month) had no significant effect ($p < 0.064$) (**Table 2**) over that of placebo [122]. Another randomized, double-blind, multicenter dose-ranging study of 380 interstitial cystitis patients showed no significant difference among the three doses (300, 600 or 900 mg/day for 32 months) using the Patients' Overall Rating of Symptoms Index, but was not designed for evaluating efficacy [123]. A more recent randomized study of 64 interstitial cystitis patients using 300 mg PPS for 6 months produced a 19% response that was indistinguishable from placebo [124].

Due to the increased incidence of allergies and high number of bladder mast cells in interstitial cystitis [89], the histamine-1 receptor antagonist hydroxyzine was used because it also exhibits anticholinergic, sedative and anxiolytic as well as bladder mast cell inhibitory properties [125], which are not shared by the hydroxyzine metabolite cetirizine. In two open-label studies [126,127] hydroxyzine (75 mg four times a day titrated over 1 month for 4 months) reduced symptoms by 55% ($n = 140$). When hydroxyzine (25 – 50 mg) was compared to PPS neither was found to be effective, even though the two together had the best response rate, although this was still not significant [122]. However, that study was underpowered and most patients did not reach the recommended dose of 50 – 75 mg of hydroxyzine per day (**Table 3**) because of worries over sedation. However, when hydroxyzine is given at night, it reduces nocturia, while morning sedation is minimized.

The histamine-2 receptor antagonist cimetidine was reported to decrease the median symptom score in 34 patients studied,

Table 3. Some key clinical trials of oral agents in interstitial cystitis.

Agent	Dose	Type of study	# Patients	Duration	Results[#]	Significance	Date	Ref.
Amitriptyline	75 mg/ml[#]	Open-label	75[‡]	3 weeks	50% ↓	NA	1989	[130]
Amitriptyline[§]	100 mg/day	Randomized, double-blind, placebo-controlled	50	4 m	31.2% ↓	$p = 0.005$	2004	[131]
Cyclosporin	1.5 mg/kg	Randomized	64	6 m	75% ↓	$p < 0.001$	2006	[139]
Hydroxyzine	75 mg/qhs	Open-label, prospective	13	3 m	40% ↓[§]	$p < 0.05$	1993	[126]
Hydroxyzine[§]	75 mg/qhs[#]	Open-label, prospective	140	3 m	40% ↓[§]	$p < 0.05$	1997	[127]
Hydroxyzine	25 – 50 mg/day	Randomized, double-blind, placebo-controlled, multicenter	121	3 m	31% ↓	0.26	2003	[122]
L-arginine	1500 mg	Randomized, double-blind, placebo-controlled	21/27 ex 25/26 pl	3 m	Only pain 48% ↓ vs 24%	$p = 0.04$	1999	[144]
L-arginine	2.4 g	Randomized double-blind, placebo-controlled, crossover	16	1 m	↓ 2.2 overall symptom score*	$p > 0.05$	2000	[145]
Misoprostol	600 mg/day	Open-label, prospective	25	6 m	56% ↓	$p < 0.05$		[129]
PPS	300 mg/day	Double-blind, placebo-controlled, multicenter	110	3 m	25 ↓[¶]	$p = 0.03$	1990	[119]
PPS	300 mg/day	Randomized, double-blind, placebo-controlled, multicenter	148	12 m	32 ↓[¶]	$p = 0.04$	1993	[120]
PPS	300 mg/day	Randomized, double-blind, placebo-controlled, multicenter	121	3 m	34% ↓	$p = 0.064$	2003	[122]
PPS	300 mg/day	Randomized	64	6 m	19%	NS	2006	[124]
Quercetin (+G+GS)	300 mg tid	Open-label, prospective	37	4 m	52.2% ↓	$p < 0.05$	2003	[141]
Quercetin (+Rutin[#] G+GS+SH)	300 mg bid	Open-label, prospective	127	6 m	51% ↓	$p < 0.0001$	2008	[142]

*no difference in voided volume, frequency or nocturia.

[‡]Symptom reduction using different evaluation techniques.

[§]Increased to 75 mg over 3 weeks.

[¶]Controlled patient rate was unusually low at 16%.

[#]55% for patients with history of allergies.

ex = Experimental; G = Glucosamine; GS = Chondroitin sulfate; m = Months; NS = Not significant; pl = Placebo; PPS = Pentosanpolysulfate; SH = Sodium hyaluronate.

but with no apparent histological changes in the bladder mucosa [128]. The leukotriene D4 receptor antagonist montelukast (single dose for 3 months) was used in 10 women with interstitial cystitis and detrusor mastocytosis was documented: there was a statistically significant improvement for urinary frequency, nocturia and pain within 1 month of treatment using a visual analog scale [116]. An open-label study also tested the oral prostaglandin agonist misoprostol (600 mg daily for 3 months) in 25 patients with refractory interstitial cystitis: 14 out of 25 (56%) of patients reported a significant improvement [129].

In view of the fact that tricyclic antidepressants have often been used in chronic pain, amitriptyline was used (75 mg four times a day over 3 weeks) in one open-label study with interstitial cystitis patients who had failed hydrodistention and intravesical DMSO: it led to a 50% reduction in pain and daytime frequency but not nocturia in 20 out of 25 patients [1,130]. A randomized, double-blind, placebo-controlled clinical trial (**Table 2**) of 50 patients with interstitial cystitis (using self-titration of up to 100 mg/day four times a day for 4 months) reported a 64% response rate using the GRA: however, during follow-up for 19 ± 12.5 months (mean dose of 55 mg/day), there was a 31% drop-out rate after 6 weeks (mean dose of 70 mg/day) due to non-response [131]. Even though no comparative studies have been conducted, it is the authors' opinion that non-tricyclic antidepressants do not appear to have the same benefit on interstitial cystitis symptoms, even though they may be useful in treating any depression experienced by such patients. In an open-label study of 48 women with interstitial cystitis, the non-tricyclic antidepressant duloxetine (titrated to 40 mg twice daily for 5 weeks) showed no significant improvement of symptoms using either the GRA or the O'Leary – Sant Symptom and Problem Index [132].

Many interstitial cystitis women of reproductive age often complain that their symptoms worsen during their menstrual cycle [48,133]. This finding and the prevalence of interstitial cystitis in women may be at least partially related to the fact that estradiol increases interstitial cystitis bladder biopsy mast cell pro-inflammatory molecule secretion [134], possibly through activation of the high-affinity estrogen receptors expressed on bladder mast cells [135]. Leuprolide acetate may be useful in such cases, as it could co-manage other CPP conditions, such as endometriosis [3].

No study has evaluated non-steroidal anti-inflammatory drugs, but they may actually be detrimental [136]. The authors' opinion is that they are not useful. However, there may be reason to consider some immunomodulators in patients with documented bladder inflammation [137].

One open-label study of 14 interstitial cystitis patients with Hunner's ulcers using 25 mg of prednisone daily for 2 months reduced ($p < 0.02$) the O'Leary – Sant Symptom and Problem Index by 22% and pain by 69% ($p < 0.001$) [138]. A randomized study of 64 patients with interstitial cystitis (meeting the NIDDK criteria) compared cyclosporin (100 mg three times daily) to PPS (1.5 mg/kg) for 6 months (**Table 2**): using the GRA, cyclosporin produced a 75% response rate as compared to 19% for PPS ($p < 0.001$) [139].

The natural flavonoid quercetin has anti-allergic, anti-inflammatory and mast cell-blocking actions [140]. In one open-label study, 37 female interstitial cystitis patients refractory to other treatments were administered quercetin (300 mg three times daily, together with 300 mg each of chondroitin sulfate and glucosamine) for 4 months, which resulted in a 52% ($p < 0.05$) reduction in their symptoms (**Table 2**) using the O'Leary – Sant Symptom and Problem Index and GRA scales [141]. A more recent open-label study (**Table 2**) of 127 interstitial cystitis patients used 300 mg quercetin twice daily (together with chondroitin sulfate, glucosamine and sodium hyaluronate at 300, 280 and 40 mg, respectively) and reported similar results (51% reduction) ($p < 0.0001$) whether taken for 6, 12 or 18 months [142]. These formulations can be given alone or together with any other treatment. In fact, they are increasingly added to or substitute for PPS when the latter has no apparent effect or results in adverse effects, such as alopecia.

In view of the fact that urine nitric oxide synthase was found to be decreased in common interstitial cystitis [72] and urine nitric oxide levels were decreased in classic interstitial cystitis that responded to treatment [143], oral L-arginine was used since it is the precursor for nitric oxide synthesis.

In one randomized, double-blind, placebo-controlled study, 21 out of 27 interstitial cystitis patients received 1500 mg of L-arginine for 3 months and were compared to 25 out of 26 patients on placebo: only pain was reduced in 48% of the patients on L-arginine as compared to 24% for placebo ($p = 0.07$) [144]. Another smaller randomized, double-blind, crossover study using 2.4 g of L-arginine in 16 interstitial cystitis patients for 1 month led to a reduction of 2.2 overall symptom score, but there was no significant difference in voided volume, frequency or nocturia [145].

A recent paper reported that a virus-induced neurogenic inflammation in mice led to an ~ 20-fold increase in degranulated mast cells in the lamina propria that was primarily dependent on TNF-α. These findings, along with the fact that TNF-α can promote mast cell trafficking [146], and can induce urothelial inflammation [98], prompted the suggestion of possible use of anti-TNF therapy.

Most interstitial cystitis patients experience pain, chronically, to various extents. However, few clinical trials have been conducted in interstitial cystitis with oral agents. Opioids (**Table 4**) could be given alone or together with hydroxyzine to increase the analgesic response and decrease adverse effects [147]. Tramadol, an opioid with weaker addiction potential and fewer adverse effects than those of morphine, is also available as an extended release preparation and, together with acetaminophen (37.5/325 mg twice daily), may be helpful. Pregabalin, a drug similar to gabapentin, has been approved for fibromyalgia pain and may also be useful in interstitial cystitis.

Table 4. Pain treatments useful interstitial cystitis.

Agent	Dose regiment	Class	Adverse effects
Systemic			
B + O Suppositories*	1 – 3 qd	Anticholinergic¶	Retention
Fentanyl patch	50 – 100 µg/h	Opioid	Dizziness, N/V
Gabapentin‡	200 – 400 mg qid	Antiepileptic	Sedation, N/V
Pregabalin		Antiepileptic	
Tramadol¶	75 – 100 mg qd	Opioid§	Nausea

*Belladonna + opium.
‡Together with morphine shown to have superior benefit.
§Weak addiction potential and fewer adverse effects compared to morphine.
¶Also available with acetaminophen (50 mg tramadol/250 mg acetaminophen).
N/V = Nausea/vomiting; qd = Once per day; qid = 4 times per day.

3.6 Intravesical treatment

Intravesical approaches include cystoscopic 'hydrodistention', as well as the instillation of DMSO, hyaluronate sodium or 'cocktails' containing heparin with lidocaine, bicarbonate, gentamicin and/or glucocorticoids. Bladder 'hydrodistension' under anesthesia is commonly used in interstitial cystitis patients, but is often associated with immediate pain and its effect in decreasing the symptoms of interstitial cystitis is unclear [1,2]. In a retrospective study comparing 47 patients with 'hydrodistension' to those without, 56% reported an improvement that lasted 2 months [13]. However, a recent study showed that, out of 33 previously untreated interstitial cystitis patients who underwent bladder hydrodistension, only 36% had at least a 30% decrease in their University of Wisconsin Symptom Instrument symptom score 1 month later and this benefit did not correlate with any reduction of urine 'markers' [69].

Dimethyl sulfoxide is the only intravesical agent approved in the USA. In a prospective randomized, double-blind study DMSO was compared to BCG in 6-weekly instillations in 11 patients with classic interstitial cystitis and 10 patients with non-classic interstitial cystitis diagnosed with the NIDDK criteria: there was a reduction in urinary frequency and pain but only in classic interstitial cystitis and there was no effect with Bacillus Calmette-Guérin (BCG) [148]. In another study of 28 interstitial cystitis patients, a series of six instillations of DMSO reduced the symptoms in 13 classic interstitial cystitis patients [149]. However, such studies are hard to control since there is a strong odor due to DMSO.

Intravesical administration of resiniferatoxin, a more potent analog of the hot pepper ingredient capsaicin, was used in some studies with variable results. A double-blind, placebo-controlled multicenter study (n = 163) using a single intravesical dose of 50 ml of resiniferatoxin (0.01, 0.05 or 0.1 µM) for 12 weeks failed to show any benefit [150]. Botulinum toxin injections in the trigone, external sphincter or bladder base may decrease interstitial cystitis symptoms. However, all studies were uncontrolled using very few patients, which are reported here in spite of the stated intent not to include studies with such few patients. One open-label study using suburothelial botulinum toxin (100 units) in 10 patients with refractory interstitial cystitis resulted in a limited improvement in the frequency and pain in only two out of 10 patients [151]. A recent open-label study of three men and 12 women with interstitial cystitis used 200 units of botulinum toxin submucosally in the bladder trigone and lateral walls: 13 out of 15 (86.6%) had a significant urinary frequency decrease ($p < 0.05$) using a visual analog scale.

Intravesical hyaluronate sodium (0.04%) is approved for interstitial cystitis in Canada (but not the USA) based on two open-label studies using weekly instillations for 4 weeks that reported some pain reduction [1]. A recent study of intravesical sodium hyaluronate (40 mg/50 ml) administered weekly in 126 women with interstitial cystitis reported an improvement in 103 out of 126 patients (85%) with a visual analog scale mean score reduction from 8.5 to 3.5 ($p < 0.0001$) [152]. However, two randomized, double-blind, placebo-controlled multicenter studies using 10 times more concentrated sodium hyaluronate (0.4%) failed to show any benefit and were terminated by the sponsor (personal communication, [153]). A recent open-label study of 23 women with refractory interstitial cystitis used intravesical administration of both hyaluronic acid (1.6%) and chondroitin sulfate (2.0%) weekly for 20 weeks and then monthly for 3 months. Even though the daily voids did not decrease, pain was reduced from 5.4 to 3.6 ($p = 0.001$) [152].

Intravesical 'cocktails' using heparin, lidocaine and bicarbonate with or without gentamicin and/or glucocorticoids are widely used [5]. In one uncontrolled study, heparin (40 000 IU) together with either 1 or 2% lidocaine and 8.4% sodium bicarbonate three times weekly for 2 weeks resulted in an over 50% improvement in ~ 75% of newly diagnosed interstitial cystitis patients [154]. One study reported an improved dyspareunia response following intravesical lidocaine, bicarbonate and heparin [155]. Another study argued for combined use of intravesical and systemic treatments [156].

4. Other invasive approaches

In one prospective study of 25 patients, 17 qualified for permanent sacral nerve stimulator implantation and 16 out of 17 sustained significant improvement [157]. In another retrospective study, the mean intramuscular morphine dose equivalents of interstitial cystitis patients refractory to other forms of therapy decreased from 81.6 to 52 mg/day (35%) ($p = 0.015$) following sacral neuromodulation and four out of 18 patients stopped narcotics [158]. In contrast, a double-blind study of daily 30-s transdermal laser stimulation of the posterior tibial nerve for 12 weeks in 29 patients with interstitial cystitis compared to 27 placebo-sham-stimulated patients showed no significant difference between groups [159].

When such treatments have failed, laser therapy and surgical approaches such as cystoplasty, bladder wall resection or bladder division with or without cystectomy may be indicated.

5. Conclusion

The pathogenesis and diagnosis of interstitial cystitis remains unknown. Interstitial cystitis appears to be much more prevalent than previously suspected and may contribute significantly to CPP, in addition to IBS and endometriosis. Treatment is still challenging and no new effective curative therapies are available. However, the symptoms in some patients could be contained with some fairly well-tolerated agents. Subgroups of interstitial cystitis patients with either distinct bladder pathology (e.g. increased mast cells) or co-morbid diseases (e.g., fibromyalgia) may respond differently to specific treatments. Nevertheless, some patients fail all treatments and are debilitated and disabled.

As was also concluded elsewhere recently, many clinical studies have a poor description of interstitial cystitis patients, with variable inclusion and exclusion criteria [160]. In general, it was felt that small, well-controlled studies using newly diagnosed patients with a recent onset of symptoms and no co-morbidities may yield better information than larger studies using chronic patients who have already been on numerous treatments and have many co-morbid diseases, making any conclusion difficult to reach. The possibility of using CRH receptor antagonists [161] certainly warrants consideration.

6. Expert opinion

In spite of considerable funding from the US NIH, the pathogenesis, diagnosis and treatment of interstitial cystitis remains elusive. There are a number of key areas that appear to have escaped serious research. These include the following.

1. The reason(s) why interstitial cystitis occurs primarily in females and the role of female sex hormones.
2. Common pathogenetic mechanism(s) explaining why interstitial cystitis is co-morbid with other diseases, also occurring more often in females.
3. The relationship between bladder mastocytosis and many interstitial cystitis symptoms.
4. The molecular mechanisms involved in the worsening of interstitial cystitis symptoms associated with emotional or physical stress.
5. A comprehensive plasma and urine cytokine/chemokine/growth factor profile of interstitial cystitis patients and subgroups.
6. The use of oral or intravesical solutions that address inflammation or mastocytosis, such as combinations of select flavonoids and glycosaminoglycan components that could both reduce bladder inflammation and correct any glycosaminoglycan layer defects.
7. The use of newly diagnosed untreated patients with a short history of symptoms (< 12 months) in clinical trials and powered sufficiently to allow cohort analysis of interstitial cystitis subgroups.

Appropriate funding should be directed at the establishment of research alliances to address such topics, in addition to funding general themes such as ‘epidemiology’ or ‘basic science’.

Declaration of interest

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