Role of inflammation in bladder function and interstitial cystitis

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***Abstract*:** Cystitis, or inflammation of the bladder, has a direct effect on bladder function. Interstitial cystitis is a syndrome characterized by urinary bladder pain and irritative symptoms of more than 6 months duration. It commonly occurs in young to middle-aged women with no known cause and in fact represents a diagnosis of exclusion. Many factors have been suggested, including chronic or subclinical infection, autoimmunity and genetic susceptibility, which could be responsible for initiating the inflammatory response. However, a central role of inflammation has been confirmed in the pathogenesis of interstitial cystitis. Patients with interstitial cystitis are usually managed with multimodal therapy to break the vicious cycle of chronic inflammation at every step. Patients who develop irreversible pathologies such as fibrosis are managed surgically, which is usually reserved for refractory cases.

***Keywords*:** bladder, inflammation, interstitial cystitis, management, painful bladder syndrome

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Bladder inflammation

Cystitis, or inflammation of the bladder, has a direct effect on bladder function. It can occur due to both infectious as well as noninfectious etiologies. Infections can be due to Gram-negative microorganisms such as *Proteus, Klebsiella, Citrobacter, Enterobacter*, and *Pseudomonas* species and Gram-positive pathogens such as *Enterococcus fecalis, Staphylococcus saprophyticus*, and group B streptococci. However, *Escherichia coli* represents the most common cause of infectious cystitis [Echols *et al.* 1999]. Noninfectious cystitis can be due to a variety of causes, such as medication, radiation, foreign bodies, chemicals, autoimmune response, and may even be idiopathic in nature such as interstitial cystitis (IC); it may also occur in association with other diseases such as, gynecological cancer, PID, and Crohn's disease. Irrespective of the cause, cystitis can be acute or chronic depending upon the duration of the insult.

The first and early response to any noxious stimulus or injury occurs in the form of acute inflammation. Acute inflammation is characterized by vasodilation and increased vascular permeability, leukocyte migration to the site of injury, and activation of biochemical cascade of inflammation causing release of mediators such as cytokines, histamines, kinins, complement factors, clotting factors, nitric oxide, and proteases. In the case of acute cystitis these mediators cause erythematous swelling and ulceration of the bladder mucosa, which bleeds easily. The surface layer is shred, forming small, clear cysts (sacs with liquid, gas, or semisolid contents) frequently seen on urine analysis. In addition, these mediators cause bladder mucosal irritation, which is responsible for urgency, increased frequency, and dysuria. The systemic release of inflammatory mediators causes low-grade fever. In general, these mediators have a short half-life and are quickly degraded, therefore enabling rapid resolution of inflammation as soon as the noxious stimulus is removed. However, if the stimulus is not removed, chronic inflammation ensues, such as seen in IC. This is characterized by infiltration of mononuclear cells such as macrophages, lymphocytes, eosinophils, mast cells, and plasma cells leading to irreversible tissue destruction, dysfunctional pathology such as fibrosis and poor compliance, detrusor overactivity, and hyperalgesia responsible for the chronic waxing and waning symptoms of pain and lower urinary tract symptoms. In this review we limit our discussion to the effects of chronic inflammatory disease such as IC on bladder function.

Interstitial cystitis

IC is a syndrome characterized by urinary bladder pain and irritative symptoms of more than 6 months duration. It commonly occurs in

young to middle-aged women with no known cause and in fact represents a diagnosis of exclusion. Over 1 million people are affected by IC in the United States alone [Hanno, 2002; Jones and Nyberg, 1997], in fact; an office survey indicated that 575 in every 100,000 women have IC [Rosenberg and Hazzard, 2005]. Another study on self-reported adult IC cases in an urban community estimated its prevalence to be approximately 4% [Ibrahim *et al.* 2007]. Children and adolescents can also have IC [Shear and Mayer, 2006]; patients with IC have had 10 times higher prevalence of bladder problems as children than the general population [Hanno, 2007].

The constellation of IC symptoms has been given different names. The International Continence Society named the disease interstitial cystitis/painful bladder syndrome (IC/PBS) in 2002 [Abrams *et al.* 2002], while the Multinational Interstitial Cystitis Association have labeled it as painful bladder syndrome/interstitial cystitis (PBS/IC) [Hanno *et al.* 2005]. Recently, the European Society for the study of Interstitial Cystitis (ESSIC) proposed the moniker, 'bladder pain syndrome' (BPS) [van de Merwe *et al.* 2008].

Etiology

The precise etiology of IC is still unknown. Many factors have been suggested, including chronic or subclinical infection, autoimmunity, and genetic susceptibility, which could be responsible for initiating the inflammatory response.

Infection. Earlier, bacterial infection was thought to be the main cause of the changes observed in IC. Wilkins and colleagues suggested that fastidious bacteria such as *Gardnerella vaginalis* and Lactobacillus may be responsible for development of IC [Wilkins *et al.* 1989]. Domingue and colleagues demonstrated the presence of bacterial 16S rRNA genes in bladder tissue in 29% of patients with IC [Domingue *et al.* 1995]. However, several other studies failed to confirm this finding, and it is now generally accepted that infection does not represent the etiology behind IC.

Autoimmunity. An increased number of CD8+ and CD4+ T lymphocytes [MacDermott *et al.* 1991], plasma cells, and immunoglobulins such as IgG, IgA, and IgM [Christmas, 1994] are detected within the urothelium and lamina propria layer of the bladder in IC compared with normal bladders. However, no consistent profile of immune activity has been reported so there remains significant doubt about whether these findings are causative or a reaction to the cause.

Environmental factors. Studies have also shown worsening of IC symptoms with stress, spicy food, and smoking. Recently, the Events Preceding IC Study reported that the pain in 97% worsened with certain foods and drinks such as alcohol, citrus fruits, coffee, carbonated drinks, tea, chocolate, and tomatoes [Warren *et al.* 2008] comparable to findings from the Interstitial Cystitis Database (ICDB) where 262 out of 270 (97%) patients reported worsening of pain [Simon *et al.* 1997].

Association with other diseases. IC patients also been shown to have a higher incidence of other comorbid diseases [Peeker *et al.* 2003; Aaron and Buchwald, 2001; Erickson *et al.* 2001; Alagiri *et al.* 1997; Koziol *et al.* 1993] including allergies (in roughly 40–60% of patients) [Stanford *et al.* 2005; Yamada, 2003], fibromyalgia, irritable bowel syndrome (IBS; 35% cases) [Novi *et al.* 2005], vulvodynia (20–51.4% of patients) [Peters *et al.* 2008; Stanford *et al.* 2005], endometriosis, panic disorders, and inflammatory bowel disease (IBD), particularly in patients with Hunner's ulcers [Peeker *et al.* 2003; Alagiri *et al.* 1997].

Genetic link. Studies have shown that IC is more common in twins with chronic fatigue syndrome. Recently, Warren and colleagues studied the prevalence of IC in first-degree relatives of patients with IC, reporting that adult female first-degree relatives have a prevalence of IC 17 times greater that found in the general population [Warren *et al.* 2004]. They also studied the prevalence of IC in monozygotic and dizygotic twins, reporting a greater concordance of IC among monozygotic compared with dizygotic twins, suggesting a genetic contribution to IC [Warren *et al.* 2001].

Pathophysiology and role of inflammation in the presentation of IC

Many theories have been suggested to exemplify the pathogenesis behind IC. However, a central role of inflammation has been confirmed in both human and animal studies using electron microscopy and immunohistochemical staining techniques. Irrespective of the etiology, if the noxious stimulus persists for a longer duration, it leads chronic inflammation. As a result,

a cascade of events, which are interrelated with each other is initiated, resulting in a vicious, self-reinforcing cycle of persistent inflammation and recurrent injury to bladder epithelium [Sant *et al.* 2007] (Figure 1).

Dysfunctional urothelium. The urothelium is covered by a layer of glycosaminoglycans chondroitin sulfate, hyaluronate sodium, glycoproteins, and mucins to protect the bladder [Hanno, 2007]. In IC damage occurs to the mucous or glycosaminoglycans layer, causing altered permeability of the urothelium to various urinary cations such as potassium. Damage also occurs to the urothelium after an initial insult, followed by cytokine production, leading to the proliferation and activation of mast cells [Theoharides *et al.* 2001]. Influx of potassium ions causes upregulation of sensory afferent nerves, which further activates the mast cells, thus initiating a vicious, self-reinforcing cycle [Parsons *et al.* 1998; Lilly and Parsons, 1990]. In addition, studies have suggested that the urothelium releases a number of neuropeptides (e.g. nerve growth factor) neurotransmitters and antiproliferative factor (APF), which activates submucosal afferent nerves and mast cells during this process [Theoharides *et al.* 2001] resulting in hyperalgesia in patients with IC. APF induces increased permeability of normal urothelium and regulates expression of other cytokines, such as upregulating heparin-binding epidermal growth factor-like growth factor and downregulating epidermal growth factor, by the urothelium. These cytokine abnormalities could mediate increased bladder sensation and pain [Graham and Chai, 2006].

Mastocytosis and mast cell activation. An increased number of mast cells, both in submucosa and detrusor layers [Johansson and Fall, 1990], can be seen particularly in classic IC with Hunner's ulcers. A study using immunocytochemical techniques demonstrated a 6- to 10-fold increase in mast cells in classic/ulcerative IC compared with a 2-fold increase in patients with nonulcerative IC [Peeker *et al.* 2000b]. Recent studies have shown that a diagnostic cutoff of mast cell counts >20 cells/mm^2 in bladder muscle have 95% diagnostic sensitivity with 88% diagnostic specificity for IC [Kastrup *et al.* 1983].

Mast cells are activated by numerous mediators such as: (1) cytokines-like stem cell factor (SCF) [Peeker *et al.* 2000b; Pang *et al.* 1998] that are released by damaged urothelium or nerve growth factor (NGF) [Lowe *et al.* 1997], which is also increased in patients with IC; (2) bacterial and viral super antigens; (3) immunoglobulin aggregates; (4) neuropeptides, such as substance P (SP) [Theoharides *et al.* 2001]; (5) acetylcholine (ACh) [Theoharides *et al.* 2001]; and (6) neurotensin. Once activated, mast cells undergo degranulation to release vasoactive, inflammatory, and nociceptive mediators, such as histamine, kinins, proteases (e.g. tryptase), cytokines, leukotrienes (e.g. IL-6 and IL-8), prostaglandins, and nitric oxide [Cao *et al.* 2005; Sant and Theoharides, 1994].

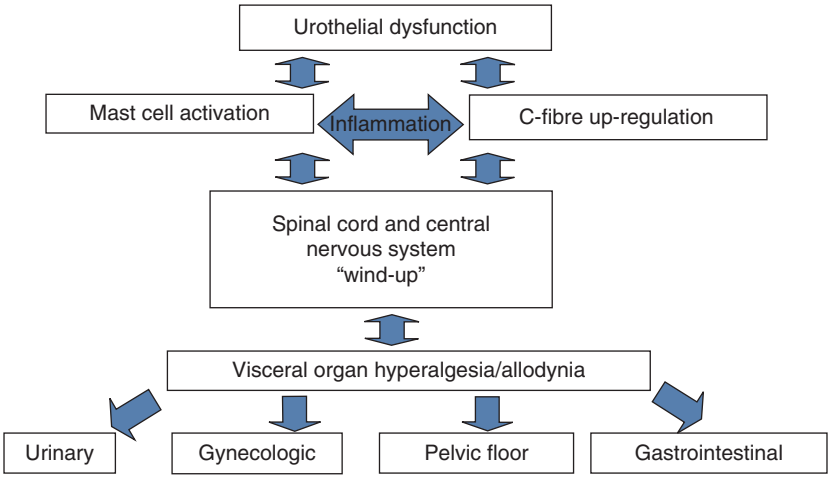

Figure 1. Integrated pathophysiology of interstitial cystitis. (Reproduced with permission from Sant *et al.* [2007]).

For example, vascular endothelial growth factor (VEGF) is overexpressed in 58% of IC bladders [Tamaki *et al.* 2004], while IL-6 and IL-8 are also overexpressed. The release of vasoactive and inflammatory mediators from mast cells may explain many IC symptoms. Tryptase can cause microvascular leakage [He and Walls, 1997] and stimulate protease-activated receptors (PARs), in turn leading to widespread inflammation and neuronal hyperexcitability [Theoharides and Cochrane, 2004]. Mast cell-derived tumor necrosis factor-α (TNF-α) activates the nuclear transcription factor-κB [Batler *et al.* 2002; Rackley *et al.* 1999], which is a key regulator of inflammatory gene expression, causing further urothelial inflammation. VEGF, another mast cell mediator, causes vasodilation and may therefore be responsible for the hypervascularity and glomerulations, which are characteristic of IC [Tamaki *et al.* 2004]. Studies have also shown an association between increased VEGF and severity of IC-associated pain [Kiuchi *et al.* 2009]. Usually, these mediators have shorter half-life, but in IC the noxious stimulus persists for a longer duration resulting in increased secretion of inflammatory mediators even when the stimulus is removed. This causes angioedema leading to vasculitis and neuroinflammation, which promote neuritis and secretion of neurotransmitters that further stimulate mast cells. Therefore, a vicious circle of events begins, causing persistent inflammation and urothelial reinjury, which clinically manifests as hyperalgesia leading to dysuria, urgency and lower urinary tract symptoms.

Neuronal inflammation and nerve upregulation. It is believed that IC also represents a visceral neuropathic pain syndrome mediated by upregulation of nerves in the pelvis, spinal cord, and brain. The vasoactive and inflammatory molecules, such as SP and NGF, secreted by mast cells potentially increase proliferation of the nerve fibers [Theoharides *et al.* 1995]. Studies have shown that there is an increase in nerve fibers in IC, particularly those containing the neuropeptide SP in patients with untreated IC [Pang *et al.* 1995b]. Perivascular sensory nerve terminals have been found to have enhanced sensitivity to SP leading to a local cascade of neurogenic inflammatory responses, which is responsible for the pathophysiological changes of IC [Marchand *et al.* 1998; Parsons *et al.* 1980]. This potentially explains the flaring of symptoms in female patients with IC before menses due to an estrogen surge that induces histamine release from mast cells with subsequent secretion of SP [Pang *et al.* 1995a]. Likewise, stress may exacerbate IC symptoms due to release of corticotropin-releasing factor (CRF) and subsequent activation of mast cells [Theoharides *et al.* 2004, 1998]. The increased levels of NGF and morphological changes (neuroplasticity) in sensory and motor neurons may be responsible for continued pain, frequency, and urgency even after the initial inflammatory stimulus has subsided.

An increased sensitivity of bladder sensory afferents may also be responsible for increased pain sensation or hyperalgesia [Dmitrieva *et al.* 1997; Cervero, 1994; Eide *et al.* 1993; Dubner and Ruda, 1992]. Pelvic and hypogastric/lumbar splanchnic nerve innervations of the bladder contain mechanosensitive Aδ and C-fibers that also respond to chemical and thermal stimuli, particularly after sensitization. These nerve fibers are found in serosa, muscle, and urothelium. As bladder volume increases, the threshold for mechanosensitive endings, which encode for changes in volume, decreases, leading to activation and discharge of these fibers at a lower bladder volume causing urgency. Numerous other mediators have also been identified in modification of this afferent pathway including SP, neurokinin A, calcitonin gene related protein (CGRP), vasoactive intestinal peptide, and enkephalins [Cervero, 1994].

The effect of local hypersensitivity reflected on the peripheral and/or central nervous systems. Hypersensitivity to nonpainful and normally painful stimuli causes an increased input from sensitized bladder afferents which in turn stimulates the release of neuroactive chemicals in the spinal cord dorsal horn, leading to central (spinal) hyperexcitability [Mayer and Gebhart, 1994]. Various mediators, including glutamate, SP, and CGRP released from the central terminals of primary afferent fibers, are involved in central sensitization [Ruda and Dubner, 1992]. *N*-methyl-D-aspartate (NMDA) and NO receptors have been identified in spinal dorsal horn neurons, may also have a role [Traub *et al.* 1992; Woolf and Thompson, 1991; Davies and Lodge, 1987]. This brings about changes in gene expression and neurotransmitter synthesis causing a state of neurologic 'wind up' manifested by visceral allodynia and

hyperalgesia in the bladder and adjacent pelvic organs (gastrointestinal, gynecologic) such as dyspareunia, vulvodynia, and IBS.

These changes in urothelial permeability, urothelial activation, sensory nerve stimulation, and mast cell activation are complex and are interrelated with multiple, simultaneous positive and negative feedback loops. This vicious circle is responsible for the irreversible dysfunctional pathology such as fibrosis and poor compliance, detrusor overactivity, and hyperalgesia responsible for the chronic waxing and waning symptoms of pain and lower urinary tract symptoms.

Presentation and diagnosis

Since IC can have a very heterogeneous clinical presentation, it is grouped according to the pathologic features as classic (ulcerative) *versus* non ulcerative cystitis, mild vs. severe inflammation with the degree and location of mast cell activation described.

IC as described originally by Hanash and Pool is characterized by urinary symptoms of severely reduced bladder capacity and cystoscopic findings of Hunner's ulcers [Hunner, 1918], which are patches of reddened mucosa exhibiting small vessels radiating to a central pale scar [Hanash and Pool, 1969]. However, the more frequent presentation of IC is the nonulcerative variety, which is characterized by glomerulation and submucosal hemorrhages.

In the past, clinicians have relied on the criteria proposed by the National Institutes of Arthritis Diabetes Digestive and Kidney Diseases (NIDDK) for the diagnosis of IC [Wein *et al.* 1990]. These stringent criteria were originally designed for research purposes and in fact based on a consensus of expert opinion, not clinical evidence. Recent studies have shown that relying on the NIDDK criteria may result in the misdiagnosis in 60% of patients who definitely or likely had IC by clinical criteria [Abrams *et al.* 2006; Kusek and Nyberg, 2001]. It is now widely accepted that the diagnosis of IC should be based on symptoms along with the exclusion of similar conditions such as, pelvic pain, urinary tract infection (UTI), yeast infections, endometriosis, pelvic organ prolapse, gynecological or urological malignancies, overactive bladder, and chronic prostatitis (Figure 2).

In 2002, the International Incontinence Society (ICS) revised the definition of PBS an effort towards diagnosis standardization [Abrams *et al.* 2002]. PBS was defined as the complaint of suprapubic pain related to bladder filling accompanied by other symptoms such as increased daytime and nighttime frequency in the absence of proven urinary infection or other obvious pathology.

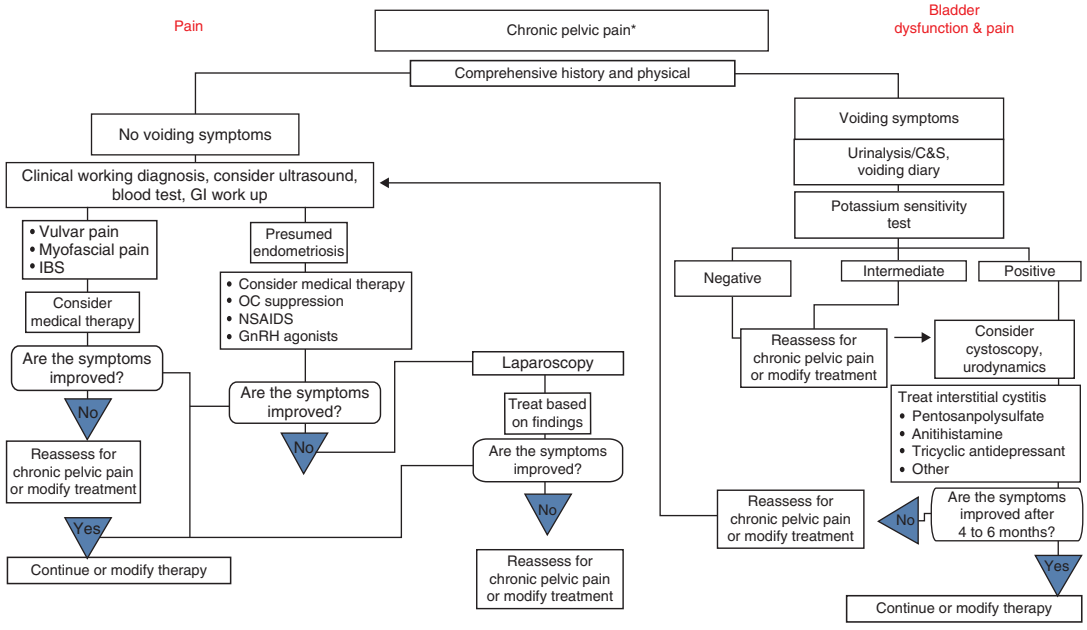

Figure 2. Algorithm for the management of patients with chronic pelvic pain. GnRH, gonadatrophin-releasing hormone; IBS, irritable bowel syndrome; OC, oral contraceptives.

Recently, the European Society for the Study of Interstitial Cystitis (ESSIC) [van de Merwe *et al.* 2008] defined IC as chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder and accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency. Further, tests such as biopsy or cystoscopy with hydrodistention are not necessary for the diagnosis of IC, but may help to classify the types of IC.

Patients with IC may also experience flares with seasonal allergies and sexual intercourse [Parsons, 2002]. Voiding typically relieves pain [Metts, 2001], and as such, patients may void frequently in small volumes to relieve pain as the bladder fills. Patients with IC are more likely to be diagnosed with other accompanying diseases such as IBS [Novi *et al.* 2005; Alagiri *et al.* 1997; Koziol, 1994], IBD, allergies, fibromyalgia, and systemic lupus erythematosus (SLE) [Alagiri *et al.* 1997]. A voiding diary may be helpful to establish frequency, nocturia, and the presence of triggers such as allergies, certain foods, and/or intercourse [Nickel, 2004]. Symptom screeners such as the pelvic pain and urgency/frequency (PUF) questionnaire and the O'Leary–Sant IC symptom and problem indices can also be used in obtaining this information [Parsons *et al.* 2002a; O'Leary *et al.* 1997]. Tenderness of the urethra and bladder base on single-digit examination is typical of IC.

Laboratory studies are used to help distinguish IC from other similar conditions. Urinalysis should be done to rule out hematuria, and urine culture should be performed to identify bladder infection [Butrick, 2003; Nickel, 2000]. Cytology and CT scan with noncontrast, arterial, and delayed phase imaging should be performed whenever there is history of smoking, hematuria, and/or age >40 years, to rule out urinary tract malignancies [Ottem and Teichman, 2005]. Cystoscopy with or without hydrodistention can be helpful to confirm IC [Ottem and Teichman, 2005; Metts, 2001]. Glomerulations may be present, although these may also be present in subjects with no symptoms of IC [Waxman *et al.* 1998]. Hunner's ulcers can also be seen in patients with IC; a negative cystoscopic evaluation, however, should not be used to rule out IC as many patients with early IC do not have glomerulations or Hunner's ulcers [Ottem and Teichman, 2005]. Several other optional diagnostic tests also exist to help define the diagnosis of IC, such as the potassium sensitivity test (PST), anesthetic bladder challenge (ABC), bladder biopsy, urodynamic testing, and assessment of urinary markers. A positive PST, for example, can be indicative of a defective bladder lining, consistent with IC. The PST involves intravesical instillation of a potassium solution, which triggers symptoms of pain and urgency in patients with abnormal bladder surface permeability [Teichman and Nielsen-Omeis, 1999]. The ABC can be performed for patients who present with pain of suspected bladder origin; the patient is catheterized and an intravesical anesthetic cocktail containing alkalinized lidocaine is administered. Dissipation of pain upon instillation confirms that the bladder is the site of origin of the pain [Evans and Sant, 2007]. Bladder biopsy is advised when a lesion is found, to rule out carcinoma *in situ*, for example [Sant, 2002]. Although, urodynamic testing is not required for a diagnosis of IC, it may help rule out other bladder disorders such as detrusor instability, stress urinary incontinence, and bladder outlet obstruction [Nickel, 2004; Sant and Hanno, 2001]. Miscellaneous tests such as evaluation of urinary markers, such as, eosinophil cationic protein, glycoprotein-51, and APF can also be performed [Erickson, 2001]. Of these, the activity of APF, is specific and selective (>90%) for patients with IC compared with matched control patients ($p < 0.005$) [Erickson, 2001]. APF inhibits the proliferation of primary human bladder epithelial cells by downregulating growth factors, which are involved in the pathogenesis of IC [Keay *et al.* 2000].

Management

From our current understanding of chronic bladder inflammation, there are many steps in the pathogenesis, which can be targeted during treatment selection. As such, a multimodal treatment regimen with oral therapies, intravesical therapies, complementary therapies that utilize anti-inflammatory, neural, anesthetic, and behavioral agents as well as others, is our current approach. Finally, surgical techniques can be used as a last resort to structurally alter, modify, or remove the source of pain. Studies have shown that many patients respond well to treatment strategies that use a variety of pharmacological and non-pharmacological approaches [Nickel *et al.* 2005; Evans, 2002]. In chronic bladder inflammation, the concept of a cyclical process is often proposed, with the idea that if one breaks the cycle of recurrence, it will lead to healing. As such,

treatment is directed at the urothelial layer, nervous system, immune system to break the cycle of pain at various steps (Figure 3).

Nonpharmacological approaches

Nonpharmacological approaches involve techniques that the patients may use to reduce the severity of IC symptoms, such as stress and anxiety reduction, exercise and physical therapy, sex therapy and counseling, bladder training, pelvic floor rehabilitation training, and dietary changes [Nickel, 2004; Butrick, 2003]. Physical therapy techniques, such as biofeedback to control pelvic floor dysfunction [Whitmore, 2002], soft tissue massage including myofascial release, and bladder retraining are commonly used in patients with little or no pain [Whitmore, 1994]. Intensive physical therapy should be used at the outset of symptoms and repeated at least once a year to maintain benefit.

As a latency period between the start of the treatment and the relief of symptoms is common, reassurance and management of the patient expectations regarding IC is critical to main adherence to their treatment plan [Evans, 2002].

Pharmacological approaches

Oral medications

Bladder mucosal protectors. *1. Pentosan polysulphate (Elmiron).* Pentosan polysulphate acts by coating the bladder lining and re-establishing the normal glycosaminoglycan (GAG) layer function [Moldwin and Sant, 2002]. Parsons and colleagues conducted a double-blind multicenter study where IC patients who were treated with pentosan polysulphate showed improvement in their symptoms [Parsons *et al.* 2002b].

Anti-allergics. *1. Antihistamines.* Since mast cells and their mediators such as histamine are the key players in the inflammation and pathogenesis of IC [Moldwin and Sant, 2002], therapy that blocks the effect of histamine have been shown to improve symptoms. These include the H1 blocker hydroxyzine hydrochloride [Moldwin and Sant, 2002] as well as H2 blockers such as cimetidine which have shown to produce significant improvement in pain and nocturia in a limited trial of IC patients [Thilagarajah *et al.* 2001].

2. Leukotriene-D4 receptor antagonist montelukast. The presence of leukotriene receptors in detrusor muscle cells [Bouchelouche *et al.* 2001a] and an increased urinary level of leukotriene E4 in IC patients suggests a role for these pro-inflammatory mediators in IC. Bouchelouche and colleagues reported their experience in 10 women with IC [Bouchelouche *et al.* 2001b], who were treated with the leukotrine antagonist montelukast. They found that after 1 month of montelukast treatment, there was a statistically significant decrease in 24-hour urinary frequency, nocturia and pain, which persisted during the 3 months of treatment. After 3 months, 24-hour urinary

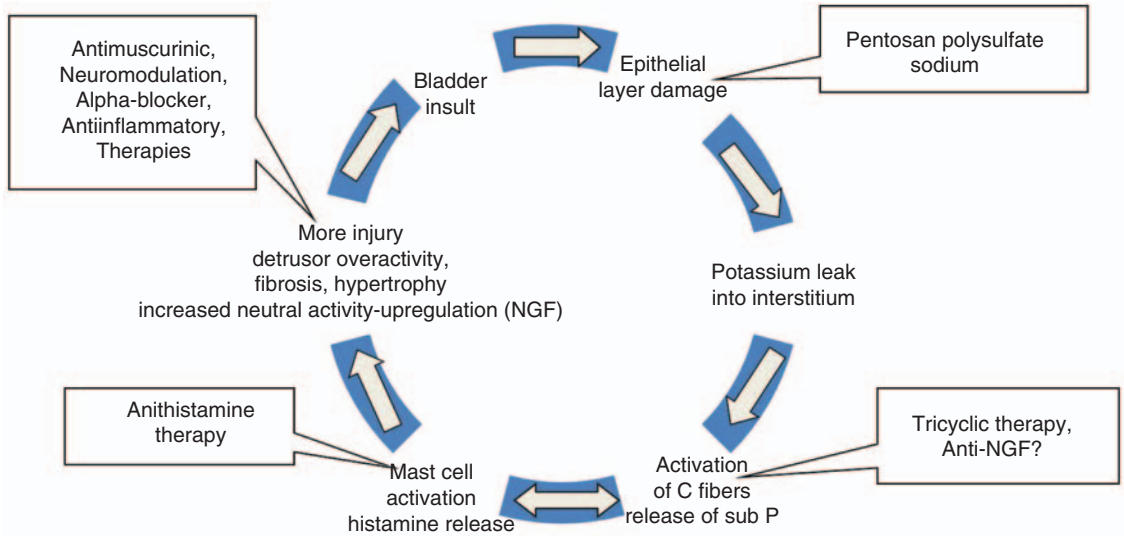

Figure 3. The cycle of interstitial cystitis: treatment directed at the urothelial layer, nervous system, and immune system to break the cycle of pain at various steps.

frequency decreased from 17.4 to 12 voidings ($p = 0.009$), nocturia decreased from 4.5 to 2.8 ($p = 0.019$) and, pain decreased from 46.8 to 19.6 mm on a visual analog scale ($p = 0.006$). There were no side effects observed during the treatment.

Pain modulators. *1. Tricyclic antidepressants*. Amitriptyline has been shown to be effective in the management of chronic pain syndromes, including IC [Hanno, 1994]. Amitriptyline modulates the transmission of nociceptive stimuli by inhibiting the presynaptic reuptake of serotonin and noradrenaline [Tura and Tura, 1990]. Amitriptyline has been found to be beneficial in a controlled trial for IC with long-term follow up using a stepwise dose escalation, and is reported to cause 50% reduction in pain and daytime frequency [Hanno *et al.* 1989]. Recently, a randomized, double-blind, placebo-controlled clinical trial of amitriptyline in 44 women and 6 men with IC that used a self-titration protocol (up to 100 mg/day at bedtime for 4 months) reported a significant improvements in all symptoms [van Ophoven *et al.* 2004]. In another study, long-term follow up of 60 patients treated with amitriptyline for 19 ± 12.5 months was associated with a response rate of 64% using the Global Response Assessment [van Ophoven and Hertle, 2005].

2. Anticonvulsants. Anticonvulsants such as gabapentin often are prescribed for neuropathic pain [Lukban *et al.* 2002; Hansen, 2000]. These drugs can be used to treat patients with refractory IC who have failed to respond to other treatments [Butrick, 2003].

Hormone modulators. *1. Leuprolide acetate*. Many women of reproductive age with IC often complain of worsening symptoms during their menstrual cycle [Powell-Boone *et al.* 2005]. This may be related to the fact that estradiol activates the estrogen receptors expressed on bladder mast cells, which in turn increases pro-inflammatory molecule secretion [Spanos *et al.* 1996]. Leuprolide acetate may be useful in such cases, as it is a gonadotropin-releasing hormone agonist causing a reduction in estradiol secretion. In 15 female patients with irritable bladder symptoms and pelvic pain without endometriosis, symptoms improved in eight of nine patients treated with leuprolide acetate and in five of six patients treated with oral contraceptives [Lentz *et al.* 2002]. The estrogen receptor antagonist has shown to significantly increase the mean maximum bladder volume by over 70% in rat chemical cystitis model [Acar *et al.* 2007].

Anti-inflammatory. *1. Anti-TNF therapy.* Recently, various research studies have focused on the neuro-inflammatory mechanism of pain to further target specific areas for therapy. A hypothetical model of a cholinergic anti-inflammatory pathway, based on bacterial LPS as a stimulant, has been proposed and therapies are being developed to specifically target and disrupt this neuro-inflammatory loop such as anti-NGF to lower SP, or anti-TNF-α or neuromodulation to break the loop and provide relief [Saini *et al.* 2008].

Animal studies have reported that a virus-induced neurogenic inflammation can lead to a 20-fold increase in degranulated mast cells in the lamina propria, that is primarily dependent on TNF-α [Chen *et al.* 2006]. In addition, TNF-α can promote mast cell trafficking and induce urothelial inflammation [Batler *et al.* 2002]. These findings have prompted the suggestion of a possible use for anti-TNF therapy, although no clinical data for its use exists.

2. Narcotics and pain relief. Most IC patients experience chronic pain, albeit to various extents. The pain could be managed with opioids either alone or in combination with hydroxyzine to increase the analgesic response and decrease adverse effects [Hupert *et al.* 1980]. Tramadol, with fewer adverse effects than those of morphine, either alone or together with acetaminophen (37.5/325 mg twice daily), may be helpful.

3. Immunosuppressive agents. Immunosuppressive agents may be used as second-line therapy in IC. Prednisone for example may be used in treatment refractory cases [Soucy and Gregoire, 2005]. Thirty patients with Hunner's ulcer subtype IC showed considerable improvement following endoscopic submucosal injection of triamcinolone [Cox *et al.* 2009]. Other drugs such as cyclosporine have also been shown to relieve the symptoms of severe IC [Sairanen *et al.* 2005; Forsell *et al.* 1996]. In an open-label study in 11 patients with intractable IC, cyclosporine treatment for up to 6 months reduced micturition, urinary frequency, and bladder pain significantly in most of the patients [Forsell *et al.* 1996]. Recently, in a randomized study on 64 patients with IC that met NIDDK criteria,

patients were treated with either cyclosporine or pentosan polysulfate for 6 months. The clinical response rate was determined using the Global Response Assessment and was found to be 75% for cyclosporine, compared with 19% for pentosan polysulfate ($p < 0.001$) [Sairanen *et al.* 2005].

Others. *1. L-arginine*. Patients with IC have decreased urine nitric oxide synthase and urine nitric oxide levels [Hosseini *et al.* 2004]. These patients respond to treatment with oral L-arginine, a precursor in nitric oxide synthesis. In one randomized, double-blind, placebo-controlled study, 21 out of 27 IC patients received 1500 mg of L-arginine for 3 months and were compared with 25 out of 26 patients on placebo: a greater global improvement in the L-arginine group (48%, 10 of 21) compared with the placebo group (24%, 6 of 25) at 3 months ($p = 0.05$) with a decrease in pain intensity ($p = 0.04$), and tendency toward improvement in urgency ($p = 0.06$) and frequency of pain ($p = 0.09$) were noticed [Korting *et al.* 1999]. In another randomized, double-blind, crossover study using 2.4 g of L-arginine in 16 IC patients for 1 month, there was a reduction of 2.2 in overall symptom score, but no significant difference in voided volume, frequency, or nocturia [Cartledge *et al.* 2000].

2. Anticholinergics. Oxybutynin and tolterodine are commonly used anticholinergic drugs for the treatment of symptoms associated with overactive bladder in IC. They both act mainly on the muscarin-3 (M3) subtype receptor, which causes contraction of bladder detrusor, urgency, and urinary incontinence. Unfortunately, salivary glands also have M3 receptor, and therefore dry mouth is a major side effect especially with oxybutynin [Cannon and Chancellor, 2002]. A long-acting once-a-day formation of tolterodine (Detrol LA) was approved by the US Food and Drug Administration (FDA). Tolterodine LA has fewer side effects and similar or modestly better efficacy than the twice-a-day tolterodine formulation [Van Kerrebroeck *et al.* 2001]

Intravesical treatment

Pain modulators. *1. Dimethylsulfoxide (DMSO*). DMSO can have analgesic, anti-inflammatory, collagenolytic, muscle relaxant effects, and in fact represents a standard treatment for IC. In a controlled, crossover trial, 33 patients with IC were allocated randomly to receive 50% DMSO solution or placebo (saline). The medication was administered intravesically every 2 weeks for two sessions of four treatments each. Response was assessed urodynamically and symptomatically. Subjective improvement was noted in 53% of patients receiving DMSO versus 18% receiving placebo and objective improvement in 93% and 35%, respectively [Perez-Marrero *et al.* 1988].

2. Bacillus Calmette–Guerin (BCG). BCG is most commonly used in the treatment of high-grade recurrent or multifocal bladder cancer. A prospective double-blind, placebo-controlled study with IC patients showed 60% positive response in patients on BCG compared with 27% in patients receiving placebo [Peters *et al.* 1997]. In another randomized, placebo-controlled, double-blind trial in 260 patients with refractory IC, BCG demonstrated a global response rate of 21% *versus* 12% for placebo ($p = 0.062$) [Mayer *et al.* 2005]. Other multicenter trials are currently under way to determine the role of BCG in the treatment of IC patients.

Bladder mucosal protectors. *1. Hyaluronic acid*. Intravesical administration of hyaluronic acid is thought to protect the bladder surface and has shown benefit in open clinical studies. Morales and colleagues reported a response rate of 56% at week 4 and 71% at week 7, in 25 patients treated with intravesical instillation of hyaluronic acid [Morales *et al.* 1996]. After week 24, effectiveness decreased, but there was no significant toxicity.

Others. Other drugs such as chondroitin sulfate, vanilloids, and intravesical botulinum toxin can also be used either alone or can be combined in a cocktail for intravesical instillation. Intravesical therapy is required for patients who do not respond to oral treatments or who experience intolerable side effect [Forrest and Dell, 2007].

Surgical treatment

Surgery is reserved as a last-line therapy when more conservative options have been exhausted.

Bladder distension. While bladder distension can be used as a diagnostic procedure for IC, it can also serve in a therapeutic role [Moldwin and Sant, 2002]. Most patients demonstrated a worsening of symptoms for 2–3 weeks after hydrodistension but then experience symptom relief after that period of time. Glemain and colleagues tested the efficacy of hydrodistension for symptomatic treatment of IC with follow up at 6 and

12 months [Glemain *et al.* 2002]. Treatment efficacy was reported as 60% at 6 months, declining to 43.3% at 12 months. Erickson and colleagues reported that the median symptom score for newly diagnosed patients decreases after hydrodistention, but only a minority of patients had at least 30% symptom improvement [Erickson *et al.* 2007].

Transurethral resection of visible ulcers. Transurethral resection (TUR) is reserved only for patients with visible Hunner's lesions. Fall reported his experience with TURs in 30 patients with classic IC, and found that a complete TUR of all visible lesions resulted in initial disappearance of pain in all, and decreased frequency in 21 patients [Fall, 1985]. Although a relapse was reported in one third of the patients, the remaining two thirds were still free of pain even after 2–20 months. In another study, Peeker and colleagues performed 259 TURs in 103 IC patients [Peeker *et al.* 2000a]; 92 experienced amelioration, and in 40% symptom relief lasted more than 3 years. In the remaining patients, although symptom recurrence was common, the majority responded well to subsequent TUR.

Laser coagulation. Transurethral ablation of bladder tissue aims to eliminate visible Hunner's ulcers. Use of the neodymium:yttrium–aluminum–garnet (Nd:YAG) laser has been suggested as an alternative to TUR for patients with IC. Shanberg and colleagues initially treated five patients with refractory IC with the Nd:YAG laser, of whom four demonstrated cessation of pain and frequency within several days [Shanberg *et al.* 1985]. Follow up at 3–15 months revealed no relapse, with the exception of mild recurrent voiding symptoms.

Neuromodulation. Recently, unilateral sacral nerve (S3) stimulation has emerged as a promising treatment option for IC. Peters demonstrated that IC patients refractory to conventional therapies responded well to sacral nerve stimulation and can maintain this improvement after permanent implantation of a neurostimulator [Peters, 2002]. More recently, Comiter confirmed the positive results with sacral neuromodulation on voiding and pelvic pain in patients with IC [Comiter, 2003].

Cystectomy. When all conservative efforts fail, surgical removal of the diseased bladder represents the last and most extreme treatment option [Moldwin and Sant, 2002]. Three types of cystectomy have been described in the setting of IC: supratrigonal (i.e. trigone-sparing), subtrigonal cystectomy, or radical cystectomy including excision of the urethra. van Ophoven and colleagues, for example, reported their experience with trigone-preserving cystectomy with orthotopic substitution enteroplasty for 18 patients, using ileocecal ($n = 10$) or ileal ($n = 8$) segments [van Ophoven *et al.* 2002]. At 5 years, 14 (77.78%) patients were completely pain free, 12 (66.67%) were able to void spontaneously, while 15 (83.33%) reported complete resolution of dysuria.

Management guidelines

Since IC has a wide range of presentation, management must be individualized. Frequent follow up and patient counseling about disease and expectations from the treatment plays an important role in the management of IC [Kahn *et al.* 2005]. Management should focus on the treatment of all possible external sources of pain, including endometriosis, fibromyalgia, and vulvodynia [Aaron and Buchwald, 2003; Butrick, 2003]. Regular follow-up visits to monitor patients' progress and address their concerns are important for optimal outcomes. Treatment plans should be modified based on patient response to therapy.

Conclusion

Inflammation has a direct effect on bladder function. In cases of acute inflammation, for example UTI, the inflammatory mediators are released and cause urothelial injury and bladder wall irritation. These inflammatory changes are responsible for clinical manifestation of urgency, dysuria, frequency, nocturia, and fever. In acute inflammation these changes are short lived and are resolve as soon as the noxious stimulus is removed. If the noxious stimulus persists for a longer duration it leads to chronic inflammation, resulting in recurrent injury to bladder mucosa and other dysfunctional pathologies such as fibrosis. These pathological changes lead to urgency, frequency, dysuria, and cystoscopic findings of Hunner's ulcers, which are typically seen in IC. Patients with IC are usually managed with multimodal therapy to break the vicious cycle of chronic inflammation at every step. Patients who develop irreversible pathologies such as fibrosis are managed surgically, which is usually reserved for refractory cases.

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References

Aaron, L.A. and Buchwald, D. (2001) A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 134: 868–881.

Aaron, L.A. and Buchwald, D. (2003) Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. *Best Pract Res Clin Rheumatol* 17: 563–574.

Abrams, P., Baranowski, A., Berger, R.E., Fall, M., Hanno, P. and Wesselmann, U. (2006) A new classification is needed for pelvic pain syndromes–are existing terminologies of spurious diagnostic authority bad for patients? *J Urol* 175: 1989–1990.

Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U. *et al.* (2002) The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 21: 167–178.

Acar, D., Cayan, S., Aktas, S., Tek, M. and Akbay, E. (2007) The effect of tamoxifen on bladder functions and histology, and the role of estrogen receptor beta in a rat chemical cystitis model. *Neurourol Urodyn* 26: 309–316.

Alagiri, M., Chottiner, S., Ratner, V., Slade, D. and Hanno, P.M. (1997) Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology* 49(5A Suppl): 52–57.

Batler, R.A., Sengupta, S., Forrestal, S.G., Schaeffer, A.J. and Klumpp, D.J. (2002) Mast cell activation triggers a urothelial inflammatory response mediated by tumor necrosis factor-alpha. *J Urol* 168: 819–825.

Bouchelouche, K., Horn, T., Nordling, J., Larsen, S. and Hald, T. (2001a) The action of cysteinyl-leukotrienes on intracellular calcium mobilization in human detrusor myocytes. *BJU Int* 87: 690–696.

Bouchelouche, K., Nordling, J., Hald, T. and Bouchelouche, P. (2001b) The cysteinyl leukotriene D4 receptor antagonist montelukast for the treatment of interstitial cystitis. *J Urol* 166: 1734–1737.

Butrick, C.W. (2003) Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. *Clin Obstet Gynecol* 46: 811–823.

Cannon, T.W. and Chancellor, M.B. (2002) Pharmacotherapy of the overactive bladder and advances in drug delivery. *Clin Obstet Gynecol* 45: 205–217.

Cao, J., Papadopoulou, N., Kempuraj, D., Boucher, W.S., Sugimoto, K., Cetrulo, C.L. *et al.* (2005) Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor. *J Immunol* 174: 7665–7675.

Cartledge, J.J., Davies, A.M. and Eardley, I. (2000) A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. *BJU Int* 85: 421–426.

Cervero, F. (1994) Sensory innervation of the viscera: peripheral basis of visceral pain. *Physiol Rev* 74: 95–138.

Chen, M.C., Blunt, L.W., Pins, M.R. and Klumpp, D.J. (2006) Tumor necrosis factor promotes differential trafficking of bladder mast cells in neurogenic cystitis. *J Urol* 175: 754–759.

Christmas, T.J. (1994) Lymphocyte sub-populations in the bladder wall in normal bladder, bacterial cystitis and interstitial cystitis. *Br J Urol* 73: 508–515.

Comiter, C.V. (2003) Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. *J Urol* 169: 1369–1373.

Cox, M., Klutke, J.J. and Klutke, C.G. (2009) Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. *Can J Urol* 16: 4536–4540.

Davies, S.N. and Lodge, D. (1987) Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. *Brain Res* 424: 402–406.

Dmitrieva, N., Shelton, D., Rice, A.S. and McMahon, S.B. (1997) The role of nerve growth factor in a model of visceral inflammation. *Neuroscience* 78: 449–459.

Domingue, G.J., Ghoniem, G.M., Bost, K.L., Fermin, C. and Human, L.G. (1995) Dormant microbes in interstitial cystitis. *J Urol* 153: 1321–1326.

Dubner, R. and Ruda, M.A. (1992) Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends Neurosci* 15: 96–103.

Echols, R.M., Tosiello, R.L., Haverstock, D.C. and Tice, A.D. (1999) Demographic, clinical, and treatment parameters influencing the outcome of acute cystitis. *Clin Infect Dis* 29: 113–119.

Eide, F.F., Lowenstein, D.H. and Reichardt, L.F. (1993) Neurotrophins and their receptors—current concepts and implications for neurologic disease. *Exp Neurol* 121: 200–214.

Erickson, D.R. (2001) Urine markers of interstitial cystitis. *Urology* 57(6 Suppl. 1): 15–21.

Erickson, D.R., Kunselman, A.R., Bentley, C.M., Peters, K.M., Rovner, E.S., Demers, L.M. *et al.* (2007) Changes in urine markers and symptoms after bladder distention for interstitial cystitis. *J Urol* 177: 556–560.

Erickson, D.R., Morgan, K.C., Ordille, S., Keay, S.K. and Xie, S.X. (2001) Nonbladder related symptoms in patients with interstitial cystitis. *J Urol* 166: 557–561, discussion 561–552.

Evans, R.J. (2002) Treatment approaches for interstitial cystitis: multimodality therapy. *Rev Urol* 4(Suppl. 1): S16–S20.

Evans, R.J. and Sant, G.R. (2007) Current diagnosis of interstitial cystitis: an evolving paradigm. *Urology* 69(4 Suppl): 64–72.

Fall, M. (1985) Conservative management of chronic interstitial cystitis: transcutaneous electrical nerve stimulation and transurethral resection. *J Urol* 133: 774–778.

Forrest, J.B. and Dell, J.R. (2007) Successful management of interstitial cystitis in clinical practice. *Urology* 69(4 Suppl): 82–86.

Forsell, T., Ruutu, M., Isoniemi, H., Ahonen, J. and Alfthan, O. (1996) Cyclosporine in severe interstitial cystitis. *J Urol* 155: 1591–1593.

Hunner, G.L. (1918) A rare type of bladder ulcer: further notes and a report of 18 cases. *JAMA* 70: 208–212.

Glemain, P., Riviere, C., Lenormand, L., Karam, G., Bouchot, O. and Buzelin, J.M. (2002) Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. *Eur Urol* 41: 79–84.

Graham, E. and Chai, T.C. (2006) Dysfunction of bladder urothelium and bladder urothelial cells in interstitial cystitis. *Curr Urol Rep* 7: 440–446.

Hanash, K.A. and Pool, T.L. (1969) Interstitial cystitis in men. *J Urol* 102: 427–428.

Hanno, P., Keay, S., Moldwin, R. and Van Ophoven, A. (2005) International Consultation on IC - Rome, September 2004/Forging an International Consensus: progress in painful bladder syndrome/interstitial cystitis. Report and abstracts. *Int Urogynecol J Pelvic Floor Dysfunct* 16(Suppl. 1): S2–S34.

Hanno, P.M. (1994) Amitriptyline in the treatment of interstitial cystitis. *Urol Clin North Am* 21: 89–91.

Hanno, P.M. (2002) Interstitial cystitis-epidemiology, diagnostic criteria, clinical markers. *Rev Urol* 4(Suppl 1): S3–S8.

Hanno, P.M. (2007) Painful bladder syndrome, In: Wein, A.J., Kavossi, L.R., Novick, A.C., Partin, A.W. and Peter, C.A. (eds). *Campbell's Urology*, 9th edn, Elsevier: Philadelphia, PA, pp. 330–370.

Hanno, P.M., Buehler, J. and Wein, A.J. (1989) Use of amitriptyline in the treatment of interstitial cystitis. *J Urol* 141: 846–848.

Hansen, H.C. (2000) Interstitial cystitis and the potential role of gabapentin. *South Med J* 93: 238–242.

He, S. and Walls, A.F. (1997) Human mast cell tryptase: a stimulus of microvascular leakage and mast cell activation. *Eur J Pharmacol* 328: 89–97.

Hosseini, A., Ehren, I. and Wiklund, N.P. (2004) Nitric oxide as an objective marker for evaluation of treatment response in patients with classic interstitial cystitis. *J Urol* 172: 2261–2265.

Hupert, C., Yacoub, M. and Turgeon, L.R. (1980) Effect of hydroxyzine on morphine analgesia for the treatment of postoperative pain. *Anesth Analg* 59: 690–696.

Ibrahim, I.A., Diokno, A.C., Killinger, K.A., Carrico, D.J. and Peters, K.M. (2007) Prevalence of self-reported interstitial cystitis (IC) and interstitial-cystitis-like symptoms among adult women in the community. *Int Urol Nephrol* 39: 489–495.

Johansson, S.L. and Fall, M. (1990) Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol* 143: 1118–1124.

Jones, C.A. and Nyberg, L. (1997) Epidemiology of interstitial cystitis. *Urology* 49(5A Suppl): 2–9.

Kahn, B.S., Stanford, E.J., Mishell Jr, D.R., Rosenberg, M.T. and Wysocki, S. (2005) Management of patients with interstitial cystitis or chronic pelvic pain of bladder origin: a consensus report. *Curr Med Res Opin* 21: 509–516.

Kastrup, J., Hald, T., Larsen, S. and Nielsen, V.G. (1983) Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. *Br J Urol* 55: 495–500.

Keay, S., Kleinberg, M., Zhang, C.O., Hise, M.K. and Warren, J.W. (2000) Bladder epithelial cells from patients with interstitial cystitis produce an inhibitor of heparin-binding epidermal growth factor-like growth factor production. *J Urol* 164: 2112–2118.

Kiuchi, H., Tsujimura, A., Takao, T., Yamamoto, K., Nakayama, J., Miyagawa, Y. *et al.* (2009) Increased vascular endothelial growth factor expression in patients with bladder pain syndrome/interstitial cystitis: its association with pain severity and glomerulations. *BJU Int* 104: 826–831, discussion 831.

Korting, G.E., Smith, S.D., Wheeler, M.A., Weiss, R.M. and Foster Jr, H.E. (1999) A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. *J Urol* 161: 558–565.

Koziol, J.A. (1994) Epidemiology of interstitial cystitis. *Urol Clin North Am* 21: 7–20.

Koziol, J.A., Clark, D.C., Gittes, R.F. and Tan, E.M. (1993) The natural history of interstitial cystitis: a survey of 374 patients. *J Urol* 149: 465–469.

Kusek, J.W. and Nyberg, L.M. (2001) The epidemiology of interstitial cystitis: is it time to expand our definition? *Urology* 57(6 Suppl. 1): 95–99.

Lentz, G.M., Bavendam, T., Stenchever, M.A., Miller, J.L. and Smalldridge, J. (2002) Hormonal manipulation in women with chronic, cyclic irritable bladder

symptoms and pelvic pain. *Am J Obstet Gynecol* 186: 1268–1271, discussion 1271–1263.

Lilly, J.D. and Parsons, C.L. (1990) Bladder surface glycosaminoglycans is a human epithelial permeability barrier. *Surg Gynecol Obstet* 171: 493–496.

Lowe, E.M., Anand, P., Terenghi, G., Williams-Chestnut, R.E., Sinicropi, D.V. and Osborne, J.L. (1997) Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis. *Br J Urol* 79: 572–577.

Lukban, J.C., Whitmore, K.E. and Sant, G.R. (2002) Current management of interstitial cystitis. *Urol Clin North Am* 29: 649–660.

MacDermott, J.P., Miller, C.H., Levy, N. and Stone, A.R. (1991) Cellular immunity in interstitial cystitis. *J Urol* 145: 274–278.

Marchand, J.E., Sant, G.R. and Kream, R.M. (1998) Increased expression of substance P receptor-encoding mRNA in bladder biopsies from patients with interstitial cystitis. *Br J Urol* 81: 224–228.

Mayer, E.A. and Gebhart, G.F. (1994) Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 107: 271–293.

Mayer, R., Propert, K.J., Peters, K.M., Payne, C.K., Zhang, Y., Burks, D. *et al.* (2005) A randomized controlled trial of intravesical bacillus Calmette–Guerin for treatment refractory interstitial cystitis. *J Urol* 173: 1186–1191.

Metts, J.F. (2001) Interstitial cystitis: urgency and frequency syndrome. *Am Fam Physician* 64: 1199–1206.

Moldwin, R.M. and Sant, G.R. (2002) Interstitial cystitis: a pathophysiology and treatment update. *Clin Obstet Gynecol* 45: 259–272.

Morales, A., Emerson, L., Nickel, J.C. and Lundie, M. (1996) Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *J Urol* 156: 45–48.

Nickel, J.C. (2000) Interstitial cystitis. Etiology, diagnosis, and treatment. *Can Fam Physician* 46: 2430–2434, 2437–2440.

Nickel, J.C. (2004) Interstitial cystitis: a chronic pelvic pain syndrome. *Med Clin North Am* 88: 467–481, xii.

Nickel, J.C., Barkin, J., Forrest, J., Mosbaugh, P.G., Hernandez-Graulau, J., Kaufman, D. *et al.* (2005) Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology* 65: 654–658.

Novi, J.M., Jeronis, S., Srinivas, S., Srinivasan, R., Morgan, M.A. and Arya, L.A. (2005) Risk of irritable bowel syndrome and depression in women with interstitial cystitis: a case-control study. *J Urol* 174: 937–940.

O'Leary, M.P., Sant, G.R., Fowler Jr, F.J., Whitmore, K.E. and Spolarich-Kroll, J. (1997) The interstitial cystitis symptom index and problem index. *Urology* 49(5A Suppl): 58–63.

Ottem, D.P. and Teichman, J.M. (2005) What is the value of cystoscopy with hydrodistension for interstitial cystitis? *Urology* 66: 494–499.

Pang, X., Cotreau-Bibbo, M.M., Sant, G.R. and Theoharides, T.C. (1995a) Bladder mast cell expression of high affinity oestrogen receptors in patients with interstitial cystitis. *Br J Urol* 75: 154–161.

Pang, X., Marchand, J., Sant, G.R., Kream, R.M. and Theoharides, T.C. (1995b) Increased number of substance P positive nerve fibres in interstitial cystitis. *Br J Urol* 75: 744–750.

Pang, X., Sant, G. and Theoharides, T.C. (1998) Altered expression of bladder mast cell growth factor receptor (c-kit) in interstitial cystitis. *Urology* 51: 939–944.

Parsons, C.L. (2002) Interstitial cystitis: epidemiology and clinical presentation. *Clin Obstet Gynecol* 45: 242–249.

Parsons, C.L., Dell, J., Stanford, E.J., Bullen, M., Kahn, B.S., Waxell, T. *et al.* (2002a) Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 60: 573–578.

Parsons, C.L., Forrest, J., Nickel, J.C., Evans, R., Lloyd, L.K., Barkin, J. *et al.* (2002b) Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. *Urology* 59: 329–333.

Parsons, C.L., Greenberger, M., Gabal, L., Bidair, M. and Barme, G. (1998) The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 159: 1862–1866, discussion 1866–1867.

Parsons, C.L., Pollen, J.J., Anwar, H., Stauffer, C. and Schmidt, J.D. (1980) Antibacterial activity of bladder surface mucin duplicated in the rabbit bladder by exogenous glycosaminoglycan (sodium pentosanpolysulfate). *Infect Immun* 27: 876–881.

Peeker, R., Aldenborg, F. and Fall, M. (2000a) Complete transurethral resection of ulcers in classic interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct* 11: 290–295.

Peeker, R., Atanasiu, L. and Logadottir, Y. (2003) Intercurrent autoimmune conditions in classic and non-ulcer interstitial cystitis. *Scand J Urol Nephrol* 37: 60–63.

Peeker, R., Enerback, L., Fall, M. and Aldenborg, F. (2000b) Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. *J Urol* 163: 1009–1015.

Perez-Marrero, R., Emerson, L.E. and Feltis, J.T. (1988) A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol* 140: 36–39.

Peters, K., Diokno, A., Steinert, B., Yuhico, M., Mitchell, B., Krohta, S. *et al.* (1997) The efficacy of

intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. *J Urol* 157: 2090–2094.

Peters, K., Girdler, B., Carrico, D., Ibrahim, I. and Diokno, A. (2008) Painful bladder syndrome/interstitial cystitis and vulvodynia: a clinical correlation. *Int Urogynecol J Pelvic Floor Dysfunct* 19: 665–669.

Peters, K.M. (2002) Neuromodulation for the treatment of refractory interstitial cystitis. *Rev Urol* 4(Suppl. 1): S36–S43.

Powell-Boone, T., Ness, T.J., Cannon, R., Lloyd, L.K., Weigent, D.A. and Fillingim, R.B. (2005) Menstrual cycle affects bladder pain sensation in subjects with interstitial cystitis. *J Urol* 174: 1832–1836.

Rackley, R.R., Bandyopadhyay, S.K., Fazeli-Matin, S., Shin, M.S. and Appell, R. (1999) Immunoregulatory potential of urothelium: characterization of NF-kappaB signal transduction. *J Urol* 162: 1812–1816.

Rosenberg, M.T. and Hazzard, M. (2005) Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. *J Urol* 174: 2231–2234.

Ruda, M.A. and Dubner, R. (1992) Molecular and biochemical events mediate neuronal plasticity following inflammation and hyperalgesia, In: Willis Jr, W.D. (ed.). *Hyperalgesia and Allodynia*, Raven Press: New York, pp. 331–1325.

Saini, R., Gonzalez, R.R. and Te, A.E. (2008) Chronic pelvic pain syndrome and the overactive bladder: the inflammatory link. *Curr Urol Rep* 9: 314–319.

Sairanen, J., Tammela, T.L., Leppilahti, M., Multanen, M., Paananen, I., Lehtoranta, K. *et al.* (2005) Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. *J Urol* 174: 2235–2238.

Sant, G.R. (2002) Etiology, pathogenesis, and diagnosis of interstitial cystitis. *Rev Urol* 4(Suppl. 1): S9–S15.

Sant, G.R. and Hanno, P.M. (2001) Interstitial cystitis: current issues and controversies in diagnosis. *Urology* 57(6 Suppl. 1): 82–88.

Sant, G.R., Kempuraj, D., Marchand, J.E. and Theoharides, T.C. (2007) The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. *Urology* 69(4 Suppl): 34–40.

Sant, G.R. and Theoharides, T.C. (1994) The role of the mast cell in interstitial cystitis. *Urol Clin North Am* 21: 41–53.

Shanberg, A.M., Baghdassarian, R. and Tansey, L.A. (1985) Treatment of interstitial cystitis with the neodymium-YAG laser. *J Urol* 134: 885–888.

Shear, S. and Mayer, R. (2006) Development of glomerulations in younger women with interstitial cystitis. *Urology* 68: 253–256.

Simon, L.J., Landis, J.R., Erickson, D.R. and Nyberg, L.M. (1997) The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. *Urology* 49(5A Suppl): 64–75.

Soucy, F. and Gregoire, M. (2005) Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. *J Urol* 173: 841–843, discussion 843.

Spanos, C., el-Mansoury, M., Letourneau, R., Minogiannis, P., Greenwood, J., Siri, P. *et al.* (1996) Carbachol-induced bladder mast cell activation: augmentation by estradiol and implications for interstitial cystitis. *Urology* 48: 809–816.

Stanford, E.J., Koziol, J. and Feng, A. (2005) The prevalence of interstitial cystitis, endometriosis, adhesions, and vulvar pain in women with chronic pelvic pain. *J Minim Invasive Gynecol* 12: 43–49.

Tamaki, M., Saito, R., Ogawa, O., Yoshimura, N. and Ueda, T. (2004) Possible mechanisms inducing glomerulations in interstitial cystitis: relationship between endoscopic findings and expression of angiogenic growth factors. *J Urol* 172: 945–948.

Teichman, J.M. and Nielsen-Omeis, B.J. (1999) Potassium leak test predicts outcome in interstitial cystitis. *J Urol* 161: 1791–1794, discussion 1794–1796.

Theoharides, T.C. and Cochrane, D.E. (2004) Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J Neuroimmunol* 146: 1–12.

Theoharides, T.C., Donelan, J.M., Papadopoulou, N., Cao, J., Kempuraj, D. and Conti, P. (2004) Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol Sci* 25: 563–568.

Theoharides, T.C., Kempuraj, D. and Sant, G.R. (2001) Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. *Urology* 57(6 Suppl. 1): 47–55.

Theoharides, T.C., Sant, G.R., el-Mansoury, M., Letourneau, R., Ucci Jr, A.A. and Meares Jr, E.M. (1995) Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. *J Urol* 153: 629–636.

Theoharides, T.C., Singh, L.K., Boucher, W., Pang, X., Letourneau, R., Webster, E. *et al.* (1998) Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. *Endocrinology* 139: 403–413.

Thilagarajah, R., Witherow, R.O. and Walker, M.M. (2001) Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 87: 207–212.

Traub, R.J., Pechman, P., Iadarola, M.J. and Gebhart, G.F. (1992) Fos-like proteins in the lumbosacral spinal cord following noxious and non-noxious colorectal distention in the rat. *Pain* 49: 393–403.

Tura, B. and Tura, S.M. (1990) The analgesic effect of tricyclic antidepressants. *Brain Res* 518: 19–22.

van de Merwe, J.P., Nordling, J., Bouchelouche, P., Bouchelouche, K., Cervigni, M., Daha, L.K. *et al.* (2008) Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol* 53: 60–67.

Van Kerrebroeck, P., Kreder, K., Jonas, U., Zinner, N. and Wein, A. (2001) Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology* 57: 414–421.

van Ophoven, A. and Hertle, L. (2005) Long-term results of amitriptyline treatment for interstitial cystitis. *J Urol* 174: 1837–1840.

van Ophoven, A., Oberpenning, F. and Hertle, L. (2002) Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. *J Urol* 167: 603–607.

van Ophoven, A., Pokupic, S., Heinecke, A. and Hertle, L. (2004) A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol* 172: 533–536.

Warren, J.W., Brown, J., Tracy, J.K., Langenberg, P., Wesselmann, U. and Greenberg, P. (2008) Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. *Urology* 71: 444–448.

Warren, J.W., Jackson, T.L., Langenberg, P., Meyers, D.J. and Xu, J. (2004) Prevalence of interstitial cystitis in first-degree relatives of patients with interstitial cystitis. *Urology* 63: 17–21.

Warren, J.W., Keay, S.K., Meyers, D. and Xu, J. (2001) Concordance of interstitial cystitis in monozygotic and dizygotic twin pairs. *Urology* 57(6 Suppl. 1): 22–25.

Waxman, J.A., Sulak, P.J. and Kuehl, T.J. (1998) Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol* 160: 1663–1667.

Wein, A.J., Hanno, P.M. and Gillenwater, J.Y. (1990) Interstitial cystitis: an introduction to the problem. In *Interstitial Cystitis.* London: Springer-Verlag, pp. 3–15.

Whitmore, K.E. (1994) Self-care regimens for patients with interstitial cystitis. *Urol Clin North Am* 21: 121–130.

Whitmore, K.E. (2002) Complementary and alternative therapies as treatment approaches for interstitial cystitis. *Rev Urol* 4(Suppl. 1): S28–S35.

Wilkins, E.G., Payne, S.R., Pead, P.J., Moss, S.T. and Maskell, R.M. (1989) Interstitial cystitis and the urethral syndrome: a possible answer. *Br J Urol* 64: 39–44.

Woolf, C.J. and Thompson, S.W. (1991) The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 44: 293–299.

Yamada, T. (2003) Significance of complications of allergic diseases in young patients with interstitial cystitis. *Int J Urol* 10(Suppl): S56–S58.