

**INTERNATIONAL PAINFUL BLADDER FOUNDATION**

# Interstitial Cystitis

(Painful Bladder Syndrome, Bladder Pain Syndrome,  
Hypersensitive Bladder Syndrome)

## Diagnosis & Treatment

An Overview

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[www.painful-bladder.org](http://www.painful-bladder.org)

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# INTERSTITIAL CYSTITIS

## (Painful Bladder Syndrome, Bladder Pain Syndrome, Hypersensitive Bladder Syndrome)

### Chapter 1

#### What is interstitial cystitis?

Interstitial cystitis (IC), also known as painful bladder syndrome, bladder pain syndrome and hypersensitive bladder syndrome, is a debilitating, chronic, inflammatory bladder disorder of unknown cause, with symptoms of pain, pressure or discomfort perceived to be related to the bladder and usually associated with a frequent and urgent need to urinate day and night. While the symptoms may resemble bacterial cystitis, there is no infection to be seen in the urine and tests reveal no identifiable disorder that could account for the symptoms.

#### What are the symptoms?

The characteristic symptoms of IC are **pain, frequency and urgency**:

- *Pain, pressure, discomfort or unpleasant sensation that may increase as the bladder fills; urinating often alleviates the pain and gives a temporary sense of relief;*
- *Suprapubic pain or discomfort, lower abdominal (pelvic) pain, sometimes extending to the lower part of the back; pain may also be felt in the groin and thighs;*
- *In women there may be pain in the vagina and vulva;*
- *In men, pain in the penis, testicles, scrotum and perineum;*
- *Both men and women may have pain in the urethra and rectum;*
- *Pain with sexual intercourse in both men and women (dyspareunia); pain on ejaculation in men;*
- *A frequent need to urinate (frequency), including at night (nighttime frequency);*
- *An often urgent or compelling need to urinate (urgency).*

The pain may be experienced as discomfort or tenderness, or a burning sensation in the bladder, in the form of spasms in or around the bladder, or stabbing or burning vaginal pain or simply a feeling of pressure on or in the bladder or a feeling of fullness even when there is only a little urine in the bladder. The pain may be constant or intermittent. It may also be felt throughout the pelvic floor, including the lower bowel system. In some patients the pain may be very severe and debilitating. Other patients, particularly in the early stages, may have milder frequency with/without urgency and without a true sensation of pain. What they may experience, however, is a feeling of heaviness, fullness, discomfort or pressure.

Urinary frequency means that a person needs to urinate more frequently than normal during the daytime and at night. This will partly depend on how much a patient drinks and on the climate. In IC, frequency may sometimes be very severe with some patients needing to urinate up to 60 times a day, but frequency can be anything over approximately 8 times a day. However, this figure of 8 voids a day should only be seen as an approximation since the number of voids per day depends on the individual's way of life and environment.

Frequency is by no means always related to bladder size. While some patients have a type of IC with a shrunken bladder which has a scarred, stiff wall and a small capacity under anaesthesia, other IC patients with a normal-sized bladder may nevertheless have severe frequency due to hypersensitivity on filling. A typical feature of IC is the need to empty the bladder several times during the night. The amount of urine passed may be small, even just a few drops.

While a voiding diary can be useful to show frequency and the volume of urine passed, frequency can vary from day to day and week to week, depending on whether the patient's symptoms are flaring or relatively calm.

Urinary urgency in IC is an urgent or compelling need to find a toilet to empty the bladder due to increasing pain or discomfort that becomes impossible to tolerate any longer, and may in some patients be accompanied by a feeling of malaise and/or nausea. Some patients find that having to postpone urination leads to retention or difficulty in getting the flow started. The nature and cause of urgency in IC patients is still not fully understood.

### **Who gets IC?**

IC is mainly found in **women** (80-90%). Approximately 10-20% of IC patients are **men** who may in the past have been incorrectly diagnosed as having non-bacterial prostatitis (inflammation of the prostate gland) or prostatodynia (pain in the prostate gland). A complicating factor is that chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is clinically very similar to IC and the two conditions have many overlapping symptoms. However, this possibility of misdiagnosis in men may mean that more men may have IC than hitherto thought and the percentage of male patients with IC may therefore be higher.

IC is also found in **children**. However, since in the past the old NIDDK research criteria did not allow a diagnosis of IC in those under the age of 18 years and children were not to be included in studies, there has been relatively little scientific literature on IC in children in the past two decades. It can, nevertheless, occur in children of any age.

IC is found in all countries around the world and in all races. However, prevalence figures vary enormously from study to study and country to country and depend on what criteria and definitions are used for diagnosis, what diagnostic methods are used to reach the diagnosis and how big the population is in the study. Consequently, nobody can say with any degree of certainty at the present time how many people may have IC. Some types of IC may be considerably more common than originally thought.

### **How does it start?**

The symptoms may begin for no apparent reason, or sometimes following surgery, particularly in the case of women following a hysterectomy or other gynaecological operation, after childbirth or following a severe bacterial infection of the bladder or repeated infections. Onset may be very slow, building up over many years or it may be sudden and severe.

In the very early stages of the disease or in a mild form of IC, the symptoms may only occur in attacks known as "flares". This leads many patients and their doctors to think that it may be an infection (bacterial cystitis). If the patient fails to respond to antibiotic treatment, it is important for a urine culture to be carried out in order to be absolutely sure that bacterial infection can be excluded. However, the fact that a patient has IC does not mean that the patient never develops urinary tract infections (UTIs) in addition to their IC. An infection in a hypersensitive IC bladder can considerably exacerbate the IC symptoms, severely irritating the already painful bladder. In this situation, following confirmation of an infection, the IC patient should indeed be treated with a suitable antibiotic to clear up the infection.

But the symptoms of IC do not go away, they keep on returning. In some patients the symptoms may gradually worsen, but this greatly varies from patient to patient and is not necessarily the case.

The symptoms of some IC patients may increase very slowly over a period of many years, while others may progress from an early stage to an advanced stage with a shrunken, scarred, stiff bladder wall (fibrotic bladder) and very small bladder capacity in a short space of time. A relatively small percentage of patients (estimates vary from 10-50%) develop Hunner's lesions or patches (historically known as Hunner's ulcers) and this form of the disease is sometimes known as Classic IC.

It should be emphasized, however, that many patients never progress further than a relatively mild form of IC and that many patients have a normal bladder capacity under anaesthesia and never develop a shrunken, fibrotic, contracted bladder. There is no evidence to show that patients with non-classic IC later go on to develop the lesion subtype.

## **Exacerbation and remission**

Spontaneous flares and remission are a characteristic feature of IC in many patients. Many women find that their symptoms are exacerbated just before or during menstruation, during ovulation or if they are taking contraceptive pills. Some researchers believe that this may be due to the effect of sex hormones on cells in the bladder and/or that hormonal involvement may alter pain perception in women, but this aspect still awaits further detailed research. Women may also find that their IC symptoms temporarily increase while going through the menopause.

## **Cause**

Despite considerable research into many different aspects of IC, the cause is still unknown. The many theories include an increase in mast cell activity, an abnormality in the bladder lining causing leakage of toxic elements in the urine through to the underlying layers, autoimmunity, allergy, occult infection and many more hypotheses. Some researchers have explored the possibility of heredity playing a role since IC may occur in more than one person in the same family (mother and daughter or two sisters). An important area of research concerns so-called antiproliferative factor (APF) in the urine of patients which may ultimately lead to a diagnostic marker. It is believed that APF may prevent cells from regenerating and lead to thinning of the epithelium.

While once considered specifically to be a bladder disease, a more contemporary way of viewing IC is within the context of chronic pain syndromes. Research in recent years has indicated that abnormal nerve activity may be a key factor in the chronic aspect of pain in IC and the way the pain appears to spread throughout the pelvic floor. At least a subset of patients suffer from one or more other pain syndromes in addition to IC and this is currently being looked at by researchers within the framework of the NIDDK Multidisciplinary Approach to the study of the Pelvic Pain disorders (MAPP project).

There are numerous different theories and much research has been carried out, but no answers have as yet been found.

## **Stress not a cause of IC**

Although many patients may experience a worsening of their IC symptoms as a result of emotional or physical stress, it is particularly important to emphasize that stress as such is not believed to be a cause of IC and IC is not a psychosomatic illness. The pain, frequency and urgency and consequent lack of proper sleep experienced by IC patients and the impact of the disease on every aspect of the patient's life may themselves be a significant cause of not only total exhaustion, but also stress, anxiety and depression.

## Chapter 2

### Impact on Life

IC can have a major impact on the social, psychological, occupational, domestic, physical and sexual life of the patient and affect a patient's quality of life and the structure of their life. The frequent and urgent need to urinate can form an obstacle to work, travel, visiting friends, or simply going shopping. When outside the confines of their home, the IC patient's life is dominated by the question "where am I going to find the next toilet?" Before every outing, the patient will carefully plan a network of toilets, known by the patients as "toilet-mapping". Many patients say: "If I don't think I will be able to find a toilet, I simply don't go out". This kind of situation can make a patient uncertain and afraid to leave the safety of their home. And there are many patients who tell us that they almost never go out.

#### **Social isolation**

The social consequences of IC should not be underestimated and may force a patient to adopt a completely different life-style. Through embarrassment that they have to use the toilet so frequently, patients may no longer visit even their family and friends. It's difficult for them to go out to a cinema or theatre or even just for a walk in the park. Their social life may be non-existent and they may feel – and in fact be – totally isolated from the world around them.

#### **Some jobs are impossible with IC**

The frequent need to urinate may make it difficult for some patients to carry on working or they may be forced to change to a different type of job that allows them the possibility of easy, frequent access to toilets. Work in some jobs becomes impossible when you have to keep running to the toilet. The impact of IC on their work and career may cause IC patients and their families considerable financial loss.

#### **Physical and psychological impact of sleep deprivation**

In addition to this, the pain and frequent, urgent need to urinate make patients tense and exhausted from lack of sleep. Some severe patients need to urinate 40-60 times a day and may sleep no more than 20 minutes at a time at night. Sleep deprivation can have a detrimental physical and psychological impact on people. Without proper sleep, a person deteriorates both physically and psychologically. This too can make some types of work impossible and even dangerous.

#### **Impact on family life and relationships**

IC has an impact on the entire family from many points of view. It alters your relationships with your partner and children because your bladder condition means that you cannot act like a normal parent or a normal partner. As an IC patient you are tired and irritable from lack of proper sleep, from coping with the pain and from the constant trips to the bathroom. The inability to cope, to look after the family, to do normal things with your partner and children, may give the patient a sense of guilt. Patients may be so anxious about when the next unpredictable flare is going to occur that they try to do too much at home for the family and thereby actually induce a flare. Other patients may suffer from continuous unrelenting pain that makes them so tired that they are continually exhausted. Members of the family don't understand IC at all because they can't see anything wrong on the outside. So unless they are very understanding, they may become resentful at the impact on their lives. If available, family counselling may help family members to understand the problems of the patient and help the patient to solve the needs of the family in a low-stress way.

### **Sexual relations**

IC can have a big impact on sexual relationships since sexual intercourse may be painful for both male and female patients. For some women it may be totally impossible because the urethra, bladder and vagina are too painful, while for men ejaculation may also cause them intense pain. This is an aspect of the impact of IC on a patient's quality of life which is of very great importance. Sex is a normal part of the lives of human beings. If this form of intimacy is taken away, cracks may begin to appear in a relationship about which a patient may be deeply concerned. It is important for patients to be able to discuss this with their partner and for them to try to find solutions together, if necessary with the help of a therapist. Patients may find it difficult or impossible to raise this intimate and embarrassing subject with their doctor. Optimal pain treatment can also help the problem of painful sex in female patients. However, use of painkillers such as NSAIDs may lead to erectile dysfunction in men.

### **Patient support groups**

Patients and their families need to be well-informed about IC, its diagnosis, treatment and coping strategies. Patient support groups can play an important role not only in providing this kind of information but also in providing emotional support. Patient-to-patient counselling is invaluable since only another patient truly understands what IC symptoms are actually like and their impact on life. Contact with other patients can be a great relief and a big step forward in learning how to cope.

## Chapter 3

### Brief Historical Overview

***“Previous to the latter half of the nineteenth century but little was known about diseases of the urinary apparatus in women. And while the relatively more urgent and dangerous diseases of the male organs had exacted the closest attention, the modesty of women, as well as the inaccessible nature of the affections, conspired to hinder an earlier scientific investigation of their genito-urinary organs.” (Operative Gynecology, 1912)***

In 1808, Philip Syng Physick, a renowned surgeon from Philadelphia, was reported by his students as describing a painful inflammatory bladder disorder with an “ulcer in the neck of the bladder”, producing the same symptoms as stone (a common cause of bladder pain at that time). In 1836, the Philadelphian surgeon Joseph Parrish described the condition as "tic douloureux" of the bladder, a term commonly used for trigeminal neuralgia, which he attributed to his mentor Philip Syng Physick. He wrote: “I have known instances of great suffering in the urinary organs, from this form of disease”.

In the same year in France, Louis Mercier wrote about unusual and perplexing perforation of the bladder from ulcers in males for which he could find no cause, there being no stone, no venereal history and no sign of tuberculosis.

The name interstitial cystitis first appeared in 1887 in a book on diseases of the female urethra and bladder in which Alexander J.C. Skene, a gynaecologist from Brooklyn, described a bladder condition characterized by inflammation. “When the disease has destroyed the mucous membrane partly or wholly and extended to the muscular parietes, we have what is known as interstitial cystitis”, wrote Skene.

In Germany, Maximilian Nitze (1848-1906), a founding father of modern urology, described the symptoms of a bladder disorder with frequency, pain and inflammatory ulceration of the mucosa, calling it “cystitis parenchymatosa” that caused “heftige Beschwerden” in the patients, published in a textbook in 1907 just after his untimely death at the age of only 57 years.

In 1912, the effect of diet was already attracting attention with the Boston gynaecologist Howard Kelly writing: “Such articles of diet as tomatoes, fruits or acids, should be avoided when the patient finds that they aggravate her condition”.

Meanwhile, the invention of the cystoscope in Europe was revolutionising bladder investigation, paving the way for Guy Hunner and contemporaries to examine the bladder in greater detail than hitherto possible in living patients, rather than after their demise, but without cutting the bladder open.

Guy Leroy Hunner, a Boston gynaecologist, described this ulcerative, inflammatory bladder disease in great detail for the first time in a number of papers, the first being published in 1914 (republished in 1915). In this first paper he writes: “While cystoscopy usually reveals only one inflammatory spot, there may be two or three granulation areas near together or somewhat separated, and operation usually reveals a more extensive area of inflammation than was appreciated by cystoscopy. The ulcer area may be easily overlooked and the attention may first be arrested by an area of dead white scar tissue. In the neighbourhood of this scar-looking area, one sees one or more areas of hyperemia which, on being touched with a dry cotton

pledget, or with the end of the speculum, bleed and first show their character as ulcers. In other cases, or perhaps at subsequent examination on the same case, the ulcer may be well defined as a deeply red area with granulating base and with congested vessels surrounding the area. In none of the cases has an individual ulcer area been more than a half centimetre in diameter, although two or three such ulcers have at times been grouped in a larger inflammatory area.”

By 1918 not only was cystoscopic technology improving but Hunner was gaining in experience and had many more patients. In his paper on the “Elusive Ulcer of the Bladder”, he now gives more extensive descriptions of the cystoscopic picture: “These ulcer areas are always small, usually measuring not more than 5mm. in diameter. They may be linear and measure from 0.5 to 2 cm. in length and from 1 to 2 mm. in width, and may thus resemble the mouse-eaten linear ulcer not infrequently found in a tuberculous bladder. Two or three minute ulcers may be found in a group and they may be surrounded by a small red area of edema. The ulcers always appear to be superficial, and I have never seen them covered with necrotic membrane or urinary salts and have never seen them present a picture suggesting malignancy. The ulcer area may or may not be surrounded by a zone of radially converging vessels. One may find a minute ulcer with or without edema around it, and in another portion of the mucosa an edema area without an appreciable ulcer. These edema areas are generally seen immediately after the patient has been having an unusually bad period of bladder symptoms with much strangury.” These ulcers came to be known as “Hunner's ulcers”, although it was realized very early on that the term “ulcer” was a misnomer since it did not in fact concern a true ulcer but a vulnus, and was frequently described as a lesion.

Floyd Keene, gynaecologist of Philadelphia and a contemporary of Hunner, wrote a paper on “Circumscribed Pan-mural Ulcerative Cystitis” published in 1920 in which he described the bladder as having a “flea-bite” appearance in one or more areas.

In 1944 Cristol wrote about 78 cases of interstitial cystitis in men, and in 1950 Heslin also wrote on IC in male patients.

While there were many more publications on this disorder on both sides of the Atlantic in English, French and German in this period, it was John R. Hand who published the first really comprehensive paper on the subject with a report on 223 cases (204 women and 19 men) in 1949. Hand divided the interstitial cystitis patients into 3 grades, based on the severity of the cystoscopic findings: Grade I represents minimal bladder involvement, Grade II represents a more advanced stage of the disease, Grade III represents the most advanced stage of the disease. Hand also described submucosal hemorrhages: “On distention there were small discrete, submucosal hemorrhages, showing variations in form. Near the trigone, for example, there were dot-like bleeding points” (the term glomerulations was only coined much later in 1978 by Walsh). The symptoms were described as pain, frequency day and night and extreme urgency.

At this period, it was still assumed that the milder cases would eventually progress to lesions. While earlier writers – including Hunner - were aware of possible association with rheumatic diseases, Hand also emphasized that “allergies were more common among the patients with IC than among those from the general admission.” Like all his colleagues, Hand was also concerned with the name of the disease and wrote: “For some time I have also been impressed with the inadequacy of the many names which have been given to this disease. And after considerable thought, I am inclined to agree with Folsom’s pithy comment that when Hunner “delivered this child into the urologic world he did not name it as well as he described it”. He continues: “Without doubt, some phase of the disease gives justification for each of its many names. But no one name yet proposed is wholly satisfactory because it fails to take into

account the changing picture of the disease. However, until a better name is found, 'interstitial cystitis' is the most suitable..." Hand can be said to have brought IC into the modern era.

In 1951, the term painful bladder syndrome first appeared, introduced by J.P. Bourque from Canada as an umbrella term for all disorders causing pain in the bladder.

Two articles on IC in children by Harold McDonald appeared in 1953 and 1958, followed by an article in 1960 on the same topic by Chenoweth.

In 1970, in a paper on new clinical and immunological observations, Oravisto and colleagues wrote: "Although interstitial cystitis is fairly uncommon, it is not rare and, in our experience, mild and atypical cases readily escape detection". Oravisto noted the high frequency of drug hypersensitivity in these patients.

In 1978, Messing and Stamey reported in great detail on a retrospective review of 52 patients with IC and felt that the majority of patients do not have Hunner's ulcer. They stated that "we believe that the synonymy of Hunner's ulcer with interstitial cystitis has done more to prevent recognition of this disease than any other single factor". It is indeed most probably this historic association between Guy Hunner's ulcers and IC that has resulted in many patients with the non-ulcerative type remaining undiagnosed and untreated over so many decades.

In 1987, encouraged by the American Interstitial Cystitis Association (ICA) that was founded in 1984, the NIDDK in the USA drew up a first consensus definition of IC, revised in 1988. These criteria were specifically intended for research purposes to provide a common basis for much-needed studies and allow comparison between the studies. The criteria were never intended as a definition for the clinician. However, due to the lack of any other guidelines for clinical diagnosis, they were widely used for the diagnosis of patients in a clinical setting. It was later estimated that some 60% of patients with IC symptoms failed to meet these strict criteria, resulting in many patients remaining undiagnosed and consequently untreated. The irony of the situation is that while doctors in the United States mainly stopped using the NIDDK criteria for clinical diagnosis, doctors in other parts of the world continued to adhere to them rigidly due to the lack of any other clear guidelines.

Although the name painful bladder syndrome had been around since the early fifties, it was only introduced into standard terminology in 2002 by the International Continence Society (ICS), defining it as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology". They reserved the term interstitial cystitis for patients with "typical cystoscopic and histological features". However, the ICS unfortunately did not specify exactly what these typical features were. This led to usage of the combined term IC/PBS or PBS/IC, due to the fact that the ICS definition did not make it any easier to diagnose patients because doctors found it difficult to understand what the distinction was supposed to be between IC and PBS, particularly in countries where it is not so customary to perform cystoscopy and/or biopsy in all patients. Furthermore, the term "suprapubic pain" and the association of pain with filling led to confusion, misunderstanding and poor sensitivity of the definition.

In 2006 the European Society for the Study of IC/PBS (ESSIC) designed a type classification system according to findings at cystoscopy and biopsy and caused some controversy on announcing that it preferred to use the name bladder pain syndrome (BPS) which is a name taken from the urogenital pain taxonomy (classification) of the International Association for the Study of Pain (IASP), a taxonomy which had already been used in EAU Guidelines for chronic pelvic pain (see: [www.essic.eu](http://www.essic.eu)).

ESSIC's definition in 2008 was as follows: BPS would be diagnosed on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.

In 2008, the NIDDK launched a 5-year multi-centre research programme entitled the Multidisciplinary Approach to the Study of Pelvic Pain (MAPP) with an innovative shift in research focus. This research project will study both interstitial cystitis (IC) and chronic prostatitis (CP/CPPS) in a wider systemic framework, exploring in more detail the relationships and overlap with disorders that often co-exist such as fibromyalgia, irritable bowel syndrome, chronic fatigue and vulvodynia and asking whether these associated disorders can provide additional insights into IC/PBS or CP/CPPS. The primary objectives of the MAPP include: to understand the underlying disease pathophysiology and risk factors through targeted epidemiological studies and use of biological samples; and to provide a translational foundation for the development of therapies. An important part of these studies will be the phenotyping (clinical characterization into types) of patients participating in the studies. The aim is to arrive at optimum treatment for the individual patient and avoid the current "hit-or-miss" approach. In connection with this study, a new term was recently introduced by the NIDDK: the Urologic Chronic Pelvic Pain Syndromes (UCPPS). For more information on the MAPP study, visit: [www2.nidk.nih.gov/Research/ScientificAreas/Urology/MAPP](http://www2.nidk.nih.gov/Research/ScientificAreas/Urology/MAPP).

The NIDDK MAPP IC Inclusion Criteria are as follows:

- Females or males having an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of at least 3 consecutive months' duration, in the absence of infection or other identifiable causes.
- Scoring at least 1 on the frequency scale and at least 1 on the pain, pressure, discomfort scale.

*Source: Philip Hanno MD, IC/PBS: A Primer and an Update. AUA Annual Meeting, Chicago, 28/4/2009*

The "snowflake hypothesis" appeared in 2009 in relation to both IC and CP, based on the concept that no two patients are the same, just like snowflakes. This led to a pilot clinical phenotyping system developed by Nickel, Shoskes and Irvine-Bird known as **UPOINT**. The purpose of this pilot phenotyping system is to classify patients with IC according to clinically relevant domains or subtypes with the ultimate aim of optimizing therapy and improving outcomes. UPOINT domains are:

- **Urinary**
- **Psychosocial**
- **Organ Specific**
- **Infection**
- **Neurologic/Systemic**
- **Tenderness**

Further information on UPOINT is available on: <http://www.upointmd.com/>

The Society of Interstitial Cystitis of Japan (SICJ) and a group of East Asian countries (Japan, Korea, Taiwan) both published detailed guidelines in 2009, in which they both proposed a new symptom complex to be known as Hypersensitive Bladder Syndrome (HBS). This would be a clinical entity that is more inclusive than pain syndromes alone since it incorporates patients

with and without pain They define interstitial cystitis (IC) as a disease of the urinary bladder diagnosed by three conditions: 1) lower urinary tract symptoms, such as bladder hypersensitivity, urinary frequency, bladder discomfort and bladder pain; 2) bladder pathology such as Hunner's ulcer and mucosal bleeding after over-distension; and 3) exclusion of confusable diseases such as infection, malignancy and calculi of the urinary tract. The authors explain that HBS can be used as a descriptive term for the symptom complex, or as a diagnostic name for the condition in a patient suspected of having IC but who has not fulfilled all the requirements for the diagnosis of IC as given above.

An Indian IC/PBS Society is also currently developing its own guidelines for IC/PBS which it defines as "recurrent pelvic pain or discomfort (pressure, burning, throbbing, etc) of at least 4-6 weeks duration, which increases with bladder filling and/or decreases with micturition in the absence of definable pathology associated with urinary frequency and/or urgency".

The lack of international consensus on the name and definition is indeed a problem because consistency in use of terminology is a basic requirement for clear communication in any field of medicine. But first we need to understand exactly what disease it is that we are trying to communicate!

In the meantime, for the sake of clarity for patients and others seeking information, the patient organizations are mainly continuing to use the name interstitial cystitis, sometimes in combination with painful bladder syndrome.

**While there is currently far greater awareness of interstitial cystitis around the world today and many more patients are now receiving a diagnosis of IC, there are still countries where knowledge of this disease scarcely exists.**

## Chapter 4

### Diagnosis

#### Referral by family doctor

Seeking medical help is a series of hurdles and, despite increased awareness, a patient may still spend years without the right diagnosis. The first hurdle is recognition at a primary care level of the possibility that a patient may have interstitial cystitis.

Diagnosing IC is often a long, complex process that starts with referral to a urologist or urogynaecologist by a family doctor. This means that it is essential to ensure that these family doctors are aware of IC and its symptoms so as to ensure referral to the right specialist and hopefully to achieve the right diagnosis and treatment at the earliest possible stage.

A primary health provider who may never have heard of IC will quite likely assume that the symptoms are caused by a bacterial infection and repeatedly prescribed antibiotics, even when urine tests for infection are negative. In the past many women have been referred to gynaecologists and have consequently been subjected to all kinds of unnecessary treatment including radical gynaecological surgery.

#### Diagnosis by the urologist/urogynaecologist

At the present time, due to the lack of specific tests or markers, diagnosis of IC is based on:

- Symptoms: pain or discomfort or hypersensitivity, urgency, frequency during the day and night lasting more than 3 months\*
- Exclusion of any identifiable infection, disease or disorder (so-called confusable diseases) that might cause the symptoms. \*\*

*\* Some definitions say 6 weeks, based on the view that if all other possibilities have been excluded in that time, treatment should be started immediately rather than leaving the patient in pain. Others say a minimum of 6 months.*

*\*\* Taking into account that the diagnosis of a confusable disease does not necessarily exclude a diagnosis of IC. A confusable disease and IC may co-exist.*

This diagnosis may be supported by:

- Cystoscopic findings with or without hydrodistension
- Biopsy findings.

Diagnosis of IC is essentially based on symptoms and exclusion of other painful bladder conditions that resemble IC but have a different identifiable cause. It may be supported by cystoscopic and biopsy findings (including inflammation, Hunner's ulcer or lesion, glomerulations). Many of the tests and investigations are aimed at eliminating all other possibilities. For example: urinary tract infections, kidney or bladder stones, bladder cancer, vaginal infections, sexually transmitted infections, radiation cystitis (caused by radiation therapy), chemical cystitis (caused by drugs), eosinophilic cystitis, tuberculosis, schistosomiasis, endometriosis (in women), prostatitis (in men), neurologic disorders including pudendal or other nerve entrapment, and low count bacterial infections that may be missed by dipstick testing. However, the diagnosis of a confusable disease does not necessarily exclude a diagnosis of IC. A confusable disease and IC may co-exist.

See **Table 1** for the list of relevant confusable diseases as proposed by the European Society for the Study of IC/PBS (ESSIC).

<b>Table 1:</b> List of relevant confusable diseases and how they can be excluded or diagnosed	
<b>Confusable diseases</b>	<b>Excluded or diagnosed by</b>
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with: Common intestinal bacteria Chlamydia trachomatis Ureaplasma urealyticum Mycoplasma hominis Mycoplasma genitalium Corynebacterium urealyticum Mycobacterium tuberculosis Candida species Herpes simplex Human Papilloma Virus	Routine bacterial culture Special culture Special culture Special culture Special culture Special culture Dipstick if "sterile", pyuria culture for <i>M. tuberculosis</i> Special culture Physical examination Physical examination
Radiation Chemotherapy, including immunotherapy with cyclophosphamide Anti-inflammatory therapy with tiaprofenic acid	Medical history Medical history Medical history Medical history
Bladder neck obstruction Neurogenic outlet obstruction Bladder stone Lower ureteric stone	Flowmetry and ultrasound Medical history, flowmetry and ultrasound Imaging or cystoscopy Medical history and/or haematuria (→upper urinary tract imaging such as CT or IVP)
Urethral diverticulum Urogenital prolapse	Medical history and physical examination Medical history and physical examination
Endometriosis Vaginal candidiasis Cervical, uterine and ovarian cancer	Medical history and physical examination Medical history and physical examination Physical examination
Incomplete bladder emptying (retention)	Post-void residual urine volume measured by ultrasound scanning
Overactive bladder Prostate cancer Benign prostatic obstruction Chronic bacterial prostatitis Chronic non-bacterial prostatitis	Medical history and urodynamics Physical examination and PSA Flowmetry and pressure-flow studies Medical history, physical examination, culture Medical history, physical examination, culture
Pudendal nerve entrapment Pelvic floor muscle related pain	Medical history, physical examination, nerve block may prove diagnosis Medical history, physical examination
Source: European Society for the Study of IC/PBS (ESSIC) www.essic.eu. 24.1.2008 Eur.Urol. 2008 Jan;53(1):60-7. Epub 2007 Sep 20.	

### **What investigations does a urologist carry out in order to arrive at a diagnosis?**

This varies from country to country and may be dictated by economic considerations, including the type of healthcare and health insurance system prevailing in a given country.

#### **No specific diagnostic tests exist**

There are still no diagnostic tests specifically for IC. However, research in the field of urinary markers looks promising and may eventually produce a diagnostic urine test. Finding a reliable urine marker could substantially speed up diagnosis.

**Medical history:** First of all a detailed and careful medical history of the patient is taken with special attention to previous pelvic surgery, any history of urinary tract infections or urological diseases, any autoimmune diseases or other chronic diseases, any previous pelvic radiation treatment, chemotherapy, location of the pain and whether it is related to bladder filling/emptying, description of the pain.

A history of previous medication or other drug history is important since certain drugs have been shown to cause symptoms similar to IC (tiaprofenic acid, cyclophosphamide, ketamine).

**Physical examination:** A general physical examination is carried out, including pain mapping. Women may have a vaginal examination and men a digital rectal examination.

**Laboratory tests:** Urine dipstick and urine cultures will be carried out to check for bacterial infection or infectious diseases including tuberculosis. Special urine, blood or swab tests may be needed to check for the presence of infectious organisms such as Ureaplasma, Chlamydia and Candida which are not detectable with normal urine tests. In men, prostatic fluid may be examined for signs of infection.

**Symptom evaluation:** the patient may then be asked to fill in **voiding charts** with volume intake and output, **symptom and bother scores or quality of life scores**. Patients may be asked to record the pain they have felt in the last 24 hours on a **Visual Analogue Scale**. The purpose of all these charts is to evaluate the level and nature of the symptoms and their impact on the patient's quality of life. These charts are not recommended for diagnostic purposes.

**Urodynamics:** A urodynamic investigation is sometimes carried out when considered necessary but is not essential for the diagnosis of IC. It is, however, considered mandatory in men. This investigation assesses how much urine the bladder can hold and when the patient first feels the desire to urinate and whether this is painful. A thin catheter is inserted via the urethra into the bladder in order to fill the bladder and measure the pressure that builds up in the bladder. A second catheter is placed in the rectum to measure the pressure in the abdomen. This investigation is also carried out if the patient is suffering from any kind of urinary retention or obstruction and either unable to empty the bladder at all or only able to partially empty it.

**Imaging:** Ultrasound scanning may be carried out to see how much urine is left in the bladder after urination (post-void residual urine).

**Cystoscopy:** Cystoscopy allows the urologist to look into the bladder and carry out a number of tests and is a standard investigation in urology when it is necessary to take a look around the bladder. A narrow tube is inserted into the bladder via the urethra. It has two or more channels: one carrying an endoscope that allows visual examination of the inside of the bladder, the other channel carries fluid for instillation into the bladder.

There are two methods of cystoscopy:

- The (office) cystoscopy using local anaesthesia but without hydrodistension (stretching the bladder) and
- the cystoscopy under general or spinal anaesthesia with hydrodistension.

While cystoscopy is recommended as a standard investigation for IC in many parts of the world, in some countries including the USA even office cystoscopy is often only carried out if the patient has haematuria (blood in the urine) and it is therefore necessary to rule out the possibility of cancer .

**The office cystoscopy with local anaesthesia** is an investigation to exclude the possibility of other causes of the symptoms, such as tumours, stones, eosinophilic cystitis etc. Office cystoscopy also makes it possible to detect any scarring of the bladder wall which might be Hunner's ulcer/lesion. At the same time the urologist will take a look at the urethra. In women a gynaecologic examination may be carried out and in men palpation of the prostate.

**Cystoscopy under general or spinal anaesthesia**, considered mandatory in Europe, is performed when IC is suspected in order to carry out **hydrodistension** in which the bladder is filled with fluid twice, the first time to maximum capacity to assess bladder capacity under anaesthesia, the second time less in order to inspect the bladder wall.

**Glomerulations:** As the walls of the bladder are stretched, pinpoint petechial haemorrhages, also known as glomerulations, may be seen in around 90% of IC patients. These glomerulations cannot be seen without hydrodistension. However, while glomerulations were once considered a hallmark of IC, they have also been found in patients who do not have IC while some patients with all the symptoms of IC have no glomerulations. Glomerulations can therefore only support the diagnosis of IC in combination with typical IC symptoms or other findings, cannot be considered diagnostic or a reason for including or excluding patients. There is also no correlation between the degree of glomerulations and symptoms. Furthermore, the findings of cystoscopy with hydrodistension can vary at different times in the same patient. Hydrodistension's main role lies in the information it produces for research purposes. It is questionable whether it is relevant as a routine clinical investigation at the present time.

**Hunner's ulcer or lesion** is less common, but if present it will best be identifiable during cystoscopy with hydrodistension. It is possible that these lesions are being undiagnosed. Some urologists claim to see them in 50% of their patients, while others say they have seen a single case. It is therefore likely that it is going unrecognised due to confusion over the old name. The name ulcer is misleading since it is not a true ulcer, but an inflammatory lesion, also known sometimes as a patch. Hydrodistension will cause any scar-like lesions to crack and bleed.

Professor Magnus Fall has described these lesions as follows on the ESSIC website:

“The Hunner's lesion typically presents as a circumscribed, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension.”

A further detailed description can be found on the ESSIC website:

[http://www.essic.eu/Hunner\\_lesion.html](http://www.essic.eu/Hunner_lesion.html)

It is particularly important for these bladder lesions to be identified in patients with IC symptoms as this form of **Classic IC** responds well to a specific type of treatment.

**Biopsy:** A bladder **biopsy** may be carried out. This involves taking a minimum of three small samples of tissue from different levels in the bladder wall, including from the detrusor muscle, at several different sites in the bladder. These samples will then be examined microscopically by the pathologist and may reveal an increase in **mast cells** in the detrusor muscle in the bladder wall. Mast cells play a role in allergic and inflammatory reactions in the body's tissues. They can degranulate and release histamine. They are considered by some researchers to play a pivotal role in IC, but are seen by others to be the result of chronic inflammation. Mast cell counts are often higher in IC patients than in patients with other bladder diseases.

The biopsy is important to exclude the possibility of other causes of the symptoms (such as cancer) and all lesions or patches should be biopsied. Biopsy is more commonly carried out in Europe and Japan than in the USA for example. While cost may play a role here, it is also considered an invasive procedure by some.

**Potassium sensitivity test:** the potassium sensitivity test which was studied for some time as a possible way of diagnosing IC is now no longer considered to be reliable for diagnostic purposes and is a painful experience for the IC patient. However a milder, modified form of this potassium test was recently successfully studied as a possible way of selecting patients who may respond well to treatment aimed at temporarily replenishing the lining of the bladder (so-called GAG-layer). Not all IC patients appear to have a leaky bladder lining, while some patients with a leaky bladder lining do not have IC.

**Anaesthetic challenge test:** Instillation of alkalized lidocaine into the bladder – commonly used as a rescue therapy with or without heparin to calm extreme pain in the bladder - is also sometimes used to assess whether the pain is actually in the bladder or elsewhere. If the pain is coming from the bladder, it will be anaesthetized by the lidocaine.

Even after all these investigations have been carried out and if the results are negative, this still does not necessarily mean that the patient does not have IC. Some patients may exhibit no abnormalities during the above investigations, while nevertheless displaying all the symptoms and bladder hypersensitivity of interstitial cystitis.

All the above tests can temporarily exacerbate the symptoms and cause burning in the bladder, urethra and when urinating for several days or longer, with blood visible in the urine. A bladder biopsy can cause burning pain for several weeks until the lining of the bladder has fully recovered.

If a patient fails to respond to any treatment for IC, reassessment is recommended to see if any confusable disease has been missed.

### **Diagnosis a relief**

Many patients will have seen numerous doctors and specialists before finally getting the right diagnosis. Patients who, despite seeing innumerable different doctors, still have no diagnosis can become absolutely desperate with pain, frequency and frustration to the point of being suicidal. Many will have been told time and time again that "it's all in the mind". It can therefore initially come as an immense relief to a patient to be given the diagnosis of IC, a disease that actually has a name to it. Patients feel that their long history of pain and debilitating symptoms is at last being taken seriously by the medical profession.

## Chapter 5

### Treatment

Once a diagnosis of IC has been established, the doctor then has the task of explaining to the patient that treatment is aimed at alleviation of the symptoms and improving the patient's quality of life. Despite all the research and studies that have been carried out, no possibility has as yet been found of curing this disease, nor is there a single drug that is effective in all patients. Nevertheless, there are many different options to try.

Treatment may consist of: patient education, diet modification and self-help, one or more oral drugs, bladder instillations or intramural injections, bladder distension, laser therapy or fulguration, neuromodulation/electrotherapy, surgery and different forms of physical therapy and pelvic floor relaxation.

Treatment is highly individual because every patient is different. A drug that has a beneficial effect on the symptoms of one patient sometimes has no effect on another patient. This is yet another reason for suspecting that IC may be a multi-factorial disease or even a collection of similar sub-categories. The different treatments for IC may be based on hypotheses concerning the cause of IC, the results of scientific studies or trials, practical experience with specific medications or sometimes purely to treat individual symptoms.

Over the years, a large number of treatments have been tried for IC patients, but only a few have reached a higher level of recommendation, and even those are only effective in some patients. This is an important reason for the current 5-year MAPP study being carried out by the NIH/NIDDK in the USA, aimed at phenotyping (subtyping) patients with the aim of finding optimum treatment for each subtype

Different patients may experience more bother from different symptoms: for example one patient may find the constant desire to urinate to be the worst aspect, another finds the lack of sleep and consequent exhaustion due to getting in and out of bed all night to go to the bathroom totally intolerable while a third may experience the pain as the worst aspect. Every patient is different, so treatment has to be tailored to each patient. Treatment in IC is symptom-driven and in order to maximize the effects of treatment, it is important to determine which symptom or symptoms are causing the most problems at each stage of the disorder in each individual patient.

Evaluation of treatment is hampered by the spontaneous flares and remission of symptoms that are so characteristic of IC. It is therefore sometimes very difficult to assess whether an improvement has been caused by the treatment or simply by a spontaneous remission.

### Patient education

Patient education plays an important role in any chronic disorder. By learning more about their condition through patient information, websites and support groups, patients can gain a better understanding of their symptoms and are reassured that they are not the only person in the world with this bladder disorder. This can be a first step along the path of learning how to

cope. Educated patients are also likely to understand much better why they are receiving a specific treatment and what this treatment is aiming to achieve.

## Diet modification

Many patients will soon discover from their own experience that certain foods and beverages appear to exacerbate their bladder symptoms.

Although there has been little or no research into this aspect other than studies based on surveys of patients, long lists of potential irritants have been compiled on websites, based on patient reports, and may be very alarming to a newly diagnosed patient.

Every patient is different and not all IC patients appear to be affected by diet, but by eliminating items known to cause irritation based on their own experience, a patient can at least avoid unnecessary exacerbation of the bladder symptoms. Patients with milder IC may even find that diet modification is the only treatment they need. They can try an elimination diet, starting with a very bland diet and gradually adding food items one at a time.

There are however, some guidelines regarding what foods and beverages are most likely to exacerbate symptoms. A study on the effects of food and drink was published in July 2007: *Effects of Comestibles on Symptoms of Interstitial Cystitis*, Barbara Shorter, Martin Lesser, Robert M. Moldwin, Leslie Kushner. *Journal of Urology*, July 2007, vol. 178, 145-152.

This study was based on a questionnaire distributed to a group of patients. The aim was to see whether certain foods, beverages and/or dietary supplements affected symptoms of IC either positively or negatively. 154 foods/drinks were studied. It was concluded that there is indeed a large number of IC patients whose symptoms are exacerbated by consumption of specific foods and beverages. The study identified the most bothersome foods as being items containing caffeine, citrus fruits and juices, tomatoes and tomato products, items containing vinegar and alcoholic beverages. Coffee was found to be the most bothersome. The study indicated that exacerbation appears to be worse in foods that contain hot pepper (for example Indian, Mexican and Thai food) suggesting that some component of hot peppers may be causing the exacerbation of symptoms. Patients participating in the study varied greatly regarding the effects of fruits and juices.

Some patients are known to experience relief through taking alkalizing agents such as calcium glycerophosphate (Prelief) if available, or baking soda (bicarbonate of soda): 1 teaspoon in a glass of water, but since baking soda has a high salt content this should not be taken by patients with salt restrictions.

<b>Table 2:</b>
<b>DIET MODIFICATION</b>
<b>The effect of food items on the bladder is highly individual but foods best avoided by IC patients include:</b>
Food/drink containing caffeine
Citrus fruit and juices
Other acidic food such as tomatoes, vinegar etc.
Artificial sweeteners
Alcoholic drinks
Carbonated drinks/soda
Highly spiced food especially containing hot pepper

Source: *Effects of Comestibles on Symptoms of Interstitial Cystitis*, Barbara Shorter, Martin Lesser, Robert M. Moldwin, Leslie Kushner. *Journal of Urology*, July 2007, vol. 178, 145-152.

**Table 2** summarises the main foods and beverages that may exacerbate the bladder. But these are simply guidelines and the patient has to find out what seems to exacerbate his/her own personal bladder symptoms.

**- Not only food and beverages**

Some patients also find that their bladder symptoms increase when taking certain oral drugs, for example antibiotics (and certain food supplements such as Vitamin C tablets). If it is a short-term drug, it is a question of gritting your teeth for a week or so. But any drug that exacerbates bladder symptoms and needs to be taken daily over a longer period can better be changed for something else.

**- Fluid intake**

Before going out anywhere, IC patients are quite likely to restrict their intake of liquid beforehand. If they have to be away for a few days, they may tend to cut down their fluid intake so much that they become dehydrated, their urine consequently becomes concentrated and this may cause even more pain. Always at the back of their mind is that fear of not being able to find a toilet in time and consequently developing so much pain that they can't cope with the situation. No patient wants to put him or herself in that position so they develop coping strategies for different situations and this includes not drinking. It is nevertheless important to maintain a balanced fluid intake. However, restricting drinking in the evening can help to reduce the need for nighttime urination.

**- Keeping bowels healthy**

Avoid constipation at all costs! Since constipation can exacerbate symptoms by causing pressure in the pelvic floor area, it is essential for IC patients to try to ensure that their diet contains sufficient fibre in addition to drinking enough fluids and to take sufficient **exercise** in some form. Many IC patients also suffer from irritable bowel syndrome (IBS) which may take the form of constipation or diarrhoea or both intermittently, sometimes with painful abdominal cramp. In this situation, a high fibre diet may actually cause more pain and bloating. If a high fibre diet is impossible because it causes bloating and spasms, mild laxatives may be necessary. Some of the drugs used to treat IC may have constipation as a side effect (including many painkillers/opioids and tricyclic antidepressants).

## **Lifestyle**

**- Stress avoidance and relaxation therapy**

Patients soon learn that the symptoms of IC can be exacerbated by physical or emotional stress which can trigger a flare-up. They consequently need to learn to pace themselves and try to avoid situations which make them physically or emotionally exhausted, while at the same time getting sufficient physical exercise. Adequate treatment for the most bothersome symptoms can also help stress reduction since not only chronic pain, but also urgency and frequency are very stressful and physically exhausting. Some patients may find professional counselling of value to learn how to cope with the impact of the disease on their lives and reduce the stress, depression and anxiety which the disease causes.

**- Clothing & hygiene**

IC patients often feel more comfortable in loose clothing and particularly in cotton underwear, not synthetic underwear. They have to be careful about the type of washing agent they use for their underwear since washing products and fabric softeners containing perfume can cause irritation. The same applies to their body: no perfumed products near the urogenital area, no soap, no bubble bath products etc.

### - Adapting lifestyle

IC often means a change in lifestyle. Everything has to be adapted to the needs and the situation created by the IC. With mild IC, these changes may be minimal; with severe IC, the disease may have an impact on all aspects of life. It is nevertheless important for the patient to try to maintain as normal a lifestyle as possible and to develop new interests to replace activities they feel they are no longer able to undertake due to their bladder disorder.

### - IC in the elderly

IC may cause additional problems in the elderly. Frequent urination at night may be hazardous and lead to the risk of falls and fractures. A commode chair next to the bed could be an option here. Some of the medications used to treat IC and overactive bladder can have cognitive side-effects which may be more pronounced in the elderly and further exacerbate any existing memory impairment or confusion.

## Oral treatments

Various oral treatments (tablets, capsules or syrup) are used for IC. The advantage of oral treatment is that it is easy to administer and non-invasive. However, there are also a number of disadvantages. When medication is given orally, it is absorbed by the body. The desired effect may be achieved via the blood or via the urine when the active medication has been excreted through the kidneys. This naturally takes some time and relatively little of the medication may actually reach the bladder. The fact that the drug is absorbed into the bloodstream means that side-effects may also occur. All drugs can have side effects and some IC patients have a problem with multiple drug intolerance.

While some doctors prefer the so-called multimodal approach, aimed at alleviating the different symptoms of pain, frequency and urgency with a combination of different drugs, others prefer to try one drug at a time.

Oral treatment may consist of one or more of the following (alphabetical order):

- anti-inflammatory drugs
- antispasmodics and anticholinergics/antimuscarinics
- anticonvulsants
- histamine-receptor antagonists
- immunosuppressive agents
- painkillers
- pentosan polysulfate sodium
- prostaglandins
- tricyclic antidepressants

### Anti-inflammatory drugs

There are several different groups of anti-inflammatory drugs including the following.

**Corticosteroids** (e.g. hydrocortisone, prednisolone and dexamethasone) are a group of drugs with a strong anti-inflammatory effect. Although prolonged use can lead to the risk of serious side-effects such as osteoporosis and lowered resistance to infection, these drugs can nevertheless be of great benefit to some IC patients. While a study indicated that prednisolone may be very effective in pain control in refractory patients with an ulcerated bladder, it may also show (even substantial) benefits in IC patients with a history of autoimmune disease.

**Montelukast** (e.g. Singulair<sup>®</sup>), a medication used to treat asthma, inhibits the release of leukotrienes from mast cells and other cell types and thereby prevents inflammation. A preliminary Danish study showed that treatment of IC patients with a daily dose of montelukast showed a significant improvement in urinary frequency and pain. However, more clinical trials with a larger number of patients are needed for its mechanism to be better understood in IC.

**NSAIDs** inhibit the production of prostaglandins, substances that play an important role in stimulating inflammation and in physiological processes in blood platelets, gastric mucosa and kidneys. In addition to their anti-inflammatory effect, NSAIDs also relieve pain but may also cause undesirable effects such as gastrointestinal ulcers and bleeding, fluid retention and hypertension. Examples are aspirin, diclofenac and ibuprofen. New NSAIDs, the so-called coxibs, have fewer gastrointestinal side-effects than the old drugs. Most old and the new NSAIDs increase the risk of ischaemic vascular disease.

There have been reports, backed up by studies, that the NSAID **tiaprofenic acid** may cause symptoms in some people similar to those of IC.

**IP 751:** an experimental anti-inflammatory, analgesic drug currently being developed for various specific conditions including IC. IP 751 is a non-psychoactive synthetic cannabinoid that appears to suppress inflammation and pain. Unlike many NSAIDs, IP 751 does not appear to cause gastrointestinal ulceration.

**MN-001:** this is a new oral anti-inflammatory compound being trialled in the USA for the treatment of IC and bronchial asthma.

**Quercetin:** this bioflavonoid is an alternative strategy for the treatment of IC. It is believed to have anti-inflammatory effects and to inhibit the activation of mast-cells. Has shown promising results and is available over the counter (OTC).

**Suplatast tosilate** (IPD/YM672 or YM672/IPD) is a new oral immuno-regulatory drug from Japan that suppresses allergic processes and has been used in Japan to treat bronchial asthma. It shows anti-inflammatory effects by inhibiting the production of cytokines (IL-4 and IL-5) deriving from type 2 helper T cells (Th2) involved in immune reactions. It is currently undergoing trials for IC and chronic, non-bacterial prostatitis. Results so far are encouraging for the treatment of non-ulcerative IC.

#### **Antispasmodics and anticholinergics/antimuscarinics**

Antispasmodics and anticholinergics/antimuscarinics are used to relax the bladder muscle. Commonly used drugs in this category include: darifenacin, solifenacin, tolterodine, trospium, oxybutynin (also available in a transdermal patch form), propiverine and the new fesoterodine fumarate. These are standard drugs for treatment of overactive bladder syndrome, but may be effective in some IC patients as part of combination treatment.

**Oxybutynin** is an older muscarinic receptor antagonist, but now available in a transdermal patch system and extended release tablets. A problem recently discovered with patches is the occurrence of erythema and pruritus at the site where the patch is placed. Tolterodine, an antimuscarinic drug, was developed for the treatment of overactive bladder. Tolterodine is claimed to have fewer adverse effects (e.g. dry mouth) than oxybutynin and may be of use in some early stage IC patients.

**Trospium chloride**, a drug used for overactive bladder symptoms, may also be useful in IC patients with an urgency-frequency problem. Trospium works by blocking cholinergic receptors found on muscle cells in the bladder, thereby preventing the action of acetylcholine. This relaxes the bladder muscle and helps make the bladder more stable. Newer drugs in this category such as darifenacin and solifenacin are said to have fewer side-effects and are better tolerated.

**Duloxetine** is a selective serotonin and noradrenalin reuptake inhibitor. Although a study did not show any significant improvement in IC patients, it may possibly have some value in selected patients. (dosage: 60 mg a day)

Although these drugs may have a sedative on the bladder in some IC patients, longer-term use has been found to lead to bladder retention/voiding difficulty by patients. All the drugs in this group tend to have bothersome side effects, the most common of which are dry mouth, dry eyes, dry nose, blurred vision, headache, constipation, drowsiness, dizziness and palpitations. Cognitive side-effects can also occur and are particularly a problem in the elderly. Drug therapy maximum dose is usually determined by the patient's tolerance of side effects. The newer drugs and once-daily drugs have fewer side effects.

#### **Anticonvulsants:**

**Gabapentin** (Neurontin®) is an anticonvulsant medication used to help control certain types of epileptic seizures that has been found to be useful in the treatment of neuropathic pain and postherpetic neuralgia. Experimentally used for IC and other genitourinary pain and may have good results in some IC patients with severe pain and reduce dependence on opioids. A newer drug on the scene in this category is **pregabalin** (Lyrica®) which is also being used for some IC patients. A common side effect of these drugs is drowsiness.

#### **Immunosuppressive agents:**

**Cyclosporine A** belongs to the group of medicines known as immunosuppressive agents that suppress the immune system and reduce the immune system's ability to produce certain reactions that can cause inflammation and tissue damage. This drug is normally used to prevent rejection of organ transplants and as a treatment for severe psoriasis, rheumatoid arthritis and many other autoimmune diseases. Recent small studies with low dose cyclosporine A have shown that it may be effective in some IC patients, but should only be used in the most severe cases that have failed to respond to other therapy.

**Mycophenolate mofetil (CellCept) and mycophenolic acid (Myfortic)** are immunosuppressants used to prevent rejection of organ transplants (FDA approved) and off-label for selected patients with systemic autoimmune diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus) and vasculitides (e.g. Wegener's granulomatosis). However, trials with IC patients have recently been halted in the USA due to lack of efficacy and potential side effects.

#### **Histamine-receptor antagonists**

There are two types of receptor for histamine, known as H1 and H2. Drugs that block the H1-receptor are also known as antihistamines.

**Hydroxyzine:** The use of the H1-receptor antagonist hydroxyzine is based on the hypothesis that the histamine released by the mast cells is responsible for the symptoms of IC. Hydroxyzine inhibits mast cell release of histamine and has sedative properties. This type of treatment may be useful in patients with a history of allergies. It requires up to 3 months for

an effect to be seen. Dosage: 10 to 25 mg every night at bedtime for a week; then up to 75 mg a day. Can cause drowsiness and in the elderly confusion.

**Cimetidine and ranitidine** are H<sub>2</sub>-receptor antagonists or blockers that were mainly used in the treatment of peptic ulcers and acid indigestion. However, they appear to be useful in alleviating the pain and symptoms of some IC patients but this has never been definitively proven.

**L-Arginine** occurs naturally in the body as an amino acid, one of the building blocks of protein, and plays a role in supplying the body with nitric oxide used by the body to keep blood vessels dilated and improve the blood supply. Its use is controversial and studies suggest that it may have little effect in IC.

### **Painkillers (analgesics)**

Pain control is a very important aspect of treatment of IC patients. Standard over-the-counter painkillers are not likely to be very effective against the pain of IC unless the pain is very mild. In cases of extreme pain that fails to respond to other treatment, long-acting opioids may be necessary (tramadol, morphine, oxycodone, hydromorphone). A problem with narcotics is that they can cause side effects including fatigue, constipation, nausea as well as dependency. Chronic opioid therapy should be considered as a last resort and can best be undertaken in a pain management clinic.

Painkillers in the form of suppositories can also be used (paracetamol, paracetamol with codeine) and are sometimes advisable for patients with gastric disorders. Patches on the skin are another method. A new patient-activated pain device to administer medication for hard-to-treat chronic pain is also available in some countries.

**Methotrexate** has shown a significant improvement in pain in IC patients, but had no effect on urgency or frequency.

**Phenazopyridine** is a urinary tract analgesic used for short-term relief of pain in the bladder. Not advisable for long-term treatment as it can build up in the body and cause harmful side effects.

See also under **NSAIDs** for more pain treatment.

Referral to a pain management clinic should be considered for the treatment of severe chronic pain particularly if chronic opioid therapy is required.

### **Pentosan polysulfate sodium (PPS)**

PPS is a heparinoid drug. One of the hypotheses concerning the causes of IC is the existence of a defect in the glycosaminoglycan (GAG) layer that acts as a protective lining for the wall of the bladder. It is believed that PPS temporarily repairs this defect, creating a synthetic layer that protects the underlying bladder wall from being attacked by irritant elements in the urine. Studies suggest that it may also have an anti-inflammatory effect. This medication is obtainable in tablet or capsule form in the United States under the name Elmiron<sup>®</sup>, in Italy as Fibrase<sup>®</sup>, in Germany as SP54<sup>®</sup> and South Africa and other African countries as Tavan 54<sup>®</sup>.

PPS is often used in combination with amitriptyline and hydroxyzine as “multimodal” therapy. A number of studies have been carried out in with the oral form and while they have produced contradictory results appear to have a beneficial effect in some patients. PPS takes some time to show an effect, usually after 12-16 weeks of treatment. Studies have indicated as long as 6

months. The duration of treatment is now considered to be of more importance in relation to efficacy than any increase in the daily dose. It is used as a second-line treatment, when other oral drugs have failed to show any improvement. This drug is unlicensed and difficult to obtain in many countries. See also intravesical treatment.

Side effects include reversible hair loss, gastrointestinal pain, diarrhoea and nausea, rash, and dizziness. Dosage: 100 mg three times a day.

### **Prostaglandins:**

**Misoprostol**, an oral prostaglandin E<sub>1</sub> analogue, used to treat gastric ulcers resulting from the use of certain NSAIDs, has also been found successful in treating some IC patients.

### **Tricyclic antidepressants**

This mainly concerns **amitriptyline**, but nortriptyline and doxepin are also used. Tricyclic antidepressants are used in the treatment of IC because they block the release of histamine, block reuptake of serotonin + norepinephrine, are sodium channel blockers, have central and peripheral anticholinergic action and alleviate pain. They may also have a relaxing effect on the bladder, thereby reducing the desire to urinate and consequently frequency. Patients who have a reasonable bladder capacity appear to respond better to this medication. Amitriptyline is currently recommended as a standard first-line oral treatment, is generic and inexpensive. It should be taken at dinner in the evening and will help the patient to sleep. This drug has multiple qualities. It is usual to start with a low dosage (10-25 mg) and gradually increase to optimum level (with minimum side effects) for the individual patient (up to maximum 75 mg). Side effects include constipation, dry mouth, urinary retention, weight gain, palpitations and daytime drowsiness.

### **Transdermal (skin) patches**

A number of drugs are available for the treatment of pain or urgency/frequency in the form of adhesive skin patches.

## **Intravesical and intramural bladder treatment**

Intravesical therapies are treatments where the medication is applied directly to the bladder or bladder wall by means of instillation. Intramural treatment is when the treatment is injected into the bladder wall. This means that the medication immediately reaches the right place and far higher concentrations come into contact with the bladder wall than in the case of oral medication. Adverse effects are limited due to the fact that short treatment times mean that there is relatively little absorption of the drug from the bladder into the bloodstream. This is one of the main advantages of bladder instillations. A disadvantage is that the patient has to be catheterised to allow the bladder to be emptied and the medication to be instilled. There is always a risk of infection occurring during catheterization, but these days this is relatively minor bearing in mind the high quality, sterile material that is used. While antibiotics are sometimes given – either orally or intravesically -simultaneously with the instillation as a preventive measure, regular use in this way is not recommended since it can cause resistance to antibiotics by bacteria. When catheterising at home, careful hygiene – e.g. thorough cleansing of the area from front to back in women – can help prevent infection.

Catheterization can be an uncomfortable or even painful procedure for IC patients. Application of lidocaine gel in the urethra before insertion of the catheter can help to reduce pain on catheterization. In the case of some older drugs used for instillation (e.g. oxychlorosene sodium), general anaesthesia or epidural anaesthesia is necessary as administration of the drug causes such intense pain (these drugs are no longer recommended).

Drugs used for intravesical treatment can be used alone or as a cocktail in which several active ingredients are combined, including a painkiller such as lidocaine combined with sodium bicarbonate (the bicarbonate of sodium alkalises the lidocaine and allows it to be absorbed). A course of treatment may involve just a few instillations or numerous applications. The so-called **anaesthetic cocktails** for immediate pain relief usually comprise alkalized lidocaine with or without heparin. The effect can last for several days or even weeks. Administration of the instillation can take place at the urology clinic, but if instillations are necessary one or more times a week, the patient can be taught self-catheterization so as to be able to administer the drug at home. Many patients find this an advantage.

Some of the drugs used for instillation are aimed at replenishment of a deficit in the GAG (glycosaminoglycan) layer of the bladder. This is the protective layer of the surface of the bladder wall which protects the underlying layers of the bladder wall from penetration by toxic or irritative elements in the urine and by infection. This GAG layer is believed to be impaired in some patients with interstitial cystitis (and other bladder disorders including radiation cystitis).

Most of the fluids used for instillation have to remain in the bladder for 15-60 minutes to achieve an adequate effect. The time varies depending on the drug used.

### **Drugs used for bladder instillation (alphabetical order)**

**BCG (Bacillus Calmette-Guérin)**, originally a vaccine used to provide protection against tuberculosis, has been used for some time to treat different types of bladder cancer. BCG causes an immune response leading to the production of a variety of cytokines. Some of these cytokines have antiangiogenic activity whereby they inhibit the formation of blood vessels needed for tumours to grow. Despite some positive results in the past with IC patients, recent studies have indicated that it is probably ineffective in IC and not recommended.

**Chondroitin sulfate** is a substance that occurs naturally in the bladder GAG layer. Treatment with chondroitin sulphate, available in different strengths under the brand names Uracyst® (2.0%) and Gepan® Instill (0.2%) is believed to replenish deficient chondroitin sulfate in the GAG barrier and to help prevent irritants in the urine from penetrating the bladder wall. Studies have indicated that it is safe, effective and well-tolerated.

**Corticosteroids** can also be used intravesically, either alone or in a cocktail.

**Disodium cromoglycate** is a substance that inhibits mast cells. Urologists have used this drug for some time as a bladder instillation with varying success. However, any improvement in symptoms is generally short-lived and the symptoms soon return.

**DMSO (dimethylsulfoxide)** is one of the most commonly used drugs for bladder instillation and is one of only two drugs for IC approved by the American Food and Drug Administration (FDA). It is often the first drug to be tried because it has a number of properties that are of importance to IC. It is believed to be anti-inflammatory, analgesic and relaxes the bladder muscles. The symptoms are sometimes exacerbated for a few days following treatment but hopefully then show an improvement. A little of the DMSO penetrates the bladder wall and passes via the lungs into the breath, giving rise to the well-known garlic-like taste and odour coming from the breath and skin for up to 72 hours after treatment. DMSO can be combined with other drugs as a cocktail, for example with heparin and bicarbonate. Studies have shown that patients, who have undergone a period of treatment with DMSO instillations and have

responded well, maintain their improvement if they then receive a monthly maintenance therapy of heparin instillations. This development looks promising for patients who respond favourably to DMSO, although symptoms may worsen in some patients.

**The DMSO cocktail (6-8 weekly cycles):**

- 50% DMSO 50cc
- Triamcinolone 40mg
- Heparin sulphate 10,000-20,000 IU
- Sodium bicarbonate 44 meq
- +/- Gentamicin

*Source: Robert Moldwin MD, IC & Related Conditions: Practical Management Strategies AUA Annual Meeting Chicago 29/4/2009*

**Doxorubicin** (Adriamycin®) is a chemotherapy drug used in the treatment of cancer. It has been used experimentally with some positive results as a bladder instillation for IC patients with Hunner's ulcer in an advanced stage of IC.

**Heparin** is a drug commonly used as an anti-coagulant (a blood thinner to inhibit blood clotting). It is also believed to have an anti-inflammatory effect on the cell layers on the surface of the bladder wall and may temporarily repair the so-called GAG layer. Like PPS, it can take 2-3 months before it produces any effect. Can be used alone or in cocktails.

**Lidocaine** (local anaesthetic) is used for pain treatment, sometimes with only sodium bicarbonate (to alkalize the lidocaine) or in combination with other drugs such as heparin in a bladder instillation cocktail aimed at multi-modal treatment. It can also be used as a rescue treatment for the relief of severe pain in a flare. Alkalinized lidocaine is also used in the anaesthetic challenge test to assess whether the pain is actually coming from the bladder. Studies have shown that lidocaine needs to be alkalized with sodium bicarbonate otherwise it does not get absorbed. There have been reports of improved absorption using electromotive drug administration (EMDA) of lidocaine to anaesthetise the bladder.

Proprietary brands currently under development:

- **URG101:** A new investigational, proprietary bladder instillation using lidocaine to reduce the pain, urge and muscle spasm and heparin to coat the bladder wall. The phase 2 multi-centre, double-blind, placebo-controlled, crossover trial produced positive results. A USA patent was issued in August 2008.
- **PSD597** (intravesical alkalinized lidocaine) has been shown in a preliminary study to be effective in providing sustained improvement in symptoms. It is considered to be safe and well-tolerated. Further studies are in the pipe-line.

**Recipe for intravesical anaesthetic therapy:**

- 2% Lidocaine jelly
- 0.5% Marcaine
- 10,000-20,000 IU Heparin Sulfate
- 40 mg Triamcinolone
- Treatments administered 2-3 times per week

*Source: Robert Moldwin MD, IC & Related Conditions: Practical Management Strategies AUA Annual Meeting Chicago 29/4/2009*

**Liposomes** are literally globules of fat. When used intravesically, they are believed to help the absorption of other drugs they are combined with. A further hypothesis is that they may be of value when used alone by creating a temporary barrier film over the bladder lining that can prevent penetration by irritant substances in the urine and also promote wound healing. A

recent study showed a decrease in pain and urgency. Still experimental but looking promising for IC.

**Pentosan polysulfate sodium** is also used as a bladder instillation and in this form appears to have an even better effect than the oral form and is less likely to have side effects. Its main properties are believed to be strengthening the GAG layer, reduction of pain and anti-inflammatory effects. Since it does not appear to be very effective against other IC symptoms, it is generally used in a cocktail with other agents.

**Oxybutynin chloride**, an older drug commonly used for overactive bladder, is also sometimes used as bladder instillation for IC, often in cocktails. It reduces the frequent urge to urinate by increasing bladder capacity and controlling bladder spasms. With intravesical treatment, side effects are less likely than with the oral form.

**Oxychlorosene sodium** (Chlorpactin®) is a substance originally used to treat tuberculosis due to its antimicrobial properties. The 0.4% solution combined with hydrodistension frequently used in the past causes such intense pain in the bladder that it should only be administered under anaesthesia. A 0.2% concentration without hydrodistension is recommended for use in IC patients. However, oxychlorosene sodium has largely been superseded by less painful treatments and is considered an unnecessarily harsh treatment. No longer recommended and considered obsolete.

**PSD597**: an investigational proprietary bladder instillation comprising alkalized lidocaine for the treatment of pain in IC patients. Currently undergoing trials. Studies so far have indicated that the treatment is safe and well tolerated.

**RDP58**: an investigational immunomodulatory peptide with anti-inflammatory effects currently being investigated as a potential intravesical treatment for autoimmune-associated bladder inflammation such as IC. A recent study indicated that it inhibits cell-mediated bladder inflammation in an autoimmune cystitis model.

**Resiniferatoxin**, one of the so-called vanilloids, is an intravesical treatment with a desensitising effect that has been used to treat overactive bladder and hypersensitive painful bladder. Many times more potent as a pain reliever than capsaicin (an extract of chilli peppers), it is said to cause far less burning and irritation. However, studies with RTX® in the United States failed to show any positive results for IC patients, although new studies have been a little more positive and it does help some patients.

**Silver nitrate** is a very old and outdated treatment with a caustic, antiseptic and astringent effect on the bladder. Intravesical treatment of IC with silver nitrate dates back to 1928 and was used by Hunner. No longer recommended as a treatment for IC.

**Sodium hyaluronate or hyaluronan**, (also called hyaluronic acid), is one of the naturally occurring substances in the glycosaminoglycan or GAG layer of the bladder wall and all connective tissues. Like chondroitin sulphate, heparin and PPS, it is believed to temporarily repair the damaged GAG layer and thereby reduce the pain, urgency and frequency of IC. Sodium hyaluronate is reported to be well tolerated. Cystistat® has been approved for the temporary replacement of the GAG layer in the bladder and is commercially available in about 20 countries. European studies have shown positive results with a reduction in pain and some reduction in frequency. This treatment is also used for other painful bladder conditions including radiation cystitis. Recent studies have indicated that selection of patients who are

likely to respond to this treatment can be greatly improved by using the modified potassium sensitivity test.

### **Drugs used for intramural bladder injection**

**Botulinum toxin A**, a neurotoxin produced by bacterium clostridium, is the world's most potent biological toxin known to man and has generated a flurry of excitement in the urological world in recent years as a treatment for urethral and bladder dysfunction. Botox is injected into the bladder: submucosal injections preferably into the trigone. The effect wears off after some months but can then be repeated. Researchers are currently carrying out trials for IC patients. The drug works by reducing sensation and reducing the strength of the bladder contractions. Some trial results have been negative, some positive. Side effects have included urinary retention which may last several months until the effect of the treatment wears off. Recent studies have indicated that there is less risk of retention when injected into the trigone. More trials are needed to get a really clear picture. This is very experimental in IC but may help some patients.

**Triamcinolone** submucosal injections were recently studied for the treatment of Hunner's ulcer/lesion. Under general anaesthesia, 10 ml of triamcinolone acetonide (40mg/ml) was injected in 0.5 ml aliquots into the submucosal space of the centre and periphery of ulcer(s). It appeared to be well-tolerated in this Hunner subtype.

**Gene-gun therapy**, experimental therapy aimed at suppressing bladder pain responses with narcotics, is being studied for IC using a gene-gun method of transfer into the peripheral nerves of the bladder.

### **Hyperbaric Oxygenation**

Studies into Hyperbaric Oxygenation (HBO) have produced encouraging results with IC patients. The patient is placed in a pressurized treatment chamber and breathes 100% oxygen. This is a treatment that has already been successfully used for patients with radiation cystitis, appears to be safe and has shown moderately good results with a small number of IC patients, but is expensive and has limited availability.

### **Surgery**

Surgery includes surgical interventions on the nervous system (neuromodulation) and surgery on the bladder itself.

### **Laser ablation, electrocoagulation or resection for Hunner's ulcer/lesion**

This form of treatment is reserved for patients with the classic form of IC (Hunner's ulcer/lesion) and is used to treat the lesions. It has a temporarily alleviating effect on the pain for several months or even several years, but can be repeated when necessary.

### **Bladder hydrodistension (stretching)**

Bladder hydrodistension or stretching is not only used for diagnostic purposes but also for the treatment of interstitial cystitis in selected patients. Distension of the bladder has been used to treat IC patients since 1930 with varying results. Distension is carried out by filling the bladder above its known capacity. A well-known procedure is the Helmstein method where, under epidural anaesthesia, the bladder is stretched for three to six hours by means of a balloon inserted in the bladder. Distension can cause temporary exacerbation of symptoms in IC patients for a few days. Results of this procedure are variable and the duration of the

improvement unpredictable. Many patients report that their symptoms return within three months. The role and value of hydrodistension as a therapy are currently the subject of discussion. Hydrodistension should be undertaken only with the greatest caution in patients where Hunner's lesion are known or suspected to be present due to the high risk of bladder perforation and subsequent bleeding.

### **Neuromodulation / electrostimulation (nerve stimulation)**

An important development in the field of urology is neuromodulation of the sacral or pudendal nerve roots for the treatment of bladder dysfunction and urinary incontinence. Neuromodulation is a potentially important form of treatment for selected patients, but is an expensive option which is neither available nor affordable in many countries. The principle of neuromodulation is not a new one. Electric stimulation has been used as a pain therapy since the nineteen sixties (e.g. TENS, see below). It works by reconditioning the nerves that control bladder function. Unwanted contractions of the bladder are inhibited and normal bladder function is restored.

#### **TENS (Transcutaneous Electrical Nerve Stimulation)**

The oldest form of nerve stimulation is TENS. This is non-invasive and does not require surgery. With TENS, mild electric pulses are transmitted into the patient's body by placing electrode pads on the suprapubic region or the lower back. Electric stimulation is generated by a small portable unit. Many IC patients in different countries still use TENS as a form of (supplementary) pain control. Scientists believe that by stimulating nerve fibres with TENS, pain signals transmitted to the brain are blocked. This is known as the Gate-Control theory. TENS is also believed to increase the body's own natural pain-killing chemicals known as endorphins. TENS can be used at home by patients as pain relief in combination with other standard treatments. It is non-invasive, inexpensive, has no serious side effects and may help some patients.

**Percutaneous Tibial Nerve Stimulation (PTNS)** is a neuromodulation system intended to treat patients suffering from urinary urgency, urinary frequency and urgency incontinence. PTNS is a simple form of nerve stimulation via a fine needle inserted near a bundle of nerves located near the ankle. Electrical stimulation is applied to the needle using a low voltage external pulse generator. This sends a mild electric current via the posterior tibial nerve to the sacral nerves that control the bladder function. This form of stimulation is carried out for 30 minute sessions once a week and has been shown to have positive results in selected IC patients. After 12 sessions, if the patient's symptoms have subsided or improved by at least 50%, the patient will need a 30 minute stimulation session every 2 to 3 weeks. An implanted version is planned.

**Interstim® Sacral Nerve Stimulation (SNS)** is a neuromodulation option for patients who have failed to respond to standard treatments and have long-standing, invalidating symptoms. This therapy is used for an overactive bladder, i.e. an uncontrollable, frequent need to urinate and/or urgency incontinence, with either a non-neurogenic or neurogenic cause. It is also used for patients with a so-called "lazy bladder" who are unable to (fully) empty their bladder (retention). This treatment has been used to treat the above-mentioned symptoms for more than 10 years now and has a long-term success rate of about 70% in patients with a positive Percutaneous Test Evaluation. In recent years, experience has also been acquired in the treatment of IC patients and encouraging results have been published.

Pudendal Nerve Stimulation (PNS) is performed in a similar way. In a study with SNS and PNS in 2007, most of the IC patients in the study showed a preference for PNS and this could be a potential path for the future.

Two phases: test stimulation and implantation: During the test stimulation procedure, a temporary electrode is implanted low down in the patient's back. This electrode is connected to an external stimulator. During the test period (3 to 7 days), the effect of the stimulation is recorded daily in a journal. The decision to go ahead and carry out the implant is based on the information recorded in the journal before and during the test stimulation and on the patient's experiences. A definitive implant is suggested if there is at least a 50% improvement in the patient's symptoms. When definitive implantation takes place, a permanent electrode is implanted in the lower back region and connected to a kind of pacemaker (battery-powered pulse generator) that supplies a continuous, very low/mild current to the relevant nerves.

**Miniaturio™-I:** An implantable electrical stimulation device for paraurethral neuromodulation is used for female patients suffering from pelvic pain and/or urinary frequency associated with interstitial cystitis. The Miniaturio™-I is a minimally invasive implantable device for patients who have failed to respond to conservative treatment. The Miniaturio Test System (MTS) allows physicians to evaluate patient compatibility before taking the final decision to undertake implantation. Once successful test stimulation has been achieved, the miniaturio device can be implanted. An electrostimulator is placed subcutaneously in the lower abdominal area, with a lead placed adjacent to the urethral sphincter and attached to the electrostimulator. A low electrical charge stimulates the muscle and nerve to perform their natural function. The programmer allows the physician to set individual patients' parameters remotely and change those parameters should the need arise. Each patient can turn the miniaturio on and off, using a personal safety magnet.

**Bion:** The Bion is a new battery-operated neuromodulation device about the size of a matchstick, implanted under the skin near the pelvis and close to the pudendal nerve for pudendal nerve stimulation. This device uses a small amount of electrical current to stimulate the nerve and is believed to override the abnormal signals that control the bladder function. Mainly used for urgency incontinence, it may have a role to play in some IC patients.

## **Surgery on the bladder and lower urinary tract**

In some IC patients, the problems with their bladder are so extreme that surgery remains the only option. This is not something to be undertaken lightly. IC is a complex disease and surgery may lead to other complications. It is therefore important for patients to understand exactly what is involved. One problem that may occasionally occur following surgery and removal of the urinary bladder is "phantom pain". Even when the old, diseased bladder has gone, pain may still continue to be felt. Recent studies have indicated that this may be caused by changes in the pain centres in the brain and spinal cord.

Surgery includes bladder augmentation, urinary diversion, and partial or complete cystectomy and should only be undertaken by experienced surgeons.

### **Bladder augmentation cystoplasty**

Also known as a clam cystoplasty, this is a procedure where the patient's own bladder is enlarged through the addition of a piece of the patient's intestine. This may be taken from the patient's small or large intestine or the stomach lining. This has not been an unmitigated success in the majority of IC patients since the pain, urgency and frequency may either remain or return, particularly in patients with a large capacity under anaesthesia. If pain plays an important role in the patient's symptoms, this will not necessarily be reduced after the augmentation procedure. Following augmentation surgery, patients may be unable to urinate independently and need to use a catheter in order to empty the bladder (intermittent self-catheterization). Regular self-catheterization may be a painful procedure for IC patients due to the hypersensitivity of the urethra and bladder base. There is also a greater risk of urinary tract

infections because intestinal mucosa is easily colonised by bacteria, while there are also likely to be changes in the way the bowel functions. Nevertheless, it does sometimes work or is chosen as a temporary measure before taking the final step to completely remove the bladder (cystectomy). Bladder augmentation is more effective in patients with a very small, shrunken bladder where pain plays a more minor role than frequency.

### **Bladder removal, urinary diversion and urostomy**

In cases where a patient has very severe intolerable pain or pain and a small bladder capacity and has failed to respond to any other treatment, urinary diversion may be necessary with or without complete cystectomy. This involves diverting the urine flow to a new opening in the abdomen known as a urinary stoma or urostomy. Urine normally passes from the kidneys to the bladder via two ureters. In a urinary diversion, these two ureters are connected to a segment of intestine. Sometimes the old bladder is left in place. Cystectomy is complete surgical removal of the urinary bladder. Some surgeons believe that in the case of IC patients it is preferable for every piece of the bladder and urethra to be removed in a cystectomy. If the urethra is left behind – and some surgeons do prefer to leave the urethra in place – some patients may continue to have the same IC pain, even though the bladder itself has been removed. This will necessitate a further operation to remove the painful urethra. Results vary greatly from patient to patient and there is no guarantee of complete success.

#### **Ileal conduit urostomy**

This is a method where the urine is diverted to an external disposable bag attached to the outside of the body, for example the Bricker technique. A piece of tube-shaped intestine is removed from the intestines. The ureters that normally carry urine to the bladder are now attached to this at one end while the other end is formed into a “stoma” opening on the surface of the abdomen. A disposal, external bag can be attached to the stoma to collect the urine.

#### **Continent diversion urostomy**

A continent diversion, such as the Kock or Indiana pouch, consists of an internal reservoir or pouch (made from a section of intestine) serving as a new bladder where urine can be stored and drained at specific intervals through a stoma opening on the surface of the abdomen using a catheter. Although the continent diversion with its internal pouch and catheterizable stoma on the outside may be more attractive to the patient from a cosmetic point of view, it may lead to pouch complications with recurrence of pain and inflammation, nipple valve failure and leakage in IC patients. A continent stoma is also considered to be less suitable for patients who also have kidney dysfunction. Any patient with a continent stoma must be physically able to undertake the regular catheterization of the stoma.

#### **Neobladder**

An alternative method is a bladder substitute continent diversion, with a new bladder (neobladder) formed from segments of intestine at the site of the old bladder and using the old urethra to empty the bladder. This will have to be done with a catheter.

Urostomy associations will be able to provide patients with detailed information concerning the different surgical options and stoma care. Further information is also available on the NIDDK website: <http://kidney.niddk.nih.gov/kidiseases/pubs/urostomy/index.htm>.

#### **Denervation not recommended**

Peripheral/sympathetic/parasympathetic denervation is **not recommended** for IC.

## **Alternative or complementary treatment**

There are many complementary therapies and self-help possibilities that may alleviate symptoms, relax the patient and help to achieve a better quality of life. Because of the limited effectiveness of traditional treatment in many IC patients, these patients tend to seek other non-medical forms of therapy from which some patients experience benefit and relief. One of the possible reasons may be because this type of therapy involves relaxed interaction between the practitioner and patient, while by contrast conventional medicine nowadays often resembles a fast-moving production line with little time for communication with patients. This kind of therapy can often help a patient to achieve relaxation of body and mind, with progressive relaxation of tense pelvic floor muscles, which may help in reducing pain. Any therapy where the patient can relax on a couch and have the time to discuss their symptoms and the impact of these symptoms on their life is likely to have a stress-reducing effect.

Pelvic floor dysfunction is an important but under-recognised factor in both IC and CP.

Complementary approaches include biofeedback which helps patients gain awareness of and greater control over muscles that cause pain, hypnotherapy, trigger-point therapy, myofascial pain therapy, pelvic floor re-education, acupuncture and herbal supplements.

Relaxation of any kind can help in reducing stress, including yoga, Tai Chi, meditation, breathing exercises (slow diaphragmatic breathing), regular exercise, walking (even short distances), swimming, warm baths, hydrotherapy, guided imagery.

However, in order to achieve optimum results from either physical therapy or relaxation therapy, every endeavour should be made to bring the symptoms and particularly the pain aspect under control through traditional medical therapy.

### **Bladder training**

Bladder training or re-education (timed voiding, gradually increasing the voiding interval) is likely to work better in selected patients where urgency/frequency predominates. Pain limits the possibility of retraining the bladder until the pain has been brought under control. Once pain control has been achieved, the bladder can be re-educated by very slowly increasing the period of time between voids, thereby reducing frequency and increasing bladder capacity. But if the patient has a strong urgency sensation, this may be difficult and results short-lasting. In any case, it takes some months before results are seen. Bladder training should be done under medical supervision. There is little point in trying bladder training in patients with a shrunken, contracted, fibrotic bladder and it is not recommended for patients with pain.

### **Voiding diaries**

Voiding diaries or charts can provide both the patient and the doctor with an overview of the number of voids per 24 hours and if required also the volume voided. A recently designed voiding chart also includes the bladder sensation assessed by the patient on a scale of 0-5. The results of a voiding chart are likely to vary if it is a patient who experiences the strongest symptoms in the form of flares. Where frequency is concerned, a patient's drinking habits play an important role since a patient drinking 2 or more litres a day is going to have a much higher frequency than a patient drinking less than half a litre a day. The level of perspiration is also an important factor in urinary frequency and this will partly depend on the climate.

Voiding diaries (with number of voids only per day and night) can also be used to monitor the success of treatment from time to time.

## Chapter 6

### IC and associated disorders

Many patients with IC also have one or more other disorders or symptoms in addition to their bladder problem, including chronic pain syndromes, chronic fatigue, autoimmune diseases, gastrointestinal disorders, vulvodynia and chronic non-bacterial prostatitis. This has been shown by studies and patient surveys.

Since IC patients are generally treated by a urologist, some of these disorders may go undiagnosed and untreated. This underlines the need for a multi-disciplinary approach.

#### Associated disorders

A number of studies have indicated that some diseases appear to occur more frequently in IC patients than in the general population. These are known as associated disorders and include:

- allergy (and sometimes multiple allergies),
- fibromyalgia,
- gastrointestinal disorders
- migraine
- rheumatoid arthritis,
- systemic lupus erythematosus
- Sjögren's syndrome
- vulvodynia.

Associated disorders fall into three main categories: allergies, pain syndromes and systemic autoimmune diseases.

The possible relationship between IC and associated disorders and other disorders that commonly co-exist with IC, and why these should occur side by side in the same patient, is still unknown. More research into associated or related disorders may go some way to shedding light on the cause of IC. Since diagnosed IC patients are generally treated by either a urologist or urogynaecologist, some of these associated disorders may go undiagnosed and untreated. This underlines the need for a multi-disciplinary approach. Both the doctors treating IC patients and the patients themselves should be on the alert for other symptoms that may indicate another disorder since in some cases it might change the approach to treatment of the bladder disorder. See table 3.

#### Autoimmune disease and IC

One of the many theories concerning IC is that it might itself be an autoimmune disease. Rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome and thyroid disorders are examples of autoimmune diseases. In autoimmune diseases, the immune system attacks the patient's own body. Some autoimmune diseases may be "organ specific", i.e. they attack one specific organ in the body (for example thyroid disorders). Others may be "generalized": this means that they attack many different organs and systems throughout the body.

Patients with a diagnosed autoimmune disease and IC should be sure to inform their specialist of this fact, particularly if the autoimmune disease is diagnosed after the IC has been

diagnosed, since this might mean using different types of medication to treat the IC (see below systemic treatment).

### **Many sick patients may still be undiagnosed and untreated**

One problem with IC patients with symptoms indicative of autoimmune disease is that laboratory tests may reveal few or no abnormalities. The patients often do not fulfil all the criteria of any single specific disease. The result is that many sick patients may still be going undiagnosed and untreated. If autoimmune disease is suspected, patients should be referred to an internist, immunologist or rheumatologist. It may also be necessary to see a gastroenterologist or neurologist.

### **Systemic treatment**

Some IC patients who display symptoms of autoimmune diseases in addition to IC may benefit from "systemic" treatment (i.e. treatment of the whole body with one medication), for example hydroxychloroquine and sulphasalazine (commonly used to treat inflammatory bowel disease and rheumatic diseases) or corticosteroids such as prednisolone, dexamethasone or hydrocortisone. Some patients have reported a substantial improvement in their IC symptoms through this treatment. However, here too treatment is highly individual and every patient is different.

### **Multiple pain syndromes**

Attention has recently been focused on the fact that some IC patients appear to suffer from not simply multiple disorders but also multiple pain syndromes, affecting different parts of the body and not only the pelvic organs. Some patients suffer from a variety of combinations of pain conditions, for example: IC, chronic prostatitis (CP), irritable bowel syndrome, vulvodynia (also known as vulvar pain syndrome), fibromyalgia syndrome, migraine, temporomandibular disorder, and other painful disorders. It is still a mystery why this affects some IC patients and not others. The NIH/NIDDK **Multidisciplinary Approach to the Study of Pelvic Pain (MAPP)** is currently studying these pain syndromes together with IC and CP to see what they have in common and what the risk factors are and will endeavour to characterize patients into types (phenotyping) for treatment purposes. This is a 5-year study that started in 2008.

### **Many pain theories**

Pain researchers' theories concerning the occurrence of multiple pain syndromes until now include central nervous system involvement, damage or inflammation in one organ of the body affecting another organ or system either due to central nervous system processing or to so-called cross-sensitization or cross-talk with inflammation in one organ causing inflammation in another, abnormalities of autonomic function and most recently limbic dysfunction. Bearing in mind the variations in pain felt by women during their menstrual cycle, it is also theorized that there may be hormonal involvement in pain perception in these women.

## **A brief look at a few of the associated disorders**

**Allergy:** Many IC patients suffer from allergy or multiple allergies, including food, chemicals and medicines. Allergies can affect the skin, airways and sometimes organs. Examples of allergy include asthma, rhinitis, urticaria (nettle-rash), eczema and anaphylaxis. In some cases patients receiving antihistamines for their allergy find that this treatment also has a beneficial effect on their bladder. Patients with multiple medicine allergies or intolerances often respond better to intravesical treatment for their IC where less of the drug is absorbed into the system.

**Chronic non-bacterial prostatitis:** Chronic non-bacterial prostatitis/chronic pelvic pain syndrome is the most common form of prostatitis. The older term prostatodynia is also sometimes used to describe this painful prostate condition. Unlike acute or chronic bacterial prostatitis, it is not caused by any identifiable infection and therefore does not respond to treatment with antibiotics. It may be inflammatory or non-inflammatory. While its cause is unknown, one theory that has been suggested is that it could be of autoimmune origin.

**Fatigue:** many IC patients have a problem with fatigue. It may be tiredness resulting from lack of sleep due to nightly excursions to the bathroom and to the inability to relax due to constant pain. However, intense fatigue with memory and concentration problems, known by patients as 'brain fog', or extreme fatigue after very little physical exertion may indicate an autoimmune disease. If this seems to be a possibility, it may be worthwhile investigating whether there is an autoimmune disease present in addition to the IC. Fatigue on waking in the morning that improves as the day goes on may be an indication of depression. The term Chronic Fatigue Syndrome (sometimes also called myalgic encephalomyelitis or ME) is only used when no known disease has been identified that could be causing the chronic fatigue.

**Fibromyalgia syndrome (FMS)** is a chronic, debilitating multisystem pain syndrome of unknown cause with widespread musculoskeletal pain and tenderness. The term fibromyalgia means pain in the soft fibrous tissues of the body: muscles, ligaments and tendons and in multiple tender points, but inflammation is not believed to be a characteristic of FMS. Current theory concerning the cause focuses on the theory of central sensitization. Fibromyalgia may be accompanied by a range of symptoms including: morning stiffness, extreme fatigue, sleep disturbances, irritable bowel syndrome, facial pain or pain around the temporomandibular joint (TMJ), pelvic pain and bladder disorders. Patients with FMS are also prone to tingling, numbness, dizziness and cognitive or memory disorders. FMS can vary in severity from person to person: some patients may have a mild form of discomfort, but some patients may suffer from a very severe and disabling form of FMS with extreme fatigue and pain. Some researchers have suggested that the term FMS may in fact include several sub-entities. Like IC, the course of this condition can be variable with exacerbations and remissions.

**Rheumatoid arthritis (RA)** is a chronic systemic, autoimmune connective tissue disease that mainly affects the synovial membranes of joints and is characterised by pain, swelling and stiffness of joints, usually symmetrically. As the disease progresses, the ligaments are damaged, there is erosion of the bone, resulting in deformity of the joints. This deformity of the joints is an important difference with other rheumatic diseases such as Sjögren's syndrome.

**Gastrointestinal disorders** are frequently seen in association with IC.

- **Irritable bowel syndrome (IBS)**, a functional bowel disorder, is the most common disorder in IC patients, with symptoms including abdominal pain or cramp, alternating diarrhoea and constipation and a bloated feeling due to gas formation.
- **Inflammatory bowel disease (IBD)**, a group of disorders comprising Crohn's disease and ulcerative colitis, with weight loss, blood in the stools and diarrhoea at night, is also found more commonly in IC patients than in the general population. Commonly suspected to be of autoimmune origin.

**Sensitive skin:** Many IC patients have a problem with dry, itchy, sensitive skin. It is advisable to keep the skin well moisturized with cream or lotion for sensitive skin to reduce the dryness and this may also reduce some of the itchiness. Keep away from chemicals such as household cleaning products (wear protective gloves) and perfume. Use cosmetics, soap and shampoo for hypersensitive skin. Do not use (perfumed) soap or any other products around the

vulvar/genital area. Take care with contraceptive devices containing chemicals such as condoms and spermicidal creams. If possible, wash your clothes with products specially made for sensitive skin that do not contain perfume. Wear cotton underwear and loose clothes. Avoid touching garden plants that may cause skin reactions. Take care in the sun if you find that your skin is sensitive to sunshine.

**Sjögren's syndrome** is a chronic, autoimmune disease of unknown cause in which lachrymal (tear) and salivary glands malfunction. Its hallmark symptoms are sore, irritated eyes and dry mouth with a need to drink when eating because dry food otherwise sticks to the mouth and cannot be chewed or swallowed properly (so-called "cracker sign"). It is a systemic disease and may therefore affect many organs and systems of the body. Nine out of ten patients are women. Although it can affect any age group, the average age of onset is the late 40s. This disease is traditionally classified into two types: primary Sjögren's syndrome where the disease occurs alone and secondary Sjögren's syndrome when it occurs in association with another disease such as SLE, systemic sclerosis, rheumatoid arthritis and polymyositis /dermatomyositis. While some patients may experience only mild symptoms, in others their quality of life is seriously impaired by debilitating symptoms and extreme fatigue. It can often take many years for a patient to get a diagnosis, particularly in patients where the typical combination of irritated eyes and dry mouth is not recognized in patients in whom no autoantibodies can be seen and ESR is normal. In recent years, clinical studies, observation and surveys have led to an increased awareness that IC and Sjögren's syndrome can occur in association with each other.

**Systemic Lupus Erythematosus (SLE)** is a chronic, inflammatory, autoimmune connective tissue disease, involving many organs, with unpredictable flares and remissions. It may involve joints, skin, kidneys, lungs, heart, vascular system, gastrointestinal tract, central or peripheral nervous system and the bladder. A painful bladder disorder in SLE patients was known in the past as 'Lupus Cystitis', but is now generally referred to as IC. The symptoms and severity of SLE can greatly vary from patient to patient and may also undergo change in an individual patient over time. As in the case of IC, there is a high predominance of women patients.

**Thyroid disorders:** The thyroid gland is situated at the front of the neck below the skin and muscle layers. It has the form of a butterfly with the two wings represented by the right and left lobes that wrap around the trachea. The function of the thyroid gland is to make thyroid hormone which regulates the body's metabolism and is essential for mental and physical development. The thyroid gland is prone to two extremes of disorders:

- Hyperthyroidism (it makes too much hormone)
- Hypothyroidism (it makes too little hormone).

Chronic thyroiditis is an inflammatory condition of the thyroid caused by an autoimmune disorder in which lymphocytes invade the tissues of the gland. The most common type of thyroiditis is Hashimoto's thyroiditis. It includes swelling of the thyroid gland and partial or complete failure to secrete thyroid hormones. Women are affected more than men.

**Vulvodynia (or vulvar pain syndrome)** is a distressing, painful condition, difficult to diagnose and difficult to treat. It is a broad collective term used to describe any chronic pain condition of the vulvar area and embraces a number of different types of vulvar disorder causing chronic or intermittent pain, burning, rawness and pain with intercourse. There are two main types of vulvar pain:

- **Localised vulvodynia (vestibulodynia, formerly known as vulvar vestibulitis)** is pain or burning sensation caused by something touching the vestibule (entrance to the vagina). Pain is caused by sexual intercourse, insertion of tampons, riding a bicycle, gynaecological examination, tight clothes or any situation where the vestibule is touched. There is usually no pain if the area is not touched. Vestibulodynia is diagnosed by touching the vestibule with a Q-tip. Even light pressure such as this can cause pain.
- **Generalized (dysesthetic) vulvodynia** is pain, burning, stinging or rawness on or around the vulva, labia, vestibule, clitoris or perineum most of the time, whatever they are doing. It is not dependent upon touch or pressure but this can nevertheless exacerbate the symptoms. Urination may cause pain and burning. Sexual activity is sometimes so painful as to be impossible, while at other times there may be little or no pain. Generalized vulvodynia is diagnosed when there is a history of constant pain with no visible cause or other identifiable disorder such as infection.

For further information on vulvodynia, see: [www.nva.org](http://www.nva.org) (National Vulvodynia Association)

**For further detailed information on IC and associated disorders, visit the IPBF website:**

[http://www.painful-bladder.org/pbs\\_ic\\_ass\\_dis.html](http://www.painful-bladder.org/pbs_ic_ass_dis.html) :

“Interstitial cystitis and associated disorders” by Joop P. van de Merwe MD

“Interstitial cystitis and gastrointestinal disorders” by Joop P. van de Merwe MD

as well as detailed information on Sjögren’s syndrome by the same author.

**Table 3** comprises a list of questions that may be useful as a first screening to assess the possibility of a patient with IC having associated disorders.

### **Table 3.**

#### **Questions to assess the possibility of an IC patient having associated disorders as a useful first screening for the presence of these diseases**

##### **1. Allergy**

1.1 Have you ever had shortness of breath, shock, angioedema, pruritis or urticaria after exposure to or ingestion of a particular drug, food, pollen, or contact with an animal?

##### **2. Asthma**

2.1 Do you have recurrent episodes of dyspnoea, coughing and wheezing?

2.2 Are these symptoms seasonal, or do they occur shortly after exposure to antigens such as animal dander, feathers, dust mites or mould?

##### **3. Crohn's disease and ulcerative colitis**

3.1 Do you often have abdominal cramp, particularly after meals?

3.2 Have you lost weight? (what was your normal weight and what did you weigh at that time?)

3.3 Do you often have diarrhoea or loose stools?

3.4 Do you often see red blood with stools?

3.5 Have you in the past had unexplained anaemia?

3.6 Do you have/have you had fistulas?

##### **4. Fibromyalgia**

4.1 Do you have diffuse musculoskeletal achiness, stiffness or exaggerated tenderness?

4.2 Do you have visible swelling of the joints? (suggests another disease)

4.3 Do you have paraesthesia, non-restorative sleep and are you easily fatigued?

##### **5. Irritable bowel syndrome**

5.1 Do you often have abdominal pain or discomfort in association with defecation?

5.2 Do you have abdominal pain in association with a change in bowel habit?

5.3 Do you have disordered defecation such as abnormal stool frequency, abnormal stool form, defecation straining or urgency, a feeling of incomplete bowel emptying, mucus with stools or a bloated or swollen abdomen?

##### **6. Rheumatoid arthritis**

6.1 Do you have chronic symmetrical swelling and pain in multiple joints?

6.2 Do you have generalized morning stiffness lasting more than 1 hour?

##### **7. Sjögren's syndrome**

7.1 Have you had daily, persistent, troublesome dry eyes for more than 3 months?

7.2 Do you have a recurrent sensation of sand or gravel in the eyes?

7.3 Do you use tear substitutes more than 3 times a day?

7.4 Have you had a daily feeling of dry mouth for more than 3 months?

7.5 Have you had recurrently or persistently swollen salivary glands as an adult?

7.6 Do you frequently drink liquids to aid in swallowing dry food?

##### **8. Systemic lupus erythematosus**

8.1 Does the sun cause redness on areas of your skin exposed to a normal amount of sunlight?

8.2 Do you often have mouth ulcers or sores?

8.3 Do you often have painful swelling of the joints in your hands and/or feet?

8.4 Have you ever had pericarditis, pleurisy or nephritis?

*(Source: Joop P. van de Merwe MD, PhD)*

## References and further reading:

### **The Interstitial Cystitis Survival Guide**

Your Guide to the latest treatment options and coping strategies  
Robert M. Moldwin MD  
New Harbinger Publications, Inc  
ISBN 1-57224-210-8

### **Patient to Patient: Managing Interstitial Cystitis & Overlapping Conditions**

Gaye Grissom Sandler, Andrew B. Sandler  
Bon Ange LLC, 2000  
ISBN 0-9705590-0-3

### **Intersticiální Cystida** (in Czech)

By Tomáš Hanuš MD & Libor Zámečník MD  
Nucleus HK  
ISBN 80-86225-30-5

### **Interstitial Cystitis** (in Japanese)

By Tomohiro Ueda MD  
ISBN4-87151-311-4

### **Understanding Cystitis** (in Japanese)

By Dr Hikaru Tomoe MD  
ISBN 4-8376-1189-3

### **Diagnosis & Treatment of Interstitial Cystitis in Women** (in Russian)

By OB Loran MD, AW Zaitcev MD, WS Lipsky MD  
ISBN: 5-7633-0893-X

### **Penn Clinical Manual of Urology**

Hanno PM, Malkowicz SB, Wein AJ.  
Chapter 7 Painful Bladder Syndrome (Interstitial Cystitis) by Philip Hanno.p. 217-234.  
ISBN -13: 978-1-4160-3848-1

### **Campbell-Walsh Urology**, 9<sup>th</sup> Edition

Section IV, chapter 10: Interstitial Cystitis and Related Disorders by Philip M. Hanno MD. Saunders, December 2006

### **Interstitial Cystitis**,

Edited by Grannum R. Sant MD, 1997,  
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