

**INTERNATIONAL PAINFUL BLADDER FOUNDATION**

# Interstitial Cystitis

Painful Bladder Syndrome, Bladder Pain Syndrome,  
Hypersensitive Bladder Syndrome  
Chronic Pelvic Pain

## Diagnosis & Treatment

An Overview

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## CHAPTER 1 - WHAT IS INTERSTITIAL CYSTITIS (IC)?

Interstitial cystitis (IC), also known as painful bladder syndrome, bladder pain syndrome, hypersensitive bladder syndrome and chronic pelvic pain, is a distressing, chronic 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 a urinary tract infection, 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 or discomfort related to the urinary bladder,  
a frequent need to urinate (*frequency*) and/or  
an urgent need to urinate (*urgency*)**

- *Pain, pressure, discomfort or unpleasant sensation that may worsen as the bladder fills; urinating often alleviates the pain and may give a temporary sense of relief;*
- *Suprapubic pain or discomfort, pelvic pain (lower abdominal pain), sometimes extending to the lower part of the back, 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;*
- *Pain may worsen with specific foods or drinks;*
- *A frequent need to urinate (frequency), including at night (nighttime frequency or nocturia);*
- *An often urgent or compelling need to urinate (urgency).*

The pain may be experienced as discomfort or tenderness or irritation or 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. In many patients, the pain is relieved temporarily by urination, while other patients may also feel strong pain following urination. The pain or discomfort may be constant or intermittent. It may also be felt throughout the pelvic floor, including the lower bowel system and rectum. 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. However, this will partly depend on how much a patient drinks, on the climate where the patient lives and on medication the patient may be taking which could have a diuretic effect. In IC, frequency may sometimes be very severe with some patients needing to urinate up to 60 times a day, but frequency is generally seen as being 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 with a scarred, stiff wall (*fibrosis*) 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 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(s) of the urgency sensation in IC patients are still not fully understood.

### Currently two types of IC

At the present time, there are at least two types of IC identifiable: the classic inflammatory type with **Hunner's ulcer/lesion** and the **nonulcer type** which researchers now believe to be two separate entities. Investigations will result in different findings with these two types and the treatment is different. Further information is given under Chapter 4 Diagnosis and Chapter 5 Treatment. Current research into subtyping (*phenotyping*) may lead to the identification of more types.

### Who gets IC?

#### Men, women and children, of all ages, worldwide!

As diagnosed at the present time, IC is mainly found in **women** ( $\pm$  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 in fact have IC than hitherto thought and the percentage of male patients with IC may therefore be higher. A diagnosis of IC should be considered in men who have pain perceived to be related to the bladder. However, both CP/CPPS and IC can occur together.

IC is also found in **children**. However, since in the past the old NIDDK research criteria excluded children from studies, many doctors consequently thought that IC did not occur in children. There has therefore been relatively little research or scientific literature on IC in children in the past two decades and many doctors are still hesitant to give a diagnosis of IC in a child. It can, nevertheless, occur in children of any age. Many adults with IC report that they had urinary symptoms in childhood or adolescence.

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 have been used for diagnosis, what diagnostic methods have been used to reach the diagnosis and how big the population is in the study. Although nobody can say with any degree of certainty at the present time how many people may have IC, a figure of 300 per 100,000 seems to be a possibility, but it could be much higher.

Current prevalence figures tend to bundle all patients with a painful bladder together, without making any distinction between subtypes. At present the only distinction usually made is between the so-called **Classic inflammatory IC with Hunner's ulcers or lesions** and the **Non-ulcer type without lesions** in the bladder. A relatively small percentage of patients (estimates vary from 10-50%) develop Hunner's ulcers or lesions (note: the old term was Hunner's ulcer but this was a misnomer since these are not true ulcers. They are today often described as lesions). However, while this Hunner type IC used to be considered rare, it is now believed that it may be more common than originally thought. Many researchers believe that the classic type with lesions and the non-lesion form may be two different diseases. Future research may shed light on this. Further information on this is provided in Chapter 4 on Diagnosis.

### **How does IC 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 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. Some patients recall having bladder problems in childhood or adolescence, needing to go to the toilet more frequently than others, long before they developed pain.

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 (not just dipsticks) 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 or even remain stable, while others (with Hunner's ulcer/lesion) 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 shorter space of time.

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, scarred bladder. At the present time, 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. Women may also find that their IC symptoms temporarily increase while going through the menopause. Any kind of stress, physical or psychological, rushing around trying to do too much, can trigger a flare. Many IC patients also find that a flare can be triggered by certain foods and drinks and even certain medications irritating the bladder.

### **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, neurological (C-fiber upregulation, central pain sensitisation), autoimmunity, allergy/hypersensitivity, occult infection and many more hypotheses. Some researchers have explored the possibility of heredity or genetics playing a role since IC may occur in more than one person in the same family (mother and daughter or two sisters). Another 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 (pelvic) 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 non-bladder 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) in the United States.

In summary, there are numerous different theories and much research has been carried out, but no real answers have so far been found. No-one yet knows what causes IC. It is still an enigma!

### **IC is not psychosomatic**

Although many patients may experience a worsening of their IC symptoms as a result of physical or psychological 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, tension, anxiety and depression.

## CHAPTER 2 - IMPACT ON LIFE

The IC patient not only has to cope with the bladder disease itself and all its symptoms, but also the consequences of this disease on his/her life in the widest sense. 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.

### **Where am I going to find the next toilet?**

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 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. Indeed, there are sadly many patients who tell us that they almost never go out. And let us not forget the patients in less developed countries where there may be no public toilet facilities at all.

### **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. This situation is far worse if the patient has no diagnosis and consequently no access to social or medical assistance.

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

In addition to this, the pain and the 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 or disruption 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.

See Chapter 7 on Fatigue in IC patients.

### **Emotional impact, depression and frustration**

From a patient perspective, the very fact that you have a disease for which there is no known cure makes you very depressed and frustrated. You may feel anger that it took so long to diagnose, that so many doctors told you it was all in the mind and made you feel you were going crazy... The tiredness makes you listless and irritable. You feel helpless and hopeless. The fact that the disease you have affects the bladder and means that you keep looking for toilets makes you constantly embarrassed. Bladder problems are still taboo in today's world and you feel stigmatized and isolated



from your friends. You long to be able to turn the clock back to when you were normal, and find it difficult to look ahead or make plans for the future.

### **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 to 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. Anatomically, in women the bladder and vagina are close to each other and this can lead to pain or irritation during penetrative intercourse. In the case of men, ejaculation may 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 very concerned and feel deeply guilty. Communication between the partners is essential. It is important for patients to be able to discuss this problem with their partner and for them to try to find solutions together, if necessary with the help of a sex therapist or relationship counselling with sex education. Patients themselves may find it difficult or impossible to raise this intimate and embarrassing subject with their doctor. It is therefore important for the care provider to raise this issue. Optimal pain treatment can also help the problem of painful sex in female patients. (However, it should be noted that use of painkillers such as NSAIDs may lead to erectile dysfunction in men!).

Tips for sexual intercourse include: a warm bath to relax the pelvic muscles, urination before and after sex, thorough cleanliness by both partners to prevent infection, use of non-irritating lubricants, pre-medication such as painkillers 20 minutes before sex, engagement in foreplay to limit thrusting time, different positions to reduce pain and symptoms, and thinking of creative ways of sex without vaginal penetration (outercourse) so as to maintain some level of sexual intimacy.

### **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 his 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 Guy 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 including IC.

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, a milestone was reached when Chapter 19 of Campbell's Urology was entirely devoted to interstitial cystitis. Author Anthony Walsh described IC as a "disease of extremes: extremely severe symptoms; extremes of underdiagnosis; etiologic theories varying from the abstruse to the fashionable; treatment ranging from the alpha of vitamin prescription to the omega of radical bladder substitution surgery; and sadly often, extreme confusion in medical thinking," much of which is still valid today.

Walsh felt that the term Hunner's ulcer should be abandoned because "it is seriously misleading" and notes that "Hunner's ulcer has led many less experienced physicians to expect to see an ulcer at cystoscopy, and when no ulcer could be found, they erroneously failed to diagnose many genuine cases".

Walsh appears to be the first to describe punctuate red dots as glomerulations, but questions the specificity of glomerulations since "glomerulation is not absolutely pathognomonic since it has been seen after overdistension in patients with dyskenesia". However, despite Walsh's possible doubts, glomerulations continued to be considered a hallmark of IC until the mid-1990s when their diagnostic value came into question once again.

Walsh famously described IC as "an irritable bladder in an irritable patient".

Also 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. Like Walsh, they also 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 which are all different but still 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:

- **U**rinary
- **P**sychosocial
- **O**rgan Specific
- **I**nfection
- **N**eurologic/Systemic
- **T**enderness

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

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.

In 2011, the American Urological Society (AUA) decided to adopt the name IC/BPS in its guideline *"Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome"*. In the field of diagnosis, it placed the emphasis on exclusion of other diseases or disorders and the symptoms of the patient. The definition it adopted is as follows:

*"An unpleasant sensation, (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes."*

The full guideline can be read online at:

[http://www.painful-bladder.org/pdf/2011\\_AUA\\_Washington.pdf](http://www.painful-bladder.org/pdf/2011_AUA_Washington.pdf)

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 (or diseases) it is that we are trying to communicate!

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

While there is currently far greater awareness of interstitial cystitis around the world today and many more patients are now receiving a diagnosis, 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 wide spectrum of 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 an infection and repeatedly prescribe antibiotics, even when urine tests for infection are negative. The fact that many patients may have extensive pelvic pain means that 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.

If IC is suspected, it is advisable to look for a specialist with expertise and interest in this specific field.

### 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 pressure or other unpleasant sensation, accompanied by other urological symptoms such as urgency and/or 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.*

*\*\* Nevertheless, it should be taken 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
- Testing to confirm the bladder as the source of the symptoms

Diagnosis of IC is essentially based on symptoms and exclusion of other painful bladder conditions that resemble IC but have a different identifiable cause. However, it may be supported by cystoscopic and biopsy findings, including inflammation, Hunner's ulcer/lesion, glomerulations or general mild oedema. However, neither inflammation nor glomerulations nor lesions are found in all patients and the bladders of many nonulcer patients with severe symptoms may appear completely normal.

*(Videos of cystoscopies can be seen on the ESSIC website at: <http://www.essic.eu/videomenu.html>.)*

It is precisely these differences that lead many experts today to question whether this is in fact a single disease or a number of subtypes or even different bladder disorders with the same or similar symptoms. At the present time, it is the general view that Classic Hunner type IC and non-lesion IC are two separate entities. But we can expect to see more subtyping in the future.

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

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. Street ketamine abuse has also been reported in recent years as a cause of symptoms closely resembling IC.



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

#### **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.

#### **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, as well as by the medical facilities available. In some parts of the world there is a trend towards basing initial diagnosis on symptoms and exclusions, while other countries routinely perform more extensive investigations such as cystoscopy with/without hydrodistension, and with/without biopsy.

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

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

#### **Diagnostic procedures may include**

- Medical history
- Physical examination
- Laboratory tests including dipstick urinalysis, routine and special cultures, urine cytology
- Serum PSA in male patients over the age of 40 years
- Flowmetry and post-void residual urine volume measure by ultrasound scanning
- Cystoscopy with biopsy

**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, urological diseases or sexually transmitted infections, any autoimmune diseases, any other chronic pain conditions or other chronic diseases (including e.g. irritable bowel syndrome, vulvodynia), any previous pelvic radiation treatment, chemotherapy, location of the pain and whether it is related to bladder filling/emptying, description of the pain and whether there is more than one pain generator.

Does the patient have pain problems with sexual intercourse (dyspareunia). Does the patient experience worsening of the symptoms with specific foods or drinks? Is there increased pain with bladder filling. Does the pain increase around menstruation? Does the patient have to urinate during the night?

A history of previous medication or other drug history is important since certain drugs have been shown to cause bladder symptoms similar to IC (e.g. tiaprofenic acid, cyclophosphamide and more recently street ketamine abuse resulting in ketamine cystitis).

**Physical examination:** A general physical examination is carried out, including pain mapping. Women will have a vaginal examination and men a digital rectal examination. Evaluation of the pelvic floor is recommended.

**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. Urine cytology tests are carried out to check for the presence of malignant cells and to exclude bladder cancer.

### **Voiding Charts and Questionnaires for 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 also be asked to record the pain they have felt in the last 24 hours on a **Visual Analogue Scale**. The different questionnaires or scores have the purpose of evaluating the level and nature of the symptoms and their impact on the patient's quality of life. These questionnaires are **not** recommended for diagnostic purposes, but are good for documenting symptoms/quality of life and the patient's progress.

**Urodynamics:** A urodynamic investigation is sometimes carried out when considered necessary by the urologist, but is not considered essential for the diagnosis of IC. Whether this is done or not varies from country to country. 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:** This procedure 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 felt 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 main methods of cystoscopy:

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

\* hydrodistension = stretching the bladder by slowly filling with water.

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 or other disorders, or if the patient has failed to respond to conservative measures or first line treatment.

- **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 or red patches which might be **Hunner's ulcer/lesion**. This is particularly important since Hunner's lesion is a type which responds well to a specific form of treatment. 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**, largely 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 filled less in **order to inspect the bladder wall**. Hydrodistension's main role lies in the information it produces for research purposes and for the diagnosis of Hunner's ulcer/lesion. Hydrodistension will produce glomerulations in the bladder wall in some patients. In some countries it is currently questioned whether hydrodistension is relevant as a routine clinical investigation, while in other countries it is considered mandatory. Hydrodistension is sometimes used in selected patients as a form of treatment and can provide temporary relief.

### **Findings from cystoscopic investigations may include:**

#### **Glomerulations – but no longer considered diagnostic**

Glomerulations are pinpoint petechial haemorrhages, only seen after distension of the bladder. They have sometimes been described as a “cascade” or “waterfall”, also as a “weeping bladder”.

Whereas glomerulations – first mentioned by Walsh in Campbell's Urology in 1978 - were once considered a hallmark of IC, they have since then also been found in patients with normal bladders, in patients who have had for example radiation therapy, bladder cancer, exposure to chemotherapy or toxic drugs, while some patients with all the symptoms of IC have no sign of glomerulations in their bladder at all. Glomerulations are therefore no longer considered diagnostic of IC.

Since it is currently unknown what causes glomerulations to occur and why they occur in some people and not others, glomerulations can only support the diagnosis of IC in combination with typical IC symptoms or other findings, but 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. Consequently, at the present time the true role of glomerulations is unknown.

#### **Hunner's ulcer/lesion**

Hunner's ulcer or lesion is a subtype also described as **Classic IC**. The historic term “ulcer” is misleading and confusing since it is not a true ulcer, but an inflammatory lesion, also known sometimes as a “patch”. Bladder distension will cause any scar-like lesions to crack and bleed. While this Classic inflammatory type of IC with lesions is believed to be less common than the non-lesion type, if present it will best be identifiable during cystoscopy with hydrodistension.

It is possible that these lesions are being under-diagnosed. Every effort is currently being made to ensure that urologists and urogynaecologists can identify Hunner's lesions in the bladder when they see them.

Professor Magnus Fall from Sweden 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 as soon as possible in patients with IC symptoms as this **Classic Hunner type** of IC responds well to specific types of treatment.

### **Other investigations:**

#### **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.

However, completely normal biopsy results may be found in some patients who do not have Hunner's lesion.

The biopsy is important to exclude the possibility of other causes of the symptoms (such as bladder cancer, eosinophilic cystitis and tuberculous cystitis) and all lesions or patches should therefore be biopsied. Biopsy is more likely to be routinely 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 and will then only be performed if the symptoms fail to respond to first line conservative treatment.

#### **Potassium sensitivity test:**

The potassium sensitivity test which was studied for some time as a potential way of diagnosing IC is now no longer considered to be reliable for diagnostic purposes and is furthermore a painful experience for the IC patient. A milder, modified form of this potassium test was recently successfully studied as a possible way of selecting patients who may respond well to intravesical 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.

#### **Anaesthetic challenge test:**

Instillation of alkalized lidocaine into the bladder – also used as a rescue therapy with or without heparin to calm extreme pain in the bladder - is increasingly being 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.

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.

**Reassessment**

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

**Important: Negative test results do not necessarily mean that a patient does not have IC**

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 characteristic symptoms of interstitial cystitis. The most important part of the investigations is to exclude all other identifiable causes of the symptoms (so-called confusable diseases).

Exclusion of confusable disorders + IC symptoms = IC.

## 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, as yet no possibility has 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, behavioural changes and stress reduction, one or more oral drugs, topical drug treatment, bladder instillations or intramural injections, bladder distension, laser therapy or fulguration (specifically for Hunner's lesions), neuromodulation/electrotherapy, surgery, different forms of physical therapy and mind-body therapy, myofascial therapy, trigger point therapy and pelvic floor relaxation, exercise, sex therapy and/or relationship counselling to help sexual problems.

Treatment of IC should focus on a) the pain and b) urological symptoms such as urgency and frequency.

Pain management should play an important role. If the pain is very severe and fails to respond to standard treatment, a pain clinic referral may be advisable. No patient should be left in pain!

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 a collection of sub-types with similar symptoms. 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.

**Medicine intolerance** to varying degrees, including multiple drug intolerance, can be a problem in some IC patients and make treatment – particularly oral treatment – very difficult. This is very frustrating for both doctor and patient. While a few patients may have a true allergy, in most it is an intolerance or non-allergic hypersensitivity that may include cognitive functioning, dizziness, faintness, balance problems, hyperventilation, nausea, intestinal upsets, blurred eyesight, extreme fatigue or drowsiness even at low dosages. All treatment is going to be a question of trial and error since allergy tests are not likely to produce any useful results. For oral drugs, it is best to start at the lowest possible dosage, with just a fraction of a tablet. This naturally does not apply to any necessary antibiotics which have to be taken as prescribed. However, intravesical treatment may be the best option for some of these patients.

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. If this succeeds, it will save much of the trial and error of treatment at the present time.

### Symptom-driven treatment

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 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 does indeed appear to be a large number of IC patients whose symptoms are exacerbated by consumption of specific foods and beverages.

| <b>Table 2: 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<br>Citrus fruit and juices<br>Other acidic food such as tomatoes, vinegar etc.<br>Artificial sweeteners<br>Alcoholic drinks<br>Carbonated drinks/soda<br>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.

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.

**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/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**

#### **- Behavioural changes, stress reduction 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. Relaxation techniques, yoga and meditation may all help.

#### **- Clothing & hygiene**

IC patients often feel more comfortable in loose clothing and particularly in cotton underwear, not synthetic underclothes. 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. Patients suffering from vulvodynia, vulvovaginal/perineal pain or sexual pain should be particularly careful about potential irritants such as soaps, powders, shampoo, hair conditioners, shower gel, intimate sprays, detergents and fabric softeners, deodorant tampons and even adhesive on the back of minipads.

#### **- Adapting lifestyle**

IC frequently 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.

#### **- Relationships and intimacy**

Sex therapy and/or relationship counselling may help some patients to deal with intimacy problems.

#### **- 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, as already mentioned, 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 cocktail of different oral drugs, others prefer to try one drug at a time, often starting with low doses and slowly increasing to the maximum toleration level. The single drug approach will be better in patients with drug intolerance problems.

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

- antidepressants
- anti-inflammatory drugs
- antispasmodics and anticholinergics
- anticonvulsants
- histamine-receptor antagonists

- immunosuppressive agents
- painkillers (analgesics)
- pentosan polysulfate sodium
- prostaglandins

*The drugs are discussed below in alphabetical order.*

### **Antidepressants (tricyclic)**

This mainly concerns **amitriptyline**, but nortriptyline and doxepin are also used. Tricyclic antidepressants, now widely used in the treatment of chronic and neuropathic pain, are used in the treatment of IC because they are believed to 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 for the pain of IC, is generic, inexpensive and widely available. It should be taken at dinner in the evening and will help the patient to sleep. By taking at dinner time rather than just before going to sleep, morning hangover can be avoided. This drug is believed to have multiple qualities including pain relief, anticholinergic effects and neuromodulation. It is usual to start with a low dosage (10 mg or less) and gradually increase to optimum toleration level (with minimum side effects) for the individual patient (up to maximum 75 mg). Side effects can be a major drawback and include constipation, dry mouth, urinary retention, weight gain, palpitations and daytime drowsiness.

### **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 radical) 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, naproxen and ibuprofen. New NSAIDs, the so-called coxibs, have fewer gastrointestinal side-effects than the old drugs. NSAIDs should not be taken on an empty stomach and pre-treatment to protect the stomach (for example proton

pump inhibitors) may be necessary. 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.
- **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).

Experimental:

- **IP 751** (ajulemic acid): 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 developed in the USA for the treatment of IC and bronchial asthma. According to the developers, it needs another Phase 2b study at a more optimal dose level (1500mg/day).
- **Tanezumab**, a humanized monoclonal anti-nerve growth factor antibody, is a single-dose intravenous drug that recently underwent clinical trials to reduce pain in IC patients. However, the trial was terminated in November 2010 due to potential safety issues.

### Antispasmodics and anticholinergics

Antispasmodics and anticholinergics 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 newer fesoterodine fumarate. These are standard drugs for treatment of overactive bladder syndrome (OAB), but may be effective in some IC patients as part of combination treatment.

- **Oxybutynin** is an older anticholinergic drug, 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. Side effects have always been a problem with this drug.
- **Tolterodine**, also an anticholinergic 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.

Although these drugs may have a sedative effect on the bladder in some IC patients, longer-term use has been found to lead to bladder retention/difficulty in urination 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, it 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 since side effects can be severe.

#### **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. Increased levels of mast cells have been found in the lining of the bladder of some IC patients, possibly a sign of an allergic or autoimmune reaction. 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 H2-receptor antagonists or blockers that were mainly used in the treatment of peptic ulcers and acid indigestion. However, while they appear to be useful in alleviating the pain and symptoms of some IC patients this has never been definitively proven. They are nevertheless recommended in many guidelines.

**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 suggested that it may have little effect in IC. However, it has recently re-emerged in research studies, so should not be written off.

#### **Painkillers (analgesics)**

Pain management is a very important aspect of treatment of IC patients.

- **Standard over-the-counter (non-prescription) painkillers** may help if the pain is mild.
- **Methotrexate** has shown a significant improvement in pain in IC patients, but had no effect on urgency or frequency.

- **NSAIDs** follow non-prescription painkillers as the next level of pain treatment (see under NSAIDs).
- **Opioids:** In cases of extreme pain that fails to respond to other treatment, long-acting opioids may be necessary (tramadol, morphine, oxycodone, oxymorphone, hydromorphone, fentanyl). Opioids are potent analgesics and are used to relieve the most severe pain. A problem with opioids is that they can cause side effects including fatigue, constipation, nausea as well as dependency. When considering treatment with opioids, potential benefits should be weighed against the risks. Chronic opioid therapy should be considered as a last resort and can best be undertaken in a pain management clinic. Continual evaluation and monitoring is required. Patients should be counselled about the risk of driving and undertaking certain work when being treated with opioids.
- **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 patient-activated pain device to administer medication for hard-to-treat chronic pain is also available in some countries.
- **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.
- **Tapentadol** is a new analgesic available as a standard-release tablet for moderate to severe acute pain and as a prolonged-release tablet for severe chronic pain.

*Studies have shown that recreational abuse of the anaesthetic/painkiller **ketamine** (“street ketamine”) can cause pelvic/bladder pain, a small erythematous bladder with ulcerative cystitis, urgency and frequency. Clinical use of ketamine (in much lower doses than street ketamine) is not believed to have any detrimental effect on the bladder.*

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®, in Italy as Fibrase®, in Germany as SP54® and South Africa and other African countries as Tavan 54®. It is available in many countries for veterinary purposes.

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 only 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.

**TOPICAL TREATMENT (ON THE SKIN)**

- **Amitriptyline**, commonly used as an oral drug to treat pain in IC patients, is also available as an analgesic gel to apply topically on the skin
- **Oxybutynin** is now available in a gel form (Gelnique®) and is applied once daily to the thigh, abdomen, upper arm or shoulder once a day. Side effects include dry mouth and local irritation. While generally used for OAB patients, some IC patients with predominantly urgency/frequency problems may benefit.
- **Transdermal (skin) patches:** A number of drugs, including lidocaine and oxybutynin, are available for the treatment of pain or urgency/frequency in the form of adhesive skin patches. There can be local side effects such as redness and itching.

**VAGINAL & RECTAL TREATMENT FOR PAIN**

- **Valium:** Some doctors are prescribing vaginal valium suppositories or tablets to help relieve the pain of pelvic floor dysfunction, interstitial cystitis, vulvar pain and sexual pain. This causes less drowsiness as a side effect than oral valium, but nevertheless may still produce mild sedation. Dosage is usually 5-10 mg valium compounded (in a paraffin base), starting once nightly and titrating. This treatment can also be used rectally.
- **Rectal** suppositories for pain also include paracetamol, diclofenac and opioids.

**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 catheterized 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. Antibiotics are sometimes given – either orally or intravesically - simultaneously with the instillation as a preventive measure. However, regular use in this way is not recommended since it can cause resistance to antibiotics by bacteria. When catheterizing at home, scrupulously careful hygiene – e.g. thorough cleansing of the area from front to back in women, using disposable plastic gloves etc. – 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 urethral pain on catheterization.

Drugs used for intravesical instillation can be used alone or as a cocktail in which several active ingredients are combined, including for example any of the following: a steroid, an antibiotic, DMSO, heparin, PPS, a painkiller such as lidocaine combined with sodium bicarbonate (the bicarbonate of

sodium alkalizes the lidocaine and allows it to be absorbed), hyaluronic acid or chondroitin sulfate. A course of treatment may involve just a few instillations or numerous applications.

The so-called **anaesthetic cocktails** for immediate pain relief and as a rescue treatment usually comprise alkalinized lidocaine with or without heparin. The effect can last for several days or even weeks.

Some of the drugs used for instillation are aimed at replenishment of a suspected 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.

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.

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

**Antibiotic:** an antibiotic is sometimes added to bladder cocktails to help prevent any bladder infection due to catheterization. However, long-term use of antibiotics should be avoided because of the risk of resistance building up.

**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 is **not recommended**.

**Bupivacaine** is a local anaesthetic drug that can provide long acting local pain control in the bladder. It is sometimes used in patients who do not respond to intravesical lidocaine. It is more lipophilic and potent than lidocaine. (20 ml 0.5% bupivacaine). Can be used alone or in cocktails. Sometimes combined with heparin (10,000 IU of heparin, 10 ml of bupivacaine). Studies have also shown it to be effective in treating bladder spasms.

**Chondroitin sulphate**, a GAG-replenishment treatment, 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. It can be used alone or in combinations. It may help not only IC but also radiation cystitis, chemically induced cystitis, overactive bladder and chronic bacterial cystitis.

**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. The full effect of treatment may not be seen for several weeks. In some patients the symptoms may worsen after the first few treatments. 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 sulfate 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. Relatively inexpensive and widely available.

**Hyaluronic acid:** see **Sodium Hyaluronate**

**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 pipeline.

**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 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.

**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. Studies with RTX® in the United States failed to show any positive results for IC patients, although studies elsewhere were a little more positive and it does appear to help a few 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**), a GAG-replenishment treatment, 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, chemically induced cystitis, overactive bladder and chronic bacterial cystitis. Recent studies have indicated that selection of patients who are likely to respond to this treatment can be improved by using the modified potassium sensitivity test.

**Tacrolimus** is an immunosuppressive agent used to prevent rejection of transplanted organs and is currently being investigated experimentally as an intravesical therapy for IC patients. As an immunosuppressive drug, tacrolimus could be used in treating autoimmune diseases. A recent study showed that it may have many side effects. The most common complaints in a pilot study were tremor, headache, abdominal pain and pruritus. So far, it does not appear to be tolerated better than cyclosporine. It should not be used clinically outside studies.

## 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, even up to a year, 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. Studies have produced conflicting results with some trial results 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. An important point to remember is that the dosage of different brands is not equivalent.

**Triamcinolone** submucosal injection has recently been studied for the treatment of **Hunner's ulcer/lesion** with very good results. Under general anaesthesia, triamcinolone (40mg/cc) was injected with an endoscopic needle in volumes ranging from 5-10 cc (depending on the number and size of the lesions) into the submucosal space of the centre and periphery of lesion(s). It appeared to be well-tolerated in 66% of patients in this Hunner subtype. This study is ongoing and continues to produce positive results.

**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.

## EMDA - ELECTROMOTIVE DRUG ADMINISTRATION

EMDA is a method of accelerated delivery of drugs deep into the bladder using a small amount of electricity. It appears to be a safe and effective approach to treating IC. Studies have shown it to achieve significant prolongation and enhancement of symptom improvement compared to normal instillation of drugs.

## **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 transurethral resection (TUR) for Hunner's ulcer/lesion**

These forms of treatment are reserved for patients with the classic form of IC (Hunner's ulcer/lesion) and are used to treat the lesions. They have a temporarily alleviating effect on the pain for several months or even several years, but can be repeated when necessary. While good symptom improvement has been seen in studies with neodymium Yag-laser treatment, it is essential for patients to be treated by very experienced surgeons since this therapy carries the risk of complications such as accidental bowel perforation in less experienced hands. TUR has been shown to lead to considerable improvement in both pain and frequency.

### **Bladder hydrodistension or inflation (stretching)**

Bladder hydrodistension or stretching is not only used for diagnostic purposes but also sometimes 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. It is currently thought to have a beneficial effect in 30%-50% of patients. Many patients report that their symptoms return within three months. Regarding the role and value of hydrodistension as a therapy, recent studies indicate that it may improve symptoms in only a minority of patients. Hydrodistension should be undertaken only with the greatest caution in patients where Hunner's lesions 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 puddental nerve roots for the treatment of bladder dysfunction and urinary incontinence. Neuromodulation is a potentially important form of treatment for selected patients, but is still 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. 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 for selected patients. 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. It is still investigational.

**Bion:** The Bion is an experimental implantable battery-powered microstimulator 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.

## 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 since IC is a complex disease and surgery may lead to other complications. It is therefore important for patients to understand exactly what is involved and the potential side effects and consequences.

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.

Irreversible surgical options should be considered only when all conservative treatment has failed. The patient should be thoroughly informed about all aspects of the surgery and understand the consequences and potential side effects of surgery.

### **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.

### **Catheterization (indwelling) for surgery**

When undergoing surgery, including non-uological surgery, IC patients may need to be catheterized for several days or longer, using an indwelling catheter which is secured in place with a small inflatable balloon inside the bladder, preventing the catheter from slipping out of the urethra. An indwelling catheter may be left in place for a short or longer time. The urine is usually collected in a drainage bag. An indwelling catheter can cause intense irritation and pain in the bladder of an IC patient. One solution is to use a 100% silicone catheter and only partly inflate the balloon.

### **TREATMENT FOR HUNNER'S LESIONS (ALSO CALLED ULCERS or PATCHES)**

Hunner's lesions, historically known as Hunner's ulcers even though ulcer is not the correct medical description, are known as the Classic form of IC. Hunner's lesions are diagnosed with cystoscopy and hydrodistension. It is at present very difficult to detect them without hydrodistension. Pain in the bladder caused by lesions can improve dramatically when treated with fulguration/electrocoagulation, laser (burning out and sealing the lesion) or resection (surgical removal of the lesion). This treatment needs to be periodically repeated as and when the pain returns. This may be after a few months or after several years. A new promising treatment for Hunner's lesions is submucosal injection of the corticosteroid triamcinolone.

For further information on Hunner's lesions, see [http://www.essic.eu/Hunner\\_lesion.html](http://www.essic.eu/Hunner_lesion.html)

### **ALTERNATIVE OR COMPLEMENTARY TREATMENT - MIND-BODY THERAPIES**

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 and tender 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. Basic therapy should include: no pushing or straining with urination, avoid constipation, warm baths twice a day, skeletal muscle relaxants, physical therapy.

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 techniques 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.

Kegel or pelvic floor strengthening exercises are not recommended for IC patients.

### **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.

Some IC patients have multiple disorders and may be receiving treatment from several different doctors. It is therefore essential for treatment to be coordinated so as to ensure that the patient is not receiving a potentially harmful combination of drugs.

## CHAPTER 6 - IC & ASSOCIATED DISORDERS

Many patients with IC also have one or more non-bladder disorders or symptoms in addition to their IC problem, including other 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 non-bladder disorders may go undiagnosed and untreated. This underlines the need for a multi-disciplinary approach.

### **Associated disorders (*co-morbidities*)**

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

- allergy/hypersensitivity,
- fibromyalgia,
- gastrointestinal disorders
- migraine
- rheumatoid arthritis,
- systemic lupus erythematosus
- Sjögren's syndrome
- vulvodynia
- chronic fatigue

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

The possible relationship between IC and other disorders that may co-exist with IC, and why these disorders should occur alongside each other in the same patient, is still unknown and is currently the subject of much research. 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" or "systemic": this means that they attack many different organs and systems throughout the body. Patients with both a diagnosed autoimmune disease and IC should be sure to inform their specialists 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).

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 an 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/CPSP), irritable bowel syndrome, vulvodynia, fibromyalgia, 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 an extensive 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/hypersensitivity:** Many IC patients suffer from allergy/hypersensitivity, including food, chemicals and drugs. Allergies can affect the skin, airways and sometimes organs. Examples of allergy include asthma, rhinitis, urticaria (nettle-rash), eczema and anaphylaxis. True allergies can be identified by allergy tests. In some cases, patients receiving antihistamines for their allergy find that this treatment also has a beneficial effect on their IC bladder symptoms.

However, not all hypersensitivity reactions are true allergy and may in fact be a question of non-allergic hypersensitivity, often known as intolerance. The problem with this non-allergic hypersensitivity is that reactions to drugs may be unpredictable and variable, are often a question of trial and error and largely impossible to "diagnose" by standard tests. Non-allergic hypersensitivity is still a relatively unexplored, unresearched field and particularly so in relation to the drug intolerance (often multiple drug intolerance) found in some IC patients. Some IC patients may also have multiple chemical intolerance and feel sick, dizzy and faint if there are chemicals in the air or if perfumed products or chemicals touch their skin. At present, it is unknown why some IC patients have these problems and others not. It is interesting to note that multiple drug intolerance and multiple chemical intolerance are also found typically in patients with fibromyalgia.

Drug intolerance may affect, for example, cognitive functioning, eyesight and balance and cause dizziness, faintness, headache, general malaise, fatigue or drowsiness.

Patients with drug intolerance often respond better to intravesical treatment for their IC where less of the drug is absorbed into the system.

Finding a solution to drug intolerance would make it considerably easier to find an adequate treatment for many patients, thereby relieving the anxiety that multiple drug intolerance may cause and greatly improving their quality of life. And of course we should not forget that expensive drugs are being thrown away.

**Chronic non-bacterial prostatitis:** Chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of prostatitis. The older term prostatodynia is also sometimes used to describe this painful prostate condition. A new term for prostatodynia is perineal pain. 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. For further detailed information see: [www.prostatitis.org](http://www.prostatitis.org)

**Depression** is experienced by many people in the general population, either occasionally or persistently but may particularly occur in patients with chronic disorders such as IC. Sometimes it is a question of being temporarily “down” or “moody” or “sad” or unable to cope, but sometimes it is more serious and needs treatment and professional counselling. Some patients may not actually realize that they are suffering from depression and this may partly be due to confusing usage of the word depression. People so often say that something that has occurred has made them “so depressed” when in fact they mean that they are upset or sad or shocked about a specific incident. Under normal circumstances, they will adjust to the situation and soon recover. However, in cases of true depression, the sad or down feeling will persist. There may be multiple effects: people’s weight can go up or down, they may sleep too much or too little, may feel tired all the time and have no energy, have feelings of guilt, feel worthless, experience confusion or forgetfulness (*cognitive impairment*), have suicidal thoughts. Depression can make it impossible to work, study and cope with or enjoy everyday life. While depression may be caused by psychiatric disorders, it may also form part of a syndrome of symptoms in chronic diseases, as has been documented in systemic lupus erythematosus, and may potentially occur in any disease with a neurological component including pain syndromes. “Mood” disorders are caused by chemical imbalances in the brain. This may be caused by an illness, by hormone imbalance, even by certain medications. Treatment may be aimed at changing the chemical imbalances in the brain.

In IC patients, it may be a question of a temporary inability to cope which can be helped by good support and a sympathetic approach from their doctor, by a patient support group, by support in the home environment. If more serious, it should be treated with medication combined with counselling. Depression in IC patients may be combined with anxiety and/or panic attacks and this can respond to treatment. Above all, patients should not be afraid or feel guilty about admitting to their doctor that they are suffering from depression. Professional help should always be sought for suicidal patients.

*Further reading:*

*The National Institutes of health have a useful booklet on depression online:*

<http://www.nimh.nih.gov/health/publications/depression/complete-index.shtml>

*and also a specialised leaflet on Men and Depression to be downloaded at:*

<http://www.nimh.nih.gov/health/publications/men-and-depression/complete-index.shtml>.

*Wikipedia also has a useful article on Depression – differential diagnoses*

[http://en.wikipedia.org/wiki/Depression\\_\(differential\\_diagnoses\)](http://en.wikipedia.org/wiki/Depression_(differential_diagnoses))

*If you have access to UpToDate, you will find information on this topic for both patients and professionals.*

**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. See also Chapter 7: Fatigue in IC patients.

**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, drug intolerance, 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, while others 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-groups. Like IC, the course of this condition can be variable with exacerbations and remissions. For further information:

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001463/>, <http://www.fmaware.org/>,  
<http://www.ukfibromyalgia.com/>

**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.

The National Digestive Diseases Information Clearinghouse (NDDIC) has useful information on IBS at: <http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/index.aspx> and on IBD at: <http://digestive.niddk.nih.gov/ddiseases/topics/IBD.aspx>

**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 and that Sjögren's syndrome may be being underdiagnosed in IC patients. Further information: [http://www.painful-bladder.org/pbs\\_ic\\_ass\\_dis.html](http://www.painful-bladder.org/pbs_ic_ass_dis.html)

**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:

- **Localized 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)*

## CHAPTER 7 - FATIGUE IN IC PATIENTS

**Fatigue is a potentially disabling condition that can cause mental and physical dysfunction, with a severe impact on the patient's relationships, home-life, employment and social life. It can cause physical incapacity, mental fog, inability to communicate to people around you, and an overwhelming sense of isolation.**

Many IC patients suffer from fatigue, listlessness and lack of energy or drive. While fatigue is still frequently ignored, misunderstood, dismissed as psychosomatic or simply considered unimportant by many of the medical profession, it is also equally misunderstood by the patient's family and environment. This can create a very unsympathetic environment for a patient suffering from fatigue and make it so much more difficult to cope with the condition.

As with everything in IC patients, you find huge variations in fatigue with a wide spectrum varying from mild and fluctuating at one end of the scale and very severe at the other end, with an impact that may virtually paralyse the patient's life. Fatigue may on the one hand be temporary, the cause easily diagnosable and treatable or it may be persistent, unexplainable and fail to respond to any treatment. A patient may have only physical fatigue, or a combination of physical and mental fatigue.

One of the aspects that make fatigue so complex is that persistent tiredness or chronic fatigue can have multiple causes and any given patient may be suffering from more than one cause of fatigue at the same time and therefore all of these will need to be addressed. And it is certainly not always easy to see what the cause or different causes may be, especially as the symptoms from different types of fatigue may be similar and overlap.

Fatigue may on the one hand be temporary, the cause easily diagnosable and treatable or it may be persistent, unexplainable and fail to respond to any treatment.

### **Causes of fatigue (see also Table 4)**

Causes of fatigue can be roughly grouped under the following main headings:

- Sleep disruption
- Medication
- Physical (organ-based) diseases
- Psychological disorders
- Diseases without proven psychological or physical cause
- General

### **Sleep disruption**

Lack of proper sleep is the first aspect that anyone is going to think of in relation to an IC patient. We know that IC patients vary greatly in their symptom levels, including night-time voiding, and this can even fluctuate in an individual patient depending on whether the patient is in a flare or in remission. But even only 2 or 3 times a night on a regular basis can cause considerable tiredness because some people find it very difficult to get off to sleep again once they've got out of bed. The most severe IC patients, or patients in a flare, may be out of bed every 20 minutes or worse, even sitting all night on the toilet, or wrapped up in a blanket on the bathroom floor.

However, we should not forget that many other aspects can contribute either to being unable to get off to sleep or to frequent waking in the night, leading to extreme tiredness:

- pain, not only in the bladder but also elsewhere; many IC patients have one or multiple other pain syndromes which may cause pain at night.

- Restless legs syndrome, itching, burning, tingling - all of these can prevent you from sleeping.
- Medications: all kinds of medication can cause insomnia.
- You may be woken up by noise: from a snoring partner, crying babies, noisy traffic etc.
- Too much light inside or outside the home, from streetlights or outside security lights.
- Anxiety, work stress, and the stress, worry and sometimes panic of coping with IC can all keep you awake.

So each patient should carefully think about whether it is purely the bladder pain and need to void that is waking you up, or whether something else has disturbed your sleep and you then feel your bladder discomfort and get out of bed. It may be purely the IC bladder in some patients, but in others perhaps a combination.

### Physical and psychological impact of lack of sleep

“Frequent nocturnal awakenings, particularly during the first part of the night, decrease the restorative function of sleep and can cause daytime sleepiness and impaired cognitive function.”  
(Chapple C. Introduction and conclusions. *European Urology Supplements* 6 (2007) 573–575)

According to the experts, proper, restorative sleep occurs in the first part of the night and it is likely to be this early part of the night that is most disturbed in IC patients. Adequate sleep is a basic requirement for good health. You need sleep for recuperation and restoration of physical and mental functioning. Without this proper sleep, a person deteriorates both physically and psychologically. The physical and psychological impact of sleep disruption is quite extensive and can have serious consequences as you can see from the list below:

- Fatigue and lack of energy
- Mood swings, irritability, tearfulness
- Lack of motivation
- Decreased concentration
- Memory lapses
- Motor performance impairment
- Disorientation
- Depression

(adapted from Marschall-Kehrel D. Update on nocturia: the best of rest is sleep. *Urology*. 2004 Dec;64(6 Suppl1):21-4)

### Treating lack of sleep – useful tips for the patient

- It goes without saying that suitable treatment for the bladder pain and the frequency and any other pain should have absolute priority.
- If the distance to the bathroom is too far, it’s also a good idea for an IC patient to have a commode or an old-fashioned chamber pot or a portable camping toilet in the bedroom. The further you have to walk to reach the bathroom, the more time your body has to completely wake up, and the less likely you are to get off to sleep again when you’re back in bed.
- Cut down night-time voiding as far as possible by limiting drinking in the evening and avoid consuming any food or drink that you know will irritate the bladder or food and drink that is likely to keep you awake. But make up for this by drinking plenty earlier in the day to avoid concentration of urine.
- If you have to take medication that causes irritation in the bladder, either take it early in the morning or very late at night just before sleeping. But preferably change your medication to something that does not irritate the bladder. And this is very individual.
- If you are being kept awake or woken up by noise of any kind, try using ear-plugs.



- If you can't do anything about disturbing light, wear an eye-mask.
- If lack of sleep is partly caused by anxiety or stress, counselling may be needed. IC patients can become very anxious and panicky about their bladder disorder and its impact on their life and of course the fact that treatment may not be working. They worry continually about what the future may bring. And some counselling could help here.

### **Medication causing daytime drowsiness**

While some medication can cause insomnia, other drugs can cause drowsiness all day long. Unfortunately, so many treatments used for pain in IC have a sedative effect and make you feel like a zombie. However, many other drugs can have a sedative effect in some patients. We should not forget here the role played by the medicine intolerance experienced to varying degrees by some IC patients. This can make them react much more strongly to even the lowest dosages. It is therefore important to be aware that any medication could potentially either cause insomnia or daytime drowsiness or exacerbate existing chronic fatigue.

### **Physical (organ-based) diseases**

Diseases causing tiredness include anaemia, hypothyroidism, heart failure, low blood pressure, infectious diseases including glandular fever. These can all be checked out by the doctor. Cancers also cause extreme fatigue. Any diseases causing chronic pain day in day out are very exhausting. Coping with a bladder disorder like IC is also very tiring because you can never really relax. You always feel that pain or irritation in the bladder and are exhausted by continually going to and from the bathroom.

### **Chronic fatigue**

A special role is played here by systemic autoimmune diseases such as systemic lupus erythematosus and Sjögren's syndrome in which **chronic fatigue** can be a totally disabling symptom. Chronic fatigue can also occur in fibromyalgia. When no identifiable disease or cause of the fatigue can be found, it is known as chronic fatigue syndrome.

Chronic fatigue is different to other forms of tiredness. A difference with the tiredness caused by lack of sleep is that autoimmune tiredness has no bearing on whether you have slept well or not. Chronic fatigue may fluctuate from week to week, month to month and year to year and it may wax and wane during the day with flares at specific times when you then feel fluey, shivering, with a headache, total exhaustion and inability to think. You no longer have the energy to take any kind of action, to talk to people, pick up the phone or take a decision. With chronic fatigue you lose your drive, your motivation, you may have memory lapses, no concentration and experience confusion. Physically, you feel unwell all the time. Your body feels uncomfortable, it aches and you can't tolerate tight clothes. You become exhausted after the slightest exertion. While rest may sometimes alleviate the fatigue for a short time, as soon as you are busy again the fatigue returns.

### **Advice to patients with chronic fatigue**

Work out how to plan your routine each day depending on how you feel. If necessary restructure your life, change your lifestyle. Do not take on more commitments than you can cope with. Learn to say no. Recognize when you are overdoing it before you collapse. Don't feel guilty about taking naps or siestas during the day. Discover how much exercise you need and can cope with. Take sufficient exercise, but don't overdo it. With chronic fatigue you have to learn how to pace yourself, learn how to manage physical and emotional stress. Avoid overdoing things at times when you feel a bit more energetic since this can cause rapid burnout. At those rare moments when you have a window of energy, it is so tempting to try to catch up with all those tasks that have been neglected and piled up. It is important at all times to build in periods of rest and relaxation.

All patients should bear in mind that fatigue or daytime drowsiness can make driving or use of machinery dangerous.

### **Psychological disorders**

Depression can cause fatigue, but chronic fatigue can itself cause depression. Since the very nature of IC symptoms can make you depressed, it becomes a vicious circle from which it is difficult to escape.

### **Impact on the whole family**

Fatigue impacts not only the patient but the whole family and can cause disruption of the life of everyone in the family, including your children. It can make the patient unable to run the household, keep to any routine, create a normal environment for the family, lead a normal social life or have a normal relationship. The financial impact of chronic fatigue is a very important aspect for the patient since people with chronic fatigue may not be able to hold down a job.

### **For further information, including treatment, see:**

Sjögren's syndrome. Information for patients and professionals by Dr Joop P. van de Merwe.

Chapter 5 Treatment: [www.painful-bladder.org/pdf/ch5.pdf](http://www.painful-bladder.org/pdf/ch5.pdf),

Chapter 6 Fatigue: <http://www.painful-bladder.org/pdf/ch6.pdf>

**Table 4: CAUSES OF FATIGUE**

**A. Sleep disruption**

- night-time frequency
  - . e.g. IC/PBS, OAB, CP, pelvic organ prolapse, polyuria
  - . timing of drinking (too much, too late)
- pain, itching, burning, restless legs
- medication -> insomnia or nightmares
- environmental disturbance
  - . noise
  - . light
  - . uncomfortable bed, too hot, too cold
  - . snoring, restless partner
- stress, anxiety, panic attacks

**B. Medication causing fatigue, sleepiness, lethargy**

e.g. opioids, anticonvulsants, antihistamines, anticholinergics, antidepressants, proton pump inhibitors, cough & cold remedies, chemotherapy, blood pressure medications, heart medications

**C. Physical (organ-based) diseases**

Anaemia  
 Hypothyroidism  
 Heart failure  
 Low blood pressure  
 Infectious diseases  
 Systemic autoimmune diseases  
 Cancer

**D. Psychological disorders**

Depression  
 Burnout

**E. Diseases without proven physical and psychological cause**

Chronic fatigue syndrome  
 Fibromyalgia

**F. General**

Excessive activity, over-exercising

Table 4 gives a list of some causes of fatigue

## 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,  
Lippincott-Raven  
ISBN 0-397-51695-9

Sjögren's syndrome. Information for patients and professionals.

By Joop P. van de Merwe, MD.  
[www.painful-bladder.org/pdf/ch5.pdf](http://www.painful-bladder.org/pdf/ch5.pdf)

Report of the 2<sup>nd</sup> ICICJ, Japan 2007, edited by Ueda T.  
Published 2008 by the Comfortable Urology Network.

## Medical Guidelines:

American Urological Association (AUA) - Clinical Guidelines: Diagnosis & Treatment of Interstitial Cystitis/Bladder Pain Syndrome.

<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=ic-bps>

EAU guidelines on chronic pelvic pain.

Fall M, Baranowski AP, Elneil S, Engeler D, Hughes J, Messelink EJ, Oberpenning F, de C Williams AC; European Association of Urology. Eur Urol. 2010 Jan;57(1):35-48. Epub 2009 Aug 31.

A summary. The full guidelines text may be obtained from the EAU.

Hanno P, Lin A, Nordling J, Nyberg L, Van Ophoven A, Ueda T. Bladder Pain Syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence, 4th ed. Paris: Health Publications Ltd. UK; 2009. pp. 1459-1518.

Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH, Lee JG, Kim DY, Lee KS; Interstitial cystitis guideline committee. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Int J Urol. 2009 Jul;16(7):597-615.

Homma Y, Ueda T, Ito T, Takei M, Tomoe H. Japanese guideline for diagnosis and treatment of interstitial cystitis. Int J Urol. 2009 Jan;16(1):4-16.

## Scientific Literature:

Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn 21:167-178, 2002.

Abrams P. Nocturia: the effect on sleep and related health consequences. Eur Urol 2005 Suppl 3:6 1-7

Alagiri M et al. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology 1997;49 (Suppl 5A):52-7  
Chancellor MB, Yoshimura N. Treatment of Interstitial Cystitis. Urology 63 (suppl 3A): 85-92, 2004.

Chapple C. Introduction and conclusions. European Urology Supplements 6 (2007) 573-575

Cox M, Klutke JJ, Klutke CG. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. Can J Urol. 2009 Apr;16(2):4536-40.  
Fall M, Oberpenning F, Peeker R. Treatment of Bladder Pain Syndrome/Interstitial Cystitis 2008: Can we make evidence-based decisions? Eur Urol. 2008 Jul;54(1):65-75.

Fenton BW. Limbic associated pelvic pain: A hypothesis to explain the diagnostic relationships and features of patients with chronic pelvic pain. Med Hypotheses.2007;69(2):282-6.

Hand JR. Interstitial cystitis: Report of 223 cases (204 women and 19 men) J Urol 1949;61:291-310.

Hanno PM. Re-imagining Interstitial Cystitis. Urol Clin North Am. 2008 Feb;35(1):91-9.

- Hanno PM, Landis JR, Matthews-Cook Y et al. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database Study. *J Urol* 1999; 161:553-557.
- Hunner GL. A rare type of bladder ulcer in women: report of cases. *Boston Med Surg J* 1915;172:660-4.
- Hunner GL. Elusive ulcer of the bladder: further notes on a rare type of bladder ulcer with a report of twenty-five cases. *Am J Obstet Dis Child* 1918;78:3-8.
- Interstitial Cystitis 2001: An Evolving Clinical Syndrome, Urology supplement June 2001 Vol 57 6A Elsevier International Consultation on Interstitial Cystitis Japan (ICICJ)
- International Journal of Urology, Vol 10 Supplement October 2003, Blackwell Publishing.
- Jennum P. The impact on nocturia on sleep. Presented at First International Nocturia workshop, 6-8 June 2003, Malta .
- Keene FE. Circumscribed pan-mural ulcerative cystitis. *Ann Surg* 920;71:479485.
- <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17864270> available free online
- Kelly HA. Operative Gynecology. 2nd Edition 1912. D. Appleton and Company.
- Marschall-Kehrel D. Update on nocturia: the best of rest is sleep. *Urology*. 2004 Dec;64(6 Suppl1):21-4
- Messing EM, Stamey TA. Interstitial Cystitis: Early Diagnosis. Pathology and Treatment. *Urology*. 1978 Oct;12(4):381-92.
- Nickel JC, Shoskes D, Irvine-Bird K. Clinical phenotyping of women with interstitial cystitis/painful bladder syndrome: a key to classification and potentially improved management. *J Urol*. 2009 Jul;182(1):155-60.
- Nitze M. Lehrbuch der Zystoskopie: Ihre Technik und Klinische Bedeutung. Berlin: JE Bergman, 1907;410.
- Nordling J. Sensory Bladder Disorders. *Int J Clin Pract*. December 2006, 60(Suppl 151), 38-42.
- Nordling J. Interstitial cystitis: how should we diagnose it and treat it in 2004? *Curr Opin Urol* 14:323-327, 2004.
- Nordling J et al. Evaluation of Patients Suspected of Having Interstitial Cystitis, *European Urology* 45 (2004):662-669.
- Nordling J. Surgical treatment of painful bladder syndrome/interstitial cystitis. *Women's Health* (2006) 2(2).
- Panzera AK, Reishtein J, Shewokis P. Sleep disruption and interstitial cystitis symptoms in women. *Urol Nurs*. 2011 May-Jun;31(3):159-65, 172.
- Parsons JK, Parsons CL, The historical origins of interstitial cystitis, *J Urol*. 2004 Jan;171(1):20-2
- Reviews in Urology: The Clinical Management of Interstitial Cystitis, *MedReviews*, Vol 4 Suppl 1 2002, [www.medreviews.com](http://www.medreviews.com)
- Parrish J. Tic douloureux of the urinary bladder. In: Practical observations on strangulated hernia and some of the diseases of the urinary organs. Philadelphia: Key & Biddle, pp309-313, 1836.
- Rogalski MJ, Kellogg-Spadt S, Hoffmann AR, Fariello JY, Whitmore KE. Retrospective chart review of vaginal diazepam suppository use in high-tone pelvic floor dysfunction. *Int Urogynecol J Pelvic Floor Dysfunct*. 2010 Jul;21(7):895-9.
- Rosamilia A. Painful Bladder Syndrome /Interstitial Cystitis. *Best Prac Res Clin Obstet Gynaecol*. Sept.2005
- Skene AJC. Diseases of the bladder and urethra in women. New York: William Wood; 1887.
- Shorter B, Lesser M, Moldwin RM, Kushner L. Effects of Comestibles on Symptoms of Interstitial Cystitis. *Journal of Urology*, July 2007, vol. 178, 145-152.
- Stanley N. The underestimated impact of nocturia on quality of life. *Eur Urol* 2005;(Suppl 4):17-19
- Teichman JM, Thompson IM, Taichman NS. *J Urol*. 2000Nov;164(5):1473-5
- Theoharides T & Sant G. New agents for the medical treatment of interstitial cystitis. Expert Opinion on Investigational Drugs, 2001 Ashley Publications Ltd
- Van de Merwe JP, Nordling J, et al. Diagnostic Criteria, classification, and Nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: an ESSIC proposal. *Eur Urol*. 2008 Jan;53(1):60-7.
- Van de Merwe JP. Interstitial cystitis and autoimmune diseases. *Nat Clin Pract Urol*. 2007 Sep;4(9):484-91.
- Van de Merwe JP, Arendsen HJ. Interstitial Cystitis: a review of immunological aspects of the aetiology and pathogenesis, with a hypothesis. *BJU International* (2000)85, 1995
- Van de Merwe JP, Kamerling R, Arendsen HJ, Mulder AH, Hooijkaas H. Sjögren's syndrome in patients with interstitial cystitis. *J Rheumatol* 1993;20:962-6
- Winnard KP, Dmitrieva N, Berkley KJ. Cross-organ interactions between reproductive, gastrointestinal and urinary tracts: modulation by estrous stage and involvement of the hypogastric nerve. *Am J Physiol Regul Integr Comp Physiol* 2006;291:R1592-601
- Whitmore K, Fariello JY and the Pelvic and Sexual Health Institute, Philadelphia. Sexual Pain in Men & Women with IC/PBS and Chronic Pelvic Pain. *ICS News* vol 6, issue 1 January 2010

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