

International Painful Bladder Foundation

Interstitial Cystitis Bladder Pain Syndrome Hunner Lesion

An overview of Diagnosis & Treatment

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Interstitial Cystitis, Bladder Pain Syndrome, Hunner Lesion: Diagnosis & Treatment

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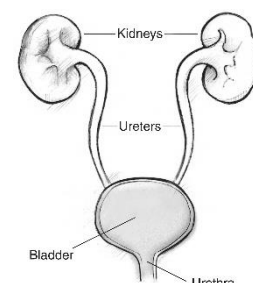
TERMINOLOGY AND ABBREVIATIONS USED:

- Interstitial Cystitis: IC
- Bladder Pain Syndrome: BPS
- Painful Bladder Syndrome: PBS
- Hypersensitive Bladder: HSB
- Chronic Pelvic Pain: CPP
- Chronic Pelvic Pain Syndrome: CPPS
- Chronic non-bacterial Prostatitis/Chronic Pelvic Pain Syndrome: CP/CPPS
- Chronic Overlapping Pain Conditions: COPCs
- Urologic Chronic Pelvic Pain Syndrome: UCPPS
- Hunner Lesion: (formerly Hunner's ulcer or Ulcerative IC) also known as Classic IC or Hunner Lesion Disease (HLD) or Hunner IC (HIC)
- Associated Disorders also known as Comorbidities or Non-Bladder Conditions
- Ketamine Cystitis: KC, also known as Ketamine Associated Cystitis

CHAPTER 1 - WHAT IS INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)?

The urinary tract

The urinary tract consists of two kidneys, two ureters, a urinary bladder and a urethra. It is divided into the upper urinary tract (kidneys and ureters) and the lower urinary tract (bladder and urethra). The kidneys filter waste products from the blood and produce urine which is transported to the bladder via the ureters. The urine is stored in the bladder and eliminated through the urethra when the need to urinate is felt.



Bladder symptoms

A normal urinary bladder should not cause pain or discomfort nor should it cause an abnormally frequent and urgent need to urinate.

Pain, discomfort or a feeling of pressure in and around the bladder, accompanied by a frequent and often urgent need to urinate, can have many different causes. It may be related to the urinary tract, genital tract, pelvic floor, bowel, nervous system or muscular system. Possible causes include bacterial, viral or fungal infections, parasitic infestations, stones, benign or malignant tumours, endometriosis and damage from drugs or chemicals including in recent years street ketamine abuse. Other causes may include side effects from chemotherapy or radiation therapy.

(Table 1 provides a summary of many possible causes of these symptoms, the so-called confusable diseases).

However, if a thorough medical history, examination and tests have revealed no evidence of bacterial urinary tract infection (UTI) or any other condition that could account for the chronic symptoms, another possibility to consider is **interstitial cystitis/bladder pain syndrome (IC/BPS)**, also known as painful bladder syndrome (PBS).

IC/BPS is a distressing, chronic bladder disorder of unknown cause, characterised by persistent or recurrent symptoms of bladder pain, irritation, discomfort or pressure. Pain typically increases as the bladder fills and is often relieved upon emptying. These symptoms are frequently accompanied by a frequent and urgent need to urinate both during the day and at night, even when the bladder contains only a small amount of urine. Symptoms can vary from very mild to very severe.

In the urology world, IC/BPS is classified as a "*functional urological disease*".

Currently two main subtypes are recognised: Hunner lesion disease and IC/BPS non-lesion disease

- Hunner lesion disease (formerly known as Hunner's ulcer or ulcerative IC, Classic IC, or Hunner IC)
- the non-Hunner lesion type.

While symptoms may be similar, cystoscopic findings are different for these two types and the approach to treatment is also different. Further information is given under Chapter 4 Diagnosis and Chapter 5 Treatment.

There is a growing international trend to view these two types as two distinct conditions. Hunner lesions can only be identified with cystoscopy.

What are the characteristic symptoms?

The three characteristic symptoms of IC/BPS are:

Pain:

- chronic pain, pressure, discomfort or other unpleasant sensation in the urinary bladder, which may worsen as the bladder fills. Urinating often alleviates the pain and may provide temporary relief.

Urinary symptoms:

- a more frequent need than normal to urinate (frequency) both during the day and at night,
- an urgent, overwhelming need to urinate due to increasing pain or discomfort (painful urgency).

Secondary symptoms may include:

- Pelvic pain (lower abdominal pain), which may radiate to the lower back, the groin or thighs.
- In women, pain in the vagina and vulva.
- In men, pain in the penis, testicles, scrotum and perineum.
- Both men and women, pain in the urethra and rectum.
- Pain and urinary symptoms may worsen or be triggered in the form of flares by certain foods or drinks, medications or supplements or by physical or emotional stress. These triggers vary greatly from patient to patient.

The pain may be experienced as discomfort, tenderness, irritation, burning or other unpleasant sensation in the bladder. It may also present as stabbing pain in or around the bladder or in the vagina. In some cases the pain is not confined to the bladder but extends throughout the pelvic floor, including the lower bowel and rectum. Some patients may simply feel pressure in or on the bladder or a sensation of fullness and an urgent need to urinate even when there the bladder contains very little urine. I

n many patients, the pain is temporarily relieved by urination, while some patients may also experience pain or burning following urination. The pain or discomfort may be constant or intermittent. In some patients the pain may be very severe and debilitating. Other patients may experience frequency with or without urgency but with only mild pain or discomfort. Pain with sexual intercourse is a typical feature in both men and women.

Urinary frequency refers to the need to urinate more frequently than normal during the day and at night, typically urinating only small amounts each time. However, frequency will also partly depend on how much a patient drinks, the climate in the country where the patient lives, how much the person perspires and on any medication the patient may be taking which could have a diuretic effect. In IC/BPS, urinary frequency may sometimes be very severe with some patients needing to urinate 60 times a day or more.

Officially, abnormal frequency is considered to be urinating more than approximately 8 times a day. However, this number should only be seen as a general guideline since it depends on individual lifestyle and environment.

Urinary frequency is by no means always related to bladder size. While some patients (with Hunner lesions) may have a shrunken bladder with a scarred, stiff wall and a small capacity under general anaesthesia, other IC/BPS patients with a normal-sized bladder and normal capacity under general anaesthesia may nevertheless experience severe frequency.

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

Urinary urgency in IC/BPS is an overwhelming and urgent need to empty the bladder due to increasing pain or discomfort or other unpleasant sensation that becomes impossible to tolerate any longer and may cause great stress and anxiety.

Note: The painful urgency of IC/BPS (also known as sensory urgency) fundamentally differs from the sudden urgency associated with fear of leakage in overactive bladder with or without urgency incontinence. These two types of urgency should not be confused.

Who gets IC/BPS?

IC/BPS can affect males, females and children, of all ages, worldwide!

As currently diagnosed, IC/BPS is predominantly found in women. Approximately 10-20% of patients are men, many of whom may have been previously misdiagnosed with chronic prostatitis (CP) or prostate pain syndrome. These conditions share many clinical similarities and overlapping symptoms with IC/BPS. Therefore, a diagnosis of IC/BPS should be considered in men experiencing chronic bladder pain, particularly when other potential causes have been ruled out. It's also important to note that CP and IC/BPS can occur simultaneously.

IC/BPS is also seen in children. Historically, the original NIDDK IC research criteria excluded children from IC studies, leading many doctors to believe that IC/BPS did not occur in children. As a result, there has been relatively little research, scientific literature or clinical data on IC/BPS in children over the past 3 decades. Some doctors are still hesitant to diagnose IC/BPS in a child. Nevertheless, it can occur in children of any age. Many adults with IC/BPS report that they needed to go to the toilet more frequently than their peers during childhood or adolescence.

Prevalence

IC/BPS is found in all countries around the world and all ethnic groups. However, prevalence figures vary greatly from study to study and country to country, depending on the diagnostic criteria, definitions and methods used for diagnosis. Furthermore, many prevalence studies have tended to group together all patients with any unexplained painful bladder symptoms, without subtyping. As a result, it is currently not possible to say with any degree of certainty how many people actually have IC/BPS with or without Hunner lesions. Although IC/BPS is officially classified as a rare disease in many countries, including throughout Europe, in others - such as the USA - it is not considered rare.

How does IC/BPS start?

The onset of IC/BPS may be very gradual, building up over many years, or it may be sudden and severe. Some patients recall experiencing urinary frequency during childhood or

adolescence long before they developed pain, while others did not experience this. If symptoms begin following gynaecological or other pelvic surgery, this warrants further pelvic evaluation to determine whether the symptoms might be being caused by previous surgical damage. In such cases, the pain felt in the bladder may actually be “referred pain” originating from damage or a disorder elsewhere in the pelvic floor.

Is the cause known?

Despite considerable research into many different aspects of IC/BPS, the cause remains unknown. Numerous theories have been proposed, including increased mast cell activity, a malfunctioning bladder lining (glycosaminoglycan GAG layer, mucosa or urothelium) allowing toxic elements in the urine to penetrate into the underlying interstitial layers of the bladder wall, as well as neurological, central nervous sensitisation, autonomic nervous dysfunction, autoimmune response, allergic, viral or bacterial infection, metabolic factors, urobiome-related factors and many more hypotheses. Some researchers have explored the possibility of heredity or genetics playing a role since IC/BPS may occur in more than one member of the same family (mother and daughter or two sisters).

In some patients, IC/BPS is associated with a systemic, autoimmune, rheumatic disease such as Sjögren’s disease, rheumatoid arthritis or lupus. These systemic diseases may be the underlying cause of the bladder symptoms in this specific group (“phenotype”) of patients. Others may have bladder pain in association with widespread pain conditions such as fibromyalgia and polyneuropathy.

Numerous theories, no conclusive answers.

While many different theories have been explored and much research has been carried out, no conclusive answers have so far been found. The underlying cause of IC/BPS remains an enigma!

Other possible causes of the symptoms

Pain in the bladder, or pain perceived to be in the bladder, may also be caused by, for example:

- a bacterial, fungal or viral infection of the bladder, including occult infection
- recurrent or persistent urinary tract infections.
- damage following gynaecological, urological or pelvic surgery,
- bladder spasms following hysterectomy
- damage resulting from childbirth
- trauma from accidents such as falls or car crashes.
- lower back injury or excessive sports training (which can also cause incontinence)
- sexual trauma causing nerves or tissue damage
- pudendal neuralgia, entrapped or damaged nerves
- ligament damage
- muscle damage
- chemotherapy-induced cystitis
- radiation-induced cystitis
- medication-induced cystitis
- ketamine-induced cystitis (due to street ketamine abuse)
- bladder endometriosis
- bladder tuberculosis
- tumours
- diverticulosis/diverticulitis

For more examples, see also list of Confusable Diseases, Table 1

Exclusion of infection

The fact that symptoms in many patients may only occur in episodes known as "flares" often leads both patients and their primary care doctors to assume that it must be a urinary tract infection (UTI or bacterial cystitis). If the patient fails to respond to antibiotic treatment, it is essential for a urine culture to be carried out (not just dipsticks) in order to be absolutely certain that a bacterial infection is not the cause of the symptoms.

However...

Having IC/BPS does not rule out the possibility of a patient developing a UTI in addition to their IC/BPS. An infection in an IC/BPS bladder can considerably worsen the IC/BPS symptoms by further irritating the already sensitive and painful bladder wall. In this situation, once an infection has been confirmed, the patient should be treated with an appropriate antibiotic to clear up the infection. Some IC/BPS patients with recurrent UTIs may require prophylactic antibiotic treatment. IC/BPS patients who experience frequent infections should maintain strict hygiene in the urogenital area.

A chronic disease

IC/BPS is a chronic disease. The symptoms do not go away; they persist or keep returning. In some patients, symptoms may gradually worsen, but this varies widely from patient to patient and is not necessarily the case. Finding the right treatment can help to alleviate the symptoms. In patients without Hunner lesions, symptoms may increase very slowly over many years or remain stable or even go into remission.

In contrast, patients with Hunner lesions may experience more rapid progression from early-stage disease to an advanced stage characterized by a shrunken, scarred, and stiff bladder wall (fibrotic bladder) and small bladder capacity under anaesthesia.

However, it is important to emphasize that many patients never progress beyond a relatively mild form of IC/BPS. Moreover, many patients without Hunner lesions have a normal bladder capacity under anaesthesia.

There is currently no evidence to suggest that patients with non-lesion IC/BPS will later develop the lesion type.

Exacerbation and remission

Spontaneous acute flares and remission are a characteristic feature of IC/BPS in many patients. Many women report that their symptoms worsen just before or during menstruation, during ovulation or when taking contraceptive pills. Women may also find that their symptoms temporarily intensify while during the menopause. Any kind of stress, whether physical or emotional, can trigger a flare. Many patients also find that a flare can be triggered by certain foods and drinks, medications or even vitamin supplements. However, patients with Hunner lesions may not necessarily experience these shorter acute flares. Instead, they may have longer-lasting symptom fluctuations when their symptoms may improve or worsen.

IC/BPS can cause immense stress and anxiety

Although many patients may experience a temporary worsening of their IC/BPS symptoms as a result of physical or emotional stress, it is particularly important to emphasize that IC/BPS is not a psychosomatic illness and is not “all in the mind”. The pain/discomfort, frequent and urgent need to urinate both day and night and the resulting lack of proper sleep experienced by IC/BPS patients, together with the impact of the disease on every aspect of the patient’s life, are themselves significant causes of stress, anxiety, exhaustion and depression.

CHAPTER 2 - IMPACT ON LIFE

The IC/BPS patient not only has to cope with the bladder disease itself and its symptoms, but also with the wide-ranging consequences of this disease on daily life. IC/BPS can have a major impact on the patient's social, psychological/emotional, occupational, domestic, physical and sexual life. It can severely affect quality of life and relationships with family, partner and others. Learning how to cope is an essential part of treatment.

“Where am I going to find the next toilet?”

The frequent and urgent need to urinate can form a major obstacle to work, travel, visiting friends, or simply going shopping. This constant worry about the bladder is a major source of stress and anxiety which is often underestimated. Outside the safety of their home, the IC/BPS patient's life is dominated by the question “where am I going to find the next toilet?” Before any 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 can make patients feel anxious and uncertain and afraid to leave the safety of their home. Sadly, some report that they almost never go out at all. And let us not forget the patients in less developed regions of the world where there may be no public toilet facilities at all.

Social isolation

The social consequences of IC/BPS should therefore not be underestimated and may compel a patient to adopt an entirely different lifestyle. Through embarrassment that they need to use the toilet so frequently, patients may no longer visit even their family and friends. Everyday activities such as shopping, going to the cinema or theatre, or simply taking a walk in the park can become difficult or impossible. Their social life may be non-existent and they may feel – and in fact be – completely isolated from the world around them. For some IC/BPS patients, it can feel like living in a state of “lockdown” every single day.

Employment challenges and financial impact – IC/BPS is an expensive disease

The frequent and urgent 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 or career that allows them the possibility of easy, frequent access to toilets. Work in some jobs becomes impossible when a patient needs to keep running to the toilet and may additionally be suffering from fatigue or even drowsy from pain medication. The impact of IC/BPS on work and career may mean missed workdays, job loss or even long-term unemployment causing patients and their family considerable financial strain. This situation is far worse if the patient has no official diagnosis and may have no access to social benefits or medical treatment.

The fact that many treatments – such as many bladder instillations – are expensive and not reimbursed in many countries also adds to the financial burden. IC/BPS can indeed prove to be an expensive and life-changing condition.

Physical and psychological impact of sleep deprivation and disruption

The pain and frequent, urgent need to urinate at night leave patients stressed and exhausted due to 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

profound impact on health as the lack of proper deep sleep leads to both physical and psychological deterioration. This too can make some types of work and everyday activities (such as driving) impossible or hazardous. *See Chapter 6 on Fatigue in IC/BPS patients.*

Emotional impact, depression and frustration

The very fact of having a chronic illness with no known cure can leave many patients very depressed and frustrated. Patients may also feel anger that it took so long to diagnose, that so many doctors may have told them that because they couldn't find any clear cause it must be "all in the mind", stress, psychological...

Patients may increasingly begin to feel that nobody in the medical profession truly believes them. Although the patients know that they have these very real symptoms, they may start to lose their self-confidence and question their own sanity. They may feel a sense of uncertainty, anxiety, helplessness and panic. Depression can cause complete inertia, isolating them from the world. Unfortunately, this situation is sometimes made worse by family and friends who say that if the doctor claims that nothing is wrong, the doctor must be right.

During this period of non-diagnosis, many patients lose faith in the healthcare system and feel rejected by it. The doctor-patient relationship has a great bearing on psychological aspects. Empathy is essential. When doctors dismiss symptoms as purely psychological and show no understanding, patients can become extremely distressed—even suicidal.

Patients long to be able to turn the clock back to when they were normal and find it difficult to look ahead or make plans for the future.

Still taboo and stigmatized

Bladder problems are still taboo in today's world, often leaving sufferers feeling stigmatized and isolated from their friends and social circles. The fact that the condition affects the bladder, which means that patients keep looking for toilets, makes them and everyone else around them constantly embarrassed.

Impact on family life and relationships

IC/BPS has a significant impact on the entire family in many ways. It alters the patient's relationships with their partner and children because the bladder condition makes it difficult to behave like a normal parent or a normal partner. The inability to cope with everyday responsibilities, to look after the family, to participate in normal family activities often leads to feelings of guilt.

Patients may also be so anxious about when the next unpredictable flare will occur that they try to do too much at home for the family or at work, thereby potentially inducing a flare, creating a vicious circle. Other patients may suffer from persistent, debilitating pain that makes them continually exhausted.

Family members often do not understand IC/BPS at all because they cannot see anything visible on the outside. So, unless they are very understanding, they may become resentful at the impact on their own lives. In such case, family counselling – if available - may help family members to understand the problems of the patient and to help the patient solve the needs of the family in a low-stress way.

IC/BPS and its impact on sexual relationships

IC/BPS can significantly affect sexual relationships since sexual intercourse may be painful for both male and female patients. For some women, intercourse may be totally impossible

because the urethra, bladder, vagina and vulva are too painful. Anatomically, the bladder and vagina are close to each other and this can lead to pain, irritation or pressure during penetrative intercourse (known as dyspareunia).

In men with IC/BPS, ejaculation may cause intense pain. Sexual pain affects all aspects of sexual response, including desire, arousal, orgasm, satisfaction as well as intercourse itself. There are two types of pain with intercourse in females: superficial (at the point of entry), often due to inflammation at the vaginal opening, and deep sexual pain. Many patients may experience pain or burning sensation after sexual intercourse.

Sex is a natural and important 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 to try to find solutions together, if necessary with the help of a sexologist/sex therapist or relationship counselling.

Patients themselves may find it difficult or impossible to raise this intimate and embarrassing subject with their doctor. It is therefore crucial for the care provider to raise this issue.

Optimal pain treatment can also help to improve 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!

Practical tips to reduce pain and discomfort during sexual intercourse include:

- taking a warm bath to relax the pelvic muscles,
- urinating before and after sex,
- ensuring good hygiene by both partners to prevent infection,
- use of non-irritating lubricants,
- taking pain relief medication 20 minutes before sex,
- engagement in foreplay to limit thrusting time,
- trying different sexual positions to minimise pain and symptoms,
- exploring alternatives to penetrative sex (“outercourse”) to maintain some level of sexual intimacy.

By addressing both the physical and emotional aspects of sex, patients and their partners can find ways to preserve intimacy and strengthen their relationship despite the challenges of IC/BPS.

Patient support groups

Patients and their families need to be well-informed about IC/BPS, 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 offering emotional and moral support. Patient-to-patient counselling is invaluable since only another patient truly understands what IC/BPS symptoms are really like and their impact on every aspect of life. Contact with other patients can be a great relief and a big step forwards in learning not only about the bladder disease itself but also learning how to cope.

While there is currently far greater awareness of interstitial cystitis/bladder pain syndrome worldwide today and many more patients are now receiving a diagnosis, there are still countries where knowledge of this disease scarcely exists. Greater awareness and education is needed at a primary care level to ensure that patients are referred to an experienced specialist at the earliest possible stage.

CHAPTER 3 - DIAGNOSIS

Patient's role in keeping track of personal medical history

The importance of maintaining a complete medical history should not be underestimated. Everyone should endeavour to keep as thorough a personal medical record as possible with dates (years) of important illnesses, surgery, accidents & trauma, diagnosed diseases and disorders, prescribed medication, allergies & adverse reactions, when the bladder symptoms started and other relevant details. In today's increasingly mobile world where people move around nationally and internationally, it can be challenging for healthcare providers to access a patient's full medical history. A methodical, up-to-date personal record of symptoms, diagnoses and treatment maintained by the patient will not only assist future healthcare providers but also benefit the patient as well.

Referral by family doctor/primary care

Seeking medical help often involves navigating a series of hurdles. 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/bladder pain syndrome.

Diagnosing IC/BPS is a process that starts with referral to a urologist or urogynaecologist by a family doctor or primary care provider. Therefore, it is essential to ensure that these frontline healthcare professionals are aware of IC/BPS and its wide spectrum of symptoms. Early recognition and timely referral to the appropriate specialist are crucial to achieving a correct diagnosis and initiating effective treatment as early as possible. A primary health provider unfamiliar with IC/BPS will quite likely assume that the symptoms are caused by an infection and repeatedly prescribe antibiotics, even when urine tests for infection are negative. This can delay proper diagnosis and prolong patient suffering. Awareness also needs to be increased among gynaecologists since many female patients with extensive pelvic pain may be referred to them. Without awareness of IC/BPS, such patients risk undergoing unnecessary treatments, including radical gynaecological surgeries. These outcomes can often be avoided through better education and awareness of IC/BPS.

If IC/BPS is suspected, it is advisable for patients and their primary care providers to seek out a specialist with expertise and a specific interest in this condition.

Diagnosis by the urologist or urogynaecologist

Currently, due to the lack of specific tests or biomarkers, the diagnosis of IC/BPS is based on:

- **Symptoms:** pain, pressure or discomfort or other unpleasant sensation in the bladder, accompanied by other urinary symptoms such as urgency and frequency during the day and nighttime for more than 3 months*
- **Exclusion:** The absence of any other identifiable infection, disease or disorder that could solely account for 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 noted that the diagnosis of a confusable disease does not necessarily exclude a diagnosis of IC/BPS. A confusable disease and IC/BPS 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 pain symptoms

Currently, there are two recognised main types: Hunner Lesion Disease and non-lesion IC/BPS. Cystoscopy is essential to distinguish between the two.

Diagnosis may be supported by cystoscopic and biopsy findings, including inflammation, mast cells, lesions, pan-cystitis or general mild oedema which may indicate Hunner lesion. If lesions are observed, they should be biopsied to rule out any malignancy. However, it is important to note that in many non-lesion patients with severe symptoms, the bladder may appear completely normal. This does not rule out underlying damage or irritation of the nerves within the bladder wall, which may result from a deficient or leaky glycosaminoglycan (GAG) layer lining the bladder wall.

Excluding other possibilities

Many of the tests and investigations are aimed at excluding all other potential causes of the symptoms, known as confusable diseases or differential diagnoses.

Importantly, the diagnosis of a confusable disease does not necessarily exclude a diagnosis of IC/BPS. They may co-exist. IC/BPS patients can of course also develop bladder infections or may have overlapping IC/BPS and overactive bladder.

See **Table 1** for a list of confusable diseases.

Pelvic pain confusable conditions

Other conditions causing pelvic pain include endometriosis, adenomyosis, ovarian cyst, pelvic inflammatory disease (PID), pelvic congestion syndrome, diverticulitis, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), myofascial/pelvic floor dysfunction, labral tear, osteitis pubis, disc disease, radiculopathy, neuropathy and centralized pain syndromes.

In addition, damage caused to tissue, nerves, ligaments etc due to pelvic surgery can also cause pain that appears to come from the bladder. For example, bladder spasms can be

TABLE 1: CONFUSABLE DISEASES TO BE EXCLUDED INCLUDE:
Carcinoma Carcinoma in situ
Infection with: <ul style="list-style-type: none"> - <i>Intestinal bacteria</i> - <i>Chlamydia trachomatis</i> - <i>Ureaplasma urealyticum</i> - <i>Mycoplasma hominis</i> - <i>Mycoplasma genitalis</i> - <i>Corynebacterium urealyticum</i> - <i>Mycobacterium tuberculosis</i> - <i>Candida species</i> - <i>Herpes simplex</i> - <i>Human Papilloma Virus</i>
Radiation cystitis Chemotherapy-induced cystitis Cyclophosphamide-induced cystitis Tiaprofenic acid-induced cystitis (Street) ketamine-induced cystitis Other drug-induced cystitis
Bladder neck obstruction Neurogenic outlet obstruction Bladder stone Lower ureteric stone
Urethral diverticulum Urogenital prolapse
Urinary tract endometriosis Vaginal candidiasis Cervical, uterine and ovarian cancer
Incomplete bladder emptying (retention) Overactive bladder
Prostate cancer Benign prostatic obstruction Chronic bacterial prostatitis Chronic non-bacterial prostatitis
Pudendal nerve entrapment Pelvic floor muscle related pain
Diverticulosis/diverticulitis of colon

caused by hysterectomy. However, pelvic pain conditions such as endometriosis and other conditions mentioned above can co-exist and overlap with IC/BPS.

Note on (street) ketamine-associated cystitis

Street ketamine abuse has also been increasingly reported in recent years as a cause of ketamine-induced cystitis, presenting with symptoms closely resembling those of IC/BPS. It may cause serious inflammation and lesions and even the need for complete removal of the bladder (cystectomy). This is particularly alarming, bearing in mind that these drug abusers are often young people.

Since use of this cheap drug is spreading rapidly around the world, it is crucial for young people to be made aware of the serious risks it poses to their urinary tract including the kidneys.

Note on urinary tract endometriosis

Endometriosis is a condition affecting female adolescents and women of reproductive age where tissue similar to the lining of the uterus (endometrial tissue) grows outside the uterus, most commonly in the pelvic region, around the uterus, ovaries and fallopian tubes.

Bladder endometriosis is one of the major confusable diseases in women with IC/BPS. Bladder endometriosis is a rare form of the condition that can cause severe discomfort when this endometrial-like tissue grows inside or on the surface of the bladder.

Bladder Endometriosis and IC/BPS share similar symptoms, including:

- chronic pelvic pain lasting 6 months or more
- pain in the bladder
- pain during sexual intercourse
- a frequent and urgent need to urinate both day and night
- symptoms affected by the menstrual cycle

There are two main types of bladder endometriosis: When it forms only on the surface of the bladder, it is called **superficial endometriosis**, and if it develops inside the bladder lining or wall, it is called **deep endometriosis**. Endometriosis in the urinary tract can also affect ureters, potentially causing blockage.

Bladder endometriosis can be detected by cystoscopy when endometriotic nodules are present on the mucosal surface inside the bladder. However, deep lesions and lesions on the outside wall of the bladder can be better visualized with ultrasound or MRI or by laparoscopy. While there is currently no cure for endometriosis, symptoms can be managed through medication and sometimes surgery. A person who does not respond to typical endometriosis treatments may have undiagnosed interstitial cystitis. Nevertheless, the two conditions can occur together.

WHAT INVESTIGATIONS DOES A UROLOGIST OR UROGYNAECOLOGIST CARRY OUT IN ORDER TO ARRIVE AT A DIAGNOSIS OF IC/BPS?

This varies from country to country and may be dictated by economic factors - including the type of healthcare and health insurance systems prevailing in a given country - as well as by the medical facilities available. In some parts of the world, the initial diagnosis may be based on symptoms and basic exclusions, while other countries routinely perform standard investigations such as cystoscopy with/without hydrodistension, and with/without biopsy. However, Hunner lesion disease can currently only be diagnosed with cystoscopy.

Diagnostic procedures may include

- Detailed medical history
- Questionnaires, voiding diaries, body pain maps, pain scales, symptoms scores etc.
- Physical examination
- Vaginal examination in women
- A prostate examination in men
- Laboratory tests including dipstick urinalysis, routine and special cultures, urine cytology
- Serum PSA in male patients over the age of 40 years
- Urodynamics if required
- Flowmetry and post-void residual urine volume measure by ultrasound scanning
- Cystoscopy with/without general anaesthesia, with/without hydrodistension and biopsy
- Laparoscopy

Medical history: First of all a detailed and careful medical history of the patient is taken with special attention to previous pelvic or gynaecological surgery, any history of urinary tract infections, urological diseases or sexually transmitted infections, presence of any rheumatic, systemic, autoimmune diseases (e.g. Rheumatoid arthritis, Sjögren's disease, Lupus), any other chronic pain conditions or other chronic diseases (including e.g. fibromyalgia, irritable bowel syndrome, gastro-esophageal reflux disease, vulvodynia, endometriosis, migraine, facial pain/temporomandibular joint disorder), 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 any memory of an event that appeared to trigger the first attack, such as a bladder infection, surgery, accident/trauma, back or pelvic injury, etc?

Does anything specific trigger the flares? Does the patient have pain with sexual intercourse (dyspareunia)? Does the patient experience worsening or flaring of the symptoms with specific food, drink or medications? Is there increased pain with bladder filling. Is the pain alleviated following urination? Does the patient feel pain immediately after urination? Does the pain increase around menstruation? Does the patient have to get up to urinate during the night?

A history of previous medication prescribed is important since certain drugs have been shown to cause bladder symptoms similar to IC/BPS (e.g. tiaprofenic acid, cyclophosphamide and more recently street ketamine abuse resulting in ketamine cystitis). This list is not inclusive and does not rule out the possibility that bladder inflammation and even lesions may have been caused by other medications prescribed for co-existing conditions.

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

Laboratory tests: Urine dipstick tests and urine cultures will be carried out to check for bacterial infection or other infectious diseases. Special urine, blood or swab tests may be

required to check for the presence of infectious organisms such as Ureaplasma, Chlamydia and Candida which are not detectable with standard 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.

Voiding Charts and Questionnaires for symptom evaluation

The patient may then be asked to fill in **voiding charts** with volume intake and output, as well as **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 (VAS)**. The different questionnaires or scores aim to evaluate the severity 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 useful for documenting symptoms/quality of life and monitoring the patient's progress.

Urodynamics: A urodynamic investigation may sometimes be carried out when deemed necessary by the urologist but is not considered essential for the diagnosis of IC/BPS. It is, however, considered mandatory in men. Urodynamic testing may also be useful in distinguishing IC/BPS from overactive bladder (OAB).

This investigation assesses how much urine the bladder can hold (capacity), when the patient first feels the desire to urinate and whether this is painful. A thin catheter is inserted through 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 inserted into the rectum to measure abdominal pressure.

Urodynamic studies are also indicated if the patient is suffering from any kind of urinary retention or obstruction and either unable to empty the bladder at all or only partially able to empty it.

Imaging: Ultrasound scanning may be performed to assess the amount of urine remaining in the bladder after urination (post-void residual urine). Magnetic resonance imaging (MRI) has been used in studies. Narrow Band Imaging (NBI) currently used in East Asia/Japan is believed to be more effective in detecting lesions.

Cystoscopy: This procedure is essential to diagnose Hunner lesions and to exclude the possibility of cancer and other disorders. It allows the urologist to look inside the bladder and carry out a number of tests and is a standard investigation in urology. A narrow tube is inserted into the bladder via the urethra. This tube has two or more channels: one carrying an endoscope that allows visual examination of the inside of the bladder, while the other channel carries fluid for instillation into the bladder.

There are two main methods of cystoscopy:

- office cystoscopy using local anaesthesia, minimal filling and without hydrodistension and
- cystoscopy under general or spinal anaesthesia with hydrodistension.

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, bladder endometriosis, or signs of infection. It also enables detection of any scarring of the bladder wall or red patches which might indicate **Hunner lesion**. This is particularly important since

Hunner lesion responds well to specific treatments. During the procedure, the urologist will also examine the urethra. In women, a gynaecologic examination may be carried out and in men palpation of the prostate.

Cystoscopy under general or spinal anaesthesia, commonly performed in Europe and Asia, is indicated when IC/BPS is suspected. It allows for hydrodistension during 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 diagnosis of certain specific types of Hunner lesion. In some countries, it is currently questioned whether hydrodistension is relevant as a routine clinical investigation, while in other countries it may be standard. Hydrodistension is sometimes used in selected patients as a form of treatment and can provide temporary relief by stretching the bladder.

More about cystoscopy at: <https://www.niddk.nih.gov/health-information/diagnostic-tests/cystoscopy-ureteroscopy>

Findings from cystoscopic investigations may include:

Hunner Lesion (formerly known as Hunner's ulcer, Ulcerated IC, Classic IC, Hunner Lesion Disease, Hunner IC)

Hunner lesion is a specific type of painful bladder condition and currently considered to be most likely a separate disease. The historical term "ulcer" is misleading since it is not a true ulcer, but rather an inflammatory lesion or form of erosion, also sometimes referred to as a "patch". Bladder distension can cause any scar-like lesions to crack and bleed.

While this classic type of IC/BPS with lesions is believed to be less common than the non-lesion type, it is possible that these Hunner lesions are being under-diagnosed. Efforts are ongoing to ensure that urologists and urogynaecologists can recognise Hunner lesions in the bladder. Narrow Band Imaging may improve the rate of diagnosis. It is particularly important for these bladder lesions to be identified at the earliest possible stage in patients with IC/BPS symptoms since Hunner Lesion Disease tends to respond well to specific treatments.

Professor Magnus Fall from Sweden has described these lesions as follows:

"The Hunner 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." Eur Urol 2008; 53:60-7

See also: Ronstrom C, Lai HH. Presenting an atlas of Hunner lesions in interstitial cystitis which can be identified with office cystoscopy. *Neurourol Urodyn*. 2020 Nov;39(8):2394-2400. doi: 10.1002/nau.24500. Epub 2020 Sep 9. PMID: 32902893.

Note: While the bladders of many non-lesion patients with severe symptoms may appear completely normal, this does not mean that there is no damage or irritation to nerves within the bladder wall caused by a deficient, leaky glycosaminoglycan (GAG) layer lining the inside of the bladder.

Glomerulations are no longer considered diagnostic

Glomerulations or pinpoint petechial haemorrhages are only observed after distension of the bladder. While glomerulations – first named as such by Walsh in Campbell's Urology in 1978 - were once mistakenly thought to be characteristic of IC/BPS, they have also been found in individuals with normal bladders, in patients who have had radiation therapy, have bladder cancer, or have been exposed to chemotherapy or toxic drugs. Conversely, some patients with all the symptoms of IC/BPS show no sign of glomerulations in their bladder.

It has therefore generally been accepted that glomerulations cannot be used as a basis for diagnosis, at least not until further research has clarified their underlying cause. However, when seen, their presence should be recorded.

Bladder Capacity

The term bladder capacity is often used and may be confusing.

- **Functional bladder capacity** is the amount of urine the bladder can hold before the need to urinate is felt. This capacity may be very low in IC/BPS patients.
- **Bladder capacity under anaesthesia** is measured during cystoscopy and is the amount of urine that can be held in the bladder when fully extended.

Other investigations:

Biopsy:

A bladder biopsy may be carried out during cystoscopy. If hydrodistension is performed, biopsy should never be carried out before hydrodistension due to the risk of perforation. Biopsy 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 for example an increased number of mast cells in the detrusor muscle.

Mast cells are involved in allergic and inflammatory reactions in the body's tissues. They can degranulate and release histamine, acting as key mediators of the inflammatory response. Mast cell counts may often be higher in IC/BPS patients than in patients with other bladder diseases but are at present not considered to be sufficiently specific to be used as a diagnosis on their own. We await further research.

The biopsy is important to exclude the possibility of other causes of the symptoms (such as bladder cancer, eosinophilic cystitis, bladder endometriosis and tuberculous cystitis). All lesions or patches should therefore be biopsied.

Biopsy is more likely to be routinely carried out in Europe and Asia than in the USA for example. While cost may play a role here, it is also considered an invasive procedure by some and is often reserved for cases where first-line conservative treatments have failed.

Note: A bladder biopsy may cause a burning sensation for several weeks until the bladder lining has fully healed.

Modified Potassium sensitivity test:

The potassium sensitivity test (PST) as formerly used in the USA and which was studied for some time as a potential way of diagnosing IC/BPS is no longer recommended for diagnostic

purposes as it is felt to be too painful for the patient. A milder, modified form of this potassium test – closer to the original European test - was developed a) to diagnose a hypersensitive and/or leaky bladder wall and b) as a possible way of selecting patients who may respond well to intravesical treatment aimed at temporarily replenishing the lining of the bladder (GAG-layer).

The above tests can temporarily exacerbate the symptoms and cause burning in the bladder, urethra and when urinating for several days or longer.

Anaesthetic challenge test:

Instillation of (alkalinized) lidocaine into the bladder is increasingly being used to assess whether the pain is actually in the bladder or elsewhere. The solution should be held in the bladder for 15-30 minutes. If the pain is coming from the bladder, it will be anaesthetised by the lidocaine. It is also used as a rescue therapy - with or without heparin - to calm severe pain in the bladder.

Reassessment

If a patient fails to respond to treatment for IC/BPS, reassessment is recommended to see if any lesions or any other disease or disorder have been missed.

Negative test results do not necessarily mean that a patient does not have IC/BPS

Even after all these investigations have been carried out, negative results do not necessarily exclude a diagnosis of IC/BPS. Some patients may show no abnormalities during the above investigations but still experience all the characteristic symptoms of IC/BPS. Cystoscopic findings often bear no correlation to the patient's symptoms. There may be very severe symptoms with little or nothing to be seen during a cystoscopy. However, this does not mean that there is no damage to the bladder lining or within the bladder wall.

Diagnosis a relief but...

Many patients will have seen numerous doctors and specialists before finally receiving the right diagnosis. Those who, despite consulting countless different medical professionals, still lack a diagnosis may become desperate due to pain, urgency and frequency, sometimes to the point of feeling suicidal. Many will have been repeatedly told 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/BPS, a disease that actually has a name to it. Patients feel that their long history of pain and debilitating symptoms is finally being taken seriously by the medical community.

On the other hand, it may also be a shock for patients to learn that there is currently no cure and no single standard treatment for the condition.

CHAPTER 4 – TREATMENT

Once a diagnosis of IC/BPS has been established, treatment focuses on alleviating symptoms and improving the patient's quality of life. Despite extensive research, no cure has currently been found for this condition, and there is no single treatment that is effective for all patients. Nevertheless, there are many different therapeutic options to try and personalized care, tailored to the individual, is essential.

If multiple treatments fail to produce a beneficial effect, re-evaluation may be necessary to rule out other conditions that could be causing the bladder symptoms.

Many IC/BPS patients also have additional disorders (often referred to as comorbidities or associated disorders) and may be under the care of several different healthcare providers. It is therefore vital for treatment to be coordinated to avoid potentially harmful drug interactions.

When treating IC/BPS, it is important for any associated disorders to be taken into account as these may significantly influence the treatment approach.

Treatment may include patient education, diet modification, behavioural changes and stress reduction, bladder retraining, one or more oral medications, topical drug treatment, bladder instillations including GAG-layer replenishment, intramural bladder injections, bladder distension, neuromodulation/electrotherapy, surgery, various forms of physical therapy and mind-body therapy, myofascial therapy, trigger point therapy, pelvic floor relaxation, acupuncture, guided imagery, exercise, sex therapy and/or relationship counselling to address sexual problems.

A multidisciplinary approach is therefore essential for successful treatment.

Symptom-driven treatment

Different patients may experience more bother from different symptoms: for example, one patient may find the persistent and/or urgent need to urinate to be the most distressing aspect; another may be most affected by the lack of sleep and resulting exhaustion from getting in and out of bed throughout the night to use the bathroom, while a third may find the pain to be the most intolerable symptom.

Because patients with IC/BPS vary so greatly, treatment must be tailored to the individual. A drug that is effective for one patient may have no effect on another.

Treatment may therefore be symptom-driven, and to maximize its effectiveness, it is important to identify which symptom or symptoms are causing the most bother at each stage of the condition for each individual patient.

In many cases, “phenotyping” may also be necessary.

Evaluation of treatment is hampered by the spontaneous flares and remission of symptoms that are so characteristic of many patients with IC/BPS. It is therefore sometimes difficult to determine whether an improvement is due to the treatment itself or simply by a spontaneous remission.

Phenotyping

Today treatment is often guided by a typing system known as “*phenotyping*”. It is currently believed that IC/BPS comprises a number of different phenotypes, each of which may have its own underlying cause, characteristic presentation and require individualised treatment.

This approach is based on specific characteristics, comorbid health problems and associated disorders in an individual patient, such as vulvodynia, fibromyalgia or migraine, chronic fatigue syndrome, allergies, gastrointestinal disorders such as irritable bowel syndrome (IBS), systemic rheumatic autoimmune diseases (e.g Sjögren’s disease, lupus, rheumatoid arthritis) and depression. These factors may significantly influence treatment choices. A single patient may exhibit more than one phenotype.

Phenotyping is still evolving. Several systems have been developed so far. The first was the UPOINT system, which includes six domains: **U**rinary symptoms, **P**sychosocial dysfunction, **O**rgan-specific findings (e.g., bladder or prostate), **I**nfection, **N**eurologic/systemic symptoms, and **T**enderness of skeletal muscles. This system was later modified into the INPUT system, which stands for **I**nfection, **N**eurologic/systemic, **P**sychosocial, **U**lcers, and **T**enderness of muscles.

The hope is that ongoing and future research will refine these phenotypes to enable more effective, targeted treatments. This is also why taking a detailed medical history remains critically important.

Medicine intolerance

Medicine intolerance—ranging from mild sensitivity to extreme forms of multiple drug and chemical intolerance—can pose a significant challenge for some patients with interstitial cystitis/bladder pain syndrome (IC/BPS). This sensitivity can make treatment, particularly with oral medications, extremely difficult and often frustrating for both the patient and the physician.

While a small number of patients may experience true allergic reactions, many more are likely to suffer from intolerance or non-allergic hypersensitivity. Symptoms may include confusion, dizziness, fainting, balance disturbances, hyperventilation, nausea, gastrointestinal issues, blurred vision, extreme fatigue, or pronounced drowsiness/sedation—even at very low doses. In some cases, these reactions may result from neurological side effects of the medication.

Interestingly, multiple drug intolerance is also seen in some patients with fibromyalgia, suggesting a potential overlap in underlying mechanisms.

Treatment for such patients is largely a matter of trial and error, as standard allergy testing often yields inconclusive results. When prescribing oral medications, it is best to begin with the lowest possible dose—often just a fraction of a tablet. However, this approach does not apply to antibiotics, which must always be taken as directed.

For drug-intolerant patients, intravesical therapy may be a better alternative, allowing local bladder treatment with a minimal risk of systemic side effects.

Patient education

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

This can serve as an important first step towards acceptance and learning how to cope. Informed patients are also likely to understand why they are receiving a specific treatment and what this treatment is aiming to achieve.

Diet modification

Many patients with IC/BPS will soon discover through personal experience that certain foods and beverages appear to worsen their bladder symptoms. Every patient is different in this respect and not all IC/BPS patients appear to be affected by diet. By identifying and eliminating items known to cause irritation based on their own experience, patients can at least avoid unnecessary flare-ups. Patients with milder IC/BPS may even find that diet modification is the only treatment they need. One approach is to follow an elimination diet—starting with a very bland diet and gradually reintroducing foods one at a time.

There are some general guidelines regarding foods and beverages most likely to exacerbate symptoms. A study entitled **Effects of Comestibles on Symptoms of Interstitial Cystitis**, Barbara Shorter, Martin Lesser, Robert M. Moldwin, Leslie Kushner was published in The Journal of Urology in July 2007 and explored the effects of various foods, beverages, and dietary supplements on IC/BPS symptoms. Based on patient questionnaires, the study evaluated 154 items and concluded that many patients with IC/BPS experience worsening of symptoms after consuming specific foods and beverages.

The study identified the most problematic items as those containing caffeine, citrus fruits and juices, tomatoes and tomato products, vinegar-containing foods, and alcoholic beverages—with coffee being the most bothersome. Spicy foods, especially those containing hot peppers (e.g., Indian, Mexican, and Thai cuisine), were also linked to greater symptom exacerbation, suggesting that some component of hot peppers may trigger symptoms. Responses to fruits and fruit juices varied significantly among participants.

Some patients find symptom relief by using alkalizing agents such as calcium glycerophosphate (Preliel®) or, when available, baking soda (sodium bicarbonate)—typically one teaspoon dissolved in a glass of water. However, due to its high sodium content, baking soda should not be used by patients on salt-restricted diets.

Table 2 provides a summary of common foods and beverages that may aggravate bladder symptoms. These are general recommendations, and it is important for each patient to determine which specific items affect their own symptoms.

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

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

A second article reviewing diet in IC/BPS patients was published in 2012: **Diet and its role in interstitial cystitis/bladder pain syndrome (IC/BPS) and comorbid conditions**. Friedlander JI, Shorter B, Moldwin RM. BJU Int. 2012 Jun;109(11):1584-91. The authors suggest that “a controlled method to determine dietary sensitivities, such as an elimination diet, may play an important role in patient management.” They also suggest that associated disorders should be taken into account since these may influence diet sensitivities.

- **Avoid Cranberries!**

Cranberries originate from America where the native inhabitants used them both as food and medicine. They later became a folk remedy for urinary tract infections. However, these berries are highly acidic and can intensely irritate the bladder of IC/BPS patients who should avoid both cranberries and their juice. Many IC/BPS patients are unaware of this and unwittingly make their bladder symptoms worse.

- **Not only food and beverages...**

Some patients also find that their bladder symptoms increase when taking certain **oral medications**, for example antibiotics, and certain food supplements such as Vitamin C tablets. If it is an essential short-term treatment, it may be a question of enduring the discomfort 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 an alternative option.

- **Fluid intake**

Patients with IC/BPS often restrict fluid intake before going out and may significantly reduce their intake when away from home for extended periods. This can lead to dehydration and concentrated urine, which may, in turn, worsen pain and symptoms. The persistent fear of not being able to find a toilet in time, of developing severe pain and discomfort and being unable to cope with the situation often leads patients to develop coping strategies that involve drinking less. It is nevertheless important to maintain a balanced fluid intake. It should be noted that although limiting fluids in the evening can help to reduce night-time urination, it may result in concentration of the urine and more pain!

- **Keeping bowels healthy**

Avoiding constipation is crucial since it can increase pelvic floor pressure and worsen symptoms. It is essential for IC/BPS patients to ensure that their diet contains adequate fibre in addition to drinking sufficient fluids and taking regular **exercise** in some form.

Many IC/BPS 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 not tolerated, mild laxatives may be necessary. It is important to note that some drugs used to treat IC/BPS 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, in addition to diet, the symptoms of IC/BPS can also be exacerbated by physical or emotional stress which can trigger flare-ups. It is therefore important for them to learn to pace themselves and avoid situations which lead to physical or emotional

exhaustion, while still ensuring they get adequate physical exercise. Effective treatment for the most bothersome symptoms can also contribute to stress reduction, since not only chronic pain, but also urgency and frequency can be highly stressful, physically exhausting and cause great anxiety.

Some patients may benefit from professional counselling to help them cope with the impact of the disease on their lives and to manage the stress, depression and anxiety which this disease causes. Relaxation techniques, breathing exercises, yoga, meditation may all help.

- Clothing & hygiene

IC/BPS patients often feel more comfortable wearing loose-fitting clothing and prefer cotton underwear rather than synthetic underclothes. Care should be taken when selecting laundry detergents, as products containing perfumes or fabric softeners can cause irritation. The same applies to personal hygiene: no perfumed products should be used near the urogenital area. Patients suffering from vulvodynia, vulvovaginal/perineal pain or sexual pain should be especially cautious with potential irritants such as soaps, powders, shampoo, hair conditioners, shower gel, intimate sprays, detergents and fabric softeners, deodorant tampons and even the adhesive on the back of minipads.

- Adapting lifestyle

IC/BPS often necessitates a change in lifestyle. A patient has to learn to adapt to the needs and the situation created by the bladder disorder. With mild IC/BPS, these changes may be minor; with severe IC/BPS, 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 may feel they are no longer able to undertake due to their bladder condition.

- Relationships and intimacy

Sex therapy and/or relationship counselling may help some patients to deal with intimacy problems. Many of the patient support groups can offer valuable advice and guidance on this topic.

- IC/BPS in the elderly

IC/BPS may pose additional challenges for elderly patients. Frequent urination at night may be hazardous and increase the risk of falls and fractures. A commode chair placed next to the bed could be an option here. Some medications used to treat IC/BPS and overactive bladder can have cognitive side-effects which may be more pronounced in the elderly, potentially worsening any existing memory impairment or confusion. Drowsiness from pain medication can also create additional hazards in the elderly.

ORAL TREATMENTS

Various oral treatments (tablets, capsules or syrups taken by mouth) are used for IC/BPS. The advantage of oral treatment is that it is easy to administer and non-invasive. However, it also has a number of disadvantages. When medication is taken orally, it is absorbed into the body. The desired effect may be achieved via the bloodstream or via the urine when the active medication has been excreted through the kidneys. This process naturally takes some time and only a small amount of the medication may actually reach the bladder or remain there for

long enough to be effective. Because the drug enters the bloodstream, side-effects may also occur in other organs. All medications (including herbal or natural remedies) can potentially cause side effects, but these vary greatly from patient to patient.

Some doctors prefer a multimodal approach, aimed at alleviating the different symptoms of pain, frequency and urgency with a combination of different oral drugs. Others prefer to try one drug at a time, often starting with low doses and slowly increasing to the maximum tolerated level. The single drug approach may be more suitable for patients known to have sensitivities or intolerances to medication.

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

- antidepressants
- anti-inflammatory drugs (including corticosteroids)
- antispasmodics and anticholinergics
- anticonvulsants
- histamine-receptor antagonists
- immunosuppressive agents
- painkillers (analgesics)
- pentosan polysulfate sodium (PPS)
- prostaglandins

The drugs are discussed below in alphabetical order.

Antidepressants (tricyclic)

This mainly concerns **amitriptyline**, although nortriptyline and doxepin are also used. Tricyclic antidepressants, now widely used in the management of chronic and neuropathic pain, are prescribed for the treatment of IC/BPS because they are believed to block the release of histamine, inhibit the reuptake of serotonin + norepinephrine, act as 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 with 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 associated with IC/BPS. It is generic, inexpensive and widely available. It is best taken with the evening meal as this timing can help improve sleep and reduce the risks of a morning “hangover”. Although traditionally used as an antidepressant, this drug is additionally believed to have multiple qualities including pain relief, smooth muscle relaxant, mast cell stabilising action sedative and relief of neurogenic pain which is why it is used for IC/BPS. 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).
However, side effects can be a significant drawback and may include constipation, dry mouth, urinary retention, weight gain, palpitations and daytime drowsiness.

Further information may be found at:

<https://www.ncbi.nlm.nih.gov/books/NBK537225/>

AMITRIPTYLINE, by Amit Thour, Raman Marwaha
 In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
 2022 Feb 7. PMID: 30725910 Bookshelf ID: NBK537225. Free Books & Documents

Anti-inflammatory drugs

While there appears to be a subtype of IC/BPS patients without inflammation who will not respond to anti-inflammatory drugs, some form of bladder inflammation has always been held to be a common feature of IC/BPS. There are several different groups of anti-inflammatory drugs including the following.

- **Corticosteroids** (e.g. hydrocortisone, prednisolone and dexamethasone) are a class of drugs with strong anti-inflammatory effects. 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 for selected patients. While a study indicated that prednisolone may be very effective in pain control in refractory patients with bladder lesions, it may also show (even radical) benefits in some IC/BPS patients without lesions who have a history of associated systemic autoimmune disease.
- **Montelukast** (e.g. Singulair®), a medication commonly used to treat asthma and allergy, works by inhibiting the release of leukotrienes from mast cells and other cell types, thereby preventing inflammation. Danish studies have shown that treatment of IC/BPS patients with a daily dose of montelukast resulted in a significant improvement in urinary frequency and pain.
 - **Warning:** the FDA recently noted that there have been continued reports of neuropsychiatric side-effects, including suicidal thoughts or actions, and has insisted on prominent warnings being given to prescribers.
- **NSAIDs** (Non-steroidal anti-inflammatory drugs) inhibit the production of prostaglandins, substances that play an important role in stimulating inflammation as well as 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 include aspirin, diclofenac, naproxen and ibuprofen.

Newer NSAIDs, known as 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 with proton pump inhibitors) may be necessary. Most older and the newer NSAIDs increase the risk of ischaemic vascular disease.

Warning: there have been reports, backed up by studies, that the NSAID tiaprofenic acid may cause bladder symptoms in some people similar to those of IC/BPS.

- **Tanezumab**, a humanized monoclonal anti-nerve growth factor antibody, is a single-dose intravenous drug that underwent clinical trials to reduce pain in IC/BPS patients. It is more likely to improve pain in women than in men.

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 as a transdermal patch), propiverine and the newer fesoterodine fumarate. These medications are standard treatments for overactive bladder syndrome (OAB) but may be also effective in some IC/BPS patients as part of combination treatment, especially in patients with overlapping IC/BPS and OAB.

- **Oxybutynin** is an older anticholinergic drug, but now available in both a transdermal patch system and extended release tablets. A recently recognised issue with patches is the development of erythema and pruritus at the application site. Side effects have consistently been a problem with this medication.
- **Tolterodine**, also an anticholinergic drug, was developed specifically for the treatment of overactive bladder. It is reported to have fewer adverse effects (e.g. dry mouth) than oxybutynin and may be beneficial in some early stage IC/BPS patients.
- **Trospium chloride**, a drug used to treat overactive bladder symptoms, may also be effective in IC/BPS patients with an urgency-frequency problem. It works by blocking cholinergic receptors on bladder muscle cells, thereby inhibiting the action of acetylcholine. This relaxes the bladder muscle and helps stabilise the bladder. Newer drugs in this class such as darifenacin and solifenacin are believed to have fewer side-effects and are generally better tolerated.

Although these drugs may have a sedative effect on the bladder in some patients, longer-term use has been found to cause urinary retention or difficulty urinating. All drugs in this class tend to have bothersome side effects, the most common of which include dry mouth, dry eyes, dry nose, blurred vision, headache, constipation, drowsiness, dizziness and palpitations. Cognitive side-effects can also occur, particularly in elderly patients. The maximum dose of drug therapy is usually determined by the patient's tolerance of these side effects. Newer and once-daily drugs generally have fewer side effects.

Anticonvulsants:

- **Gabapentin** (Neurontin®) is an anticonvulsant medication used to help control certain types of epileptic seizures. It has also been found to be effective in treating neuropathic pain and postherpetic neuralgia. Gabapentin is being used experimentally used for IC/BPS and other types of genitourinary pain. It may yield positive results in some IC/BPS patients with severe pain and could help reduce dependence on opioids. A newer drug in this class is **pregabalin** (Lyrica®) which is also being used for some IC/BPS patients. A common side effect of these medications is drowsiness/sedation.

Immunosuppressive agents:

- **Cyclosporine A** is an immunosuppressive medication that suppresses immune system activity, thereby decreasing inflammation and tissue damage. This drug is commonly used to prevent rejection of organ transplants and to treat severe psoriasis, rheumatoid arthritis and various other autoimmune diseases. Small-scale studies using low dose cyclosporine A have suggested that it may be effective in some IC/BPS patients. However, due to the potential for serious side effects, it should be reserved for the most severe cases that have failed to respond to other treatments.

Histamine-receptor antagonists

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

- **Hydroxyzine:** The use of the H1-receptor antagonist hydroxyzine is based on the hypothesis that histamine released by the mast cells contributes to the symptoms of IC/BPS. Increased levels of mast cells have been found in the lining of the bladder of some IC/BPS patients, possibly indicating an allergic or autoimmune reaction. Hydroxyzine inhibits the release of histamine from mast cells and also has sedative properties. This type of treatment may be beneficial for patients with a history of allergies. It may take up to 3 months for to see an effect. Dosage: 10 to 25 mg every night at bedtime for the first week; then up to 75 mg a day.
Side effects: can cause drowsiness and, in elderly patients, confusion.
- **Cimetidine and ranitidine** are H2-receptor antagonists or blockers traditionally used to treat peptic ulcers and acid indigestion. However, while they appear to be useful in alleviating the pain and symptoms of some IC/BPS patients, this has never been definitively proven. Nevertheless, they are still recommended in many guidelines.

L-Arginine occurs naturally in the body as an amino acid, one of the building blocks of protein. It plays a role in supplying the body with nitric oxide, which helps to keep blood vessels dilated and improve blood flow. Its use in IC/BPS is controversial and studies suggested that it may have little effect. However, it has recently re-emerged in research studies, so should not be written off as a potential treatment.

Painkillers (analgesics)

Pain management is a crucial aspect of treating IC/BPS patients. However, some painkillers may cause sedation and drowsiness.

- **Standard over-the-counter (non-prescription) painkillers** may provide relief if the pain is mild.
- **Methotrexate** has shown a significant improvement in pain in IC/BPS 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 (e.g. codeine, tramadol, morphine, oxycodone, oxymorphone, hydromorphone, fentanyl). Opioids are potent analgesics and are only used to relieve the most severe pain. However, 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 is best managed in a pain management clinic. Continual evaluation and monitoring is required. Patients should be counselled about the risk of driving and undertaking certain types of work when being treated with opioids. Serious misuse of opioids, such as in the USA, has led to a reluctance to prescribe.
- **Painkillers in the form of suppositories** can also be used (e.g. paracetamol, paracetamol with codeine) and are sometimes advisable for patients with gastric disorders.
Skin 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.

- **Palmitoylethanolamide (Normast®)** is a relatively new painkiller with anti-inflammatory and anti-pain effects for chronic pain conditions and is claimed to have negligible side effects. Available in tablet form or as powder in sachets.
- **Phenazopyridine** (Pyridium, AZO) is a urinary tract analgesic used for short-term relief of pain in the bladder. Not advisable for long-term treatment as it can accumulate in the body and cause harmful side effects.
- **Tapentadol** is a newer opioid analgesic available as a standard-release tablet for moderate to severe acute pain and as a prolonged-release tablet for severe chronic pain. It is said to have fewer side effects than comparable opioid-based drugs.

Warning: 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. This is known as ketamine-associated urinary dysfunction or ketamine cystitis. It can also cause severe damage to the kidneys. Clinical use of ketamine (in much lower doses than street ketamine) is not believed to have any detrimental effect on the bladder but should nevertheless be used with caution.

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)

One cause of IC/BPS is believed to be a defect in the glycosaminoglycan (GAG) layer which acts as a protective lining for the bladder wall, preventing it from being damaged by irritant elements in the urine.

Pentosan polysulfate sodium (PPS) is a semi-synthetic, heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles the GAG layer. PPS is a low molecular weight heparin-like compound, with anticoagulant, fibrinolytic, and anti-inflammatory properties. It is believed that PPS temporarily repairs the GAG layer, thereby protecting the underlying bladder wall.

This medication is obtainable in tablet or capsule form in the United States, Canada, Australia and Europe under the name Elmiron®, which is approved by the FDA and EMA.

Oral forms of PPS are also available in India (Comfora®, Cystopen®) and Korea (Jelmiron®, Gagron®, Penpol®). However, different brands are not the same and may vary structurally and biologically from the active ingredient PPS as used in Elmiron® (*Lenhart D et al.: Chemical and biological differences between original and mimetic pentosan polysulfates. Carbohydr Polym. 2023 Nov 1:319:121201. doi: 10.1016/j.carbpol.2023.121201.*)

PPS is often used in combination with amitriptyline and hydroxyzine as “multimodal” therapy.

Several studies have been carried out in with the oral form and have produced mixed results, but some suggest it may have a beneficial effect in some patients. PPS typically take 12 to 16 weeks to show an effect, with some studies indicating it may take as long as 6 months. The duration of treatment is now considered more important for efficacy than increasing the daily dose. Being an oral drug, not all of the medication will reach the bladder. PPS is used as a

second-line treatment, when other oral drugs have failed to show any improvement. (See also intravesical treatment).

Possible side effects include reversible hair loss, gastrointestinal pain, diarrhoea, nausea, rash, and dizziness. Due to its blood thinning effect, it may not be suitable for some patients. The usual dosage is 100 mg three times a day.

Warning: Studies have indicated that long-term use of oral PPS may cause (severe) eye problems (retinol maculopathy) in some patients. An annual eye-check with an ophthalmologist is therefore recommended, particularly if any eye problems are being experienced. It is also recommended to have an eye-check before starting PPS oral treatment.

Prostaglandins:

- **Misoprostol**, an oral prostaglandin E₁ analogue, used to treat gastric ulcers resulting from the use of certain NSAIDs, has also been found successful in treating some IC/BPS patients. One study found that misoprostol was effective in reducing IC/BPS symptoms, with a significant response rate in patients who tolerated the medication. However, adverse drug effects were reported in a considerable portion of the study participants.

Suplatast tosilate (IPD-1151T)

An anti-allergic agent from Japan, efficacious for allergic diseases, with anti-asthmatic, anti-inflammatory and antifibrotic activity, that inhibits the release of histamine and tumour necrosis factor alpha. While early reports from Japan suggested it increased bladder capacity and improved symptoms, a later study showed no significant difference between this and placebo. It is still used in Japan but for non-lesion disease rather than Hunner Lesion. It has been suggested that it may work for bladder-centric, specifically neurogenic inflammation-mediated IC/BPS.

TOPICAL TREATMENT (ON THE SKIN)

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

VAGINAL & RECTAL TREATMENT FOR PAIN

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

SUBCUTANEOUS INJECTION: Experimental Treatments

- **Adalimumab** sold under the brand name Humira®, is a tumour necrosis factor (TNF) inhibitor, a protein that plays a role in inflammation, reducing inflammation and associated symptoms. It has been investigated for the treatment of IC/BPS, but the results have been inconclusive. While studies show a statistically significant improvement compared to baseline in IC/BPS patients, adalimumab has not been shown to be more effective than placebo due to a significant placebo effect. Is given as an injection under the skin.
- **Omalizunab**, an anti-IgE antibody, has been explored as a potential treatment for IC/BPS. While primarily used for severe allergic asthma, studies have suggested its potential benefit in other conditions, including IC/BPS, due to the involvement of IgE and mast cells in the disease process. Given as injection under the skin.

INTRAVESICAL AND INTRAMURAL BLADDER TREATMENT

Intravesical therapies are treatments for bladder-based pain where the medication is applied directly into the bladder or onto the bladder wall by means of **instillation** of fluids.

Intramural treatment involves injecting the medication into the bladder wall itself.

Intravesical treatment ensures that the medication immediately reaches the target site and far higher concentrations come into contact with the bladder wall than in the case of oral medication.

One of the main advantages of bladder instillations is that side effects are limited, as the short treatment duration results in minimal absorption of the drug into the bloodstream.

A disadvantage, however, is that the patient has to be catheterized to allow the bladder to be emptied and the medication to be instilled. This procedure always carries a risk of infection. To reduce this risk, antibiotics may sometimes be given – either orally or intravesically - along with the instillation.

When self-catheterizing at home, maintaining scrupulous hygiene is essential. This includes thorough cleansing of the area (e.g. front to back cleaning for women), using disposable plastic gloves and following sterile techniques to minimise the risk of infection.

Catheterization can be uncomfortable or even painful for IC/BPS patients. Application of lidocaine gel in the urethra before insertion of the catheter may help to reduce urethral discomfort on catheterization.

Some patients may also experience “rebound pain”, either immediately after instillation or several hours later. In some cases, this discomfort can persist for 1 or more days.

A new **minimally invasive device for intravesical instillation** has been developed in Budapest. This urological syringe adapter, known as the UroDapter® and also as the laladapter®, is designed to deliver solutions directly into the bladder through the urethra. It offers a potential catheter-free alternative for patients who experience significant (urethral) pain when catheterising. Additionally, it may help reduce the risk of catheterisation-related infections. When used for self-instillation at home, it requires good eye/hand coordination, particularly in female patients.

Drugs used for intravesical instillation can be used alone or as a cocktail combining several active ingredients. These may include, for example, a steroid, an antibiotic, dimethyl sulfoxide (DMSO), heparin, pentosan polysulfate sodium (PPS), a painkiller (analgesic) such as lidocaine

combined with sodium bicarbonate (which alkalizes the lidocaine and helps absorption), hyaluronic acid (HA) or chondroitin sulfate (CS). A course of treatment may consist of just a few instillations or numerous applications.

The so-called **anaesthetic cocktails** used for immediate pain relief and as a rescue treatment usually comprise (alkalinized) lidocaine, with or without heparin. The effect may last for several days or even weeks. In some patients, lidocaine with or without alkalization can occasionally briefly cause mild systemic side effects of short duration.

Some of the drugs used for bladder instillation aim to replenish a suspected deficiency in the GAG (glycosaminoglycan) layer of the bladder. This protective layer lines the bladder wall and protects the underlying layers of the bladder wall from penetration by toxic or irritating substances in the urine and infection. This GAG layer is believed to be impaired in patients with IC/BPS.

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

Instillations can be administered at the urology clinic or hospital. However, if instillations are required once or more per week, or if the cost is not reimbursed, patients can be taught self-catheterization to administer the treatment at home. Many patients find this an advantage, but for female patients it requires good eyesight and hand/eye coordination since the patient has to insert the catheter using a mirror reflection for guidance. Not all patients are able to manage this. The most patient-friendly method is treatment provided in a pre-filled syringe.

TREATMENTS USED FOR BLADDER INSTILLATION (ALPHABETICAL ORDER)

Antibiotic: an antibiotic is sometimes added to bladder instillation cocktails to help prevent bladder infections due to catheterization. Alternatively, a single preventive (prophylactic) oral dose can be taken. However, long-term use of antibiotics should be avoided due to the risk of developing antibiotic resistance.

BCG (Bacillus Calmette-Guérin), originally developed as a vaccine against tuberculosis, BCG has been used to treat different types of bladder cancer. It induces an immune response leading to the production of several cytokines, some of which have antiangiogenic properties, meaning they inhibit the formation of blood vessels necessary for tumour growth. Despite some positive results in the past in treating IC/BPS patients, more recent studies suggest that it is likely ineffective in IC/BPS and is therefore **not recommended**.

Bupivacaine is a local anaesthetic that provides long-acting local pain relief when instilled in the bladder. It is more lipophilic and potent than lidocaine and may be used in patients who do not respond to intravesical lidocaine. (a typical dosage is 20 ml of 0.5% bupivacaine). It can be used alone or in cocktails and is 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 that mimics a substance that occurs naturally in the bladder GAG layer. Treatment with chondroitin sulphate is thought to replenish deficient chondroitin sulfate in the GAG barrier, thereby helping to prevent urinary irritants from penetrating the bladder wall. Studies have indicated that it is safe, effective and well-tolerated. It can be used alone or in combinations. In addition to IC/BPS, it may also benefit patients with 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.

Dimethylsulfoxide (DMSO) is one of the most commonly used drugs for bladder instillation and is one of only two drugs for IC/BPS approved by the American Food and Drug Administration (FDA). It is often the first drug to be tried due to its multiple beneficial properties for IC/BPS. DMSO is believed to be anti-inflammatory, analgesic and to relax the bladder muscles.

The symptoms may temporarily worsen for a few days following treatment but often then show an improvement. The full therapeutic effect may not be apparent for several weeks. In some patients the symptoms may worsen after the first few treatments.

A small amount of the DMSO penetrates the bladder wall and is excreted via the lungs, causing a characteristic garlic-like taste and odour on the breath and skin, which may last for up to 72 hours after treatment.

Combination in cocktails with other agents may be more effective than DMSO alone, for example DMSO plus a steroid, heparin, sodium bicarbonate and an antibiotic.

Studies have shown that patients who have undergone a period of treatment with DMSO instillations and have responded well, often maintain their improvement if they then receive a monthly maintenance therapy of heparin instillation. This approach looks promising for patients who respond favourably to DMSO, although symptoms can still worsen in some patients.

Doxorubicin (Adriamycin®) is a chemotherapy drug primarily used in the treatment of cancer. It has been used experimentally with some positive results, as a bladder instillation for IC/BPS patients with severe Hunner lesions.

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

Hyaluronic acid, also known as **Sodium hyaluronate** or **hyaluronan**, is a GAG-replenishment treatment and a naturally occurring substance found in the GAG layer of the bladder wall as well as in all connective tissues. Like chondroitin sulfate, heparin and PPS, it is believed to temporarily repair a damaged GAG layer, thereby reducing the pain, urgency and frequency

associated with IC/BPS. Sodium hyaluronate generally well tolerated. This treatment is also used for other (painful) bladder conditions including radiation cystitis, chemically induced cystitis, overactive bladder and chronic bacterial cystitis. Studies suggest that patient selection for this treatment can be improved using the modified potassium sensitivity test or the lidocaine anaesthetic challenge test.

A combination of **Hyaluronate acid + chondroitin sulphate** is also available as a single intravesical treatment and this has shown promising results so far. Brand names include iAluril®.

Lidocaine (a local anaesthetic) is used to treat bladder pain. It may be administered 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 to relieve severe pain during a flare. Alkalinized lidocaine is also used in the anaesthetic challenge test to help determine whether the pain is actually originates from the bladder.

Liposomes are essentially globules of fat. When used intravesically, they are believed to help the absorption of other drugs they are combined with. One area of ongoing research involves liposomes combined with botulinum toxin. Another hypothesis is that liposomes may be beneficial when used alone by forming a temporary protective film over the bladder lining, potentially preventing the penetration of irritants in the urine and promoting wound healing. One study reported a reduction in pain and urgency. However, this treatment remains experimental.

Oxybutynin chloride, an older drug commonly used for overactive bladder, is also occasionally used as a bladder instillation in the treatment of IC/BPS, often as part of a combination therapy. It works by increasing bladder capacity and reducing bladder spasms, thereby decreasing urinary urgency. When administered intravesically, it is associated with fewer side effects than the oral form.

Pentosan polysulfate sodium is used intravesically as well as orally, and in this form it appears to be more effective and better tolerated than when taken orally. Its primary actions are believed to include strengthening the GAG layer of the bladder, reducing pain, and exerting anti-inflammatory effects. However, as it does not appear to be highly effective for all IC/BPS symptoms, it is typically used in a combination cocktail with other drugs.

Resiniferatoxin, a member of the vanilloid family, is an intravesical treatment with a desensitising effect. It has been used to treat overactive bladder and painful bladder syndromes. It is significantly more potent as a pain reliever than capsaicin (an extract of chilli peppers) and is reported to cause far less burning and irritation. While studies with RTX® in the United States failed to show any significant benefits for IC/BPS patients, some international studies were a little more positive and it does appear to help a few patients. A new, more stable formulation of RTX is now available and may prove to be more effective.

Tacrolimus is an immunosuppressive agent used to prevent rejection of transplanted organs. It is currently being investigated as an intravesical therapy for IC/BPS patients. As an immunosuppressive drug, tacrolimus also has potential in treating autoimmune diseases. While one recent study showed

that it may have a range of side effects, studies conducted in India have shown some success. The most commonly reported side effects are tremor, headache, abdominal pain and pruritus.

Triamcinolone is a steroid often used in bladder instillation cocktails in patients with Hunner lesion. Also used as a submucosal injection in the bladder, see below.

DRUGS USED FOR INTRAMURAL BLADDER INJECTION

Botulinum toxin A, a neurotoxin produced by the bacterium *Clostridium botulinum*, is the most potent biological toxin known to man. In recent years, it has generated significant interest in the urological world as a potential treatment for urethral and bladder dysfunction. Botox is injected into the bladder, typically via submucosal injections, preferably into the trigone. The therapeutic effects wear off after some months, even up to a year, but treatment can then be repeated as needed. Ongoing clinical trials are investigating its use in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). The mechanism of action involves reducing bladder sensation and suppressing detrusor muscle contractions.

Studies have produced mixed 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 urinary retention when injected into the trigone.

This is still experimental and not yet approved for IC/BPS, although it may help some patients. A study from Taiwan found that this treatment may be effective in non-lesion bladder pain syndrome but not in patients with Hunner lesions.

Triamcinolone submucosal injection has shown promising results for the treatment of **Hunner lesion**. Under general anaesthesia, triamcinolone (40mg/cc) is 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 approximately 66% of patients with Hunner lesion.

Gene-gun therapy is an experimental approach being investigated for IC/BPS. It involves the use of a gene-gun to deliver narcotic genes directly into the peripheral nerves of the bladder to suppress bladder pain responses. This method remains under research.

EMDA – ELECTROMOTIVE DRUG ADMINISTRATION

EMDA is a method of accelerated delivery of drugs deep into the bladder using a mild electric current. It is considered to be a safe and effective approach of treating IC/BPS. Studies have shown that EMDA can significantly improve and prolong symptom relief compared to standard drug instillation.

HYPERBARIC OXYGENATION

Studies into Hyperbaric Oxygenation (HBO) have shown encouraging results with IC/BPS patients. The patient is placed in a pressurized treatment chamber and breathes 100% oxygen. Already an established therapy for radiation cystitis, HBO appears to be safe and has yielded moderately good results in a small number of IC/BPS cases. However, it is costly and not widely available.

BLADDER HYDRODISTENSION OR INFLATION (STRETCHING)

Bladder hydrodistension or bladder stretching is not only used for diagnostic purposes but also sometimes for the treatment of IC/BPS in selected patients. This method has been employed since the 1930s with varying levels of success. It involves filling the bladder beyond its known capacity. One technique is the Helmstein method, in which the bladder is distended under epidural anaesthesia using a balloon for three to six hours.

While some patients experience temporary symptom relief, many report symptom recurrence within three months. Overall, the procedure is estimated to benefit about 30%–50% of patients. However, hydrodistension may temporarily worsen symptoms for a few days following the procedure. Its effectiveness remains inconsistent, and its use should be approached with caution—especially in patients with known or suspected Hunner lesions—due to the increased risk of bladder perforation and bleeding.

NEUROMODULATION / ELECTROSTIMULATION (NERVE STIMULATION)

An important development in the field of urology is neuromodulation of the sacral or pudendal nerve roots for the treatment of bladder dysfunction and urinary incontinence. Neuromodulation is a potentially valuable form of treatment for selected patients; however, it remains expensive and is neither available nor affordable in many countries. The principle of neuromodulation is not new. Electric stimulation has been used as a pain therapy since the 1960s (e.g. TENS, see below). It works by reconditioning the nerves that control bladder function, inhibiting contractions of the bladder and restoring normal bladder function.

TENS (TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION)

The oldest form of nerve stimulation is TENS. It 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 lower back. Electric stimulation is generated by a small portable unit. The mild electrical pulses of TENS can relieve pelvic pain, relax bladder muscles and, in some cases, reduce urinary frequency. The patient can adjust the electrical stimulation to different intensities and frequencies, making TENS a versatile and flexible tool for self-management. Scientists believe that by stimulating nerve fibres with TENS, pain signals transmitted to the brain are blocked. TENS is also thought 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.

TENS (TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION)

Transcutaneous Electrical Nerve Stimulation (TENS) can be used at home by patients as and when they wish to alleviate pain in combination with other conventional treatments. It is non-invasive, inexpensive, has no serious side effects and may help some patients. Electric stimulation is generated by a small portable unit. Mild electric pulses are transmitted into the patient's body by placing electrode pads on the suprapubic region or the lower back. Many IC/BPS patients in different countries use TENS as a form of (supplementary) pain control. Stimulation of nerve fibres with TENS is believed to help block pain receptors. The mild electrical pulses of TENS can relieve pelvic pain, relax bladder muscles and, in some cases, reduce urinary frequency. The patient can adjust the electrical stimulation to different intensities and frequencies, making TENS a versatile and flexible tool for self-management.

PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS)

Percutaneous Tibial Nerve Stimulation (PTNS) is a neuromodulation technique intended to treat patients suffering from overactive bladder (OAB) and associated symptoms of urinary urgency, urinary frequency and urgency incontinence. It can be administered in an outpatient setting. It may be useful in IC/BPS patients with predominant urgency and frequency symptoms. PTNS involves nerve stimulation via a fine needle electrode inserted near the tibial nerve located near the ankle. Electrical stimulation is applied 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 and pelvic floor function.

Treatment consists of 30-minute sessions once a week while the patient sits comfortably. PTNS has shown very positive results in OAB patients, especially those for who have tried other therapies or drugs without success. After 12 sessions, if the symptoms have subsided or improved, the patient may need occasional on-going therapy to sustain their symptom improvement. In clinical studies this averages about one session a month. The implantable version of the device may be helpful in selected patients.

INTERSTIM® SACRAL NERVE STIMULATION (SNS)

Interstim® Sacral Nerve Stimulation is a neuromodulation option for patients who have failed to respond to standard treatments and have long-standing, debilitating symptoms. This therapy is used for an overactive bladder characterised by 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 (urinary retention).

This treatment has been used to treat the above-mentioned symptoms for some years now and has a long-term success rate of about 70% in patients who show a positive Percutaneous Test Evaluation. In recent years, experience has also been gained in treating IC/BPS patients, with encouraging results published.

PUDENDAL NERVE STIMULATION (PNS)

Pudendal Nerve Stimulation is performed in a similar manner. The procedure consists of two phases: test stimulation and implantation: During the test stimulation procedure, a temporary electrode is implanted low in the patient's back and 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 proceed with implantation is based on the information recorded in the journal before and during the test stimulation and on the patient's experiences. A permanent implant is recommended if there is at least a 50% improvement in the patient's symptoms.

For the permanent implantation, a permanent electrode is implanted in the lower back and connected to a kind of pacemaker (a battery-powered pulse generator) that delivers a continuous, low level or mild current to the relevant nerves.

SURGERY ON THE BLADDER AND LOWER URINARY TRACT

In some IC/BPS patients, their bladder problems can be so severe that surgery remains the only viable option. However, this decision should not be taken lightly since IC/BPS is a complex disease and surgery may lead to additional complications. It is therefore essential for patients

to fully understand what the procedure involves, along with its potential side effects and long-term consequences. Careful patient selection is crucial.

One complication that may occasionally occur following removal of the urinary bladder is "phantom pain", which could be related to local tissue damage.

Surgery options include bladder augmentation, urinary diversion, and partial or complete cystectomy. These procedures should only be performed by experienced surgeons.

Irreversible surgical options should be considered only after all conservative treatment options have failed. The patient must be thoroughly informed about all aspects of the procedure and clearly understand the potential risks and outcomes.

Bladder augmentation cystoplasty

Also known as a clam cystoplasty, this procedure involves enlarging the patient's own bladder using a segment of the patient's own intestine. This may be taken from the patient's small or large intestine or the stomach lining. However, this approach has not been an unmitigated success in the majority of IC/BPS patients since the symptoms, pain, urgency and frequency, may either persist or return, especially in patients with a large bladder capacity under anaesthesia. If pain is a predominant symptom, this may not necessarily improve following augmentation. Bladder augmentation tends to be more effective in patients with a very small, contracted bladder where pain plays less of a role compared to frequency.

For this reason, augmentation cystoplasty is not generally recommended for IC/BPS.

Bladder removal, urinary diversion and urostomy

In cases of severe intolerable pain or pain combined with a small bladder capacity, where all other treatments, urinary diversion may be necessary, with or without complete surgical removal of the urinary bladder (cystectomy). This procedure involves diverting the urine flow to a new opening in the abdomen, called a urinary stoma or urostomy. Normally, urine flows from the kidneys to the bladder via two ureters. In a urinary diversion, these two ureters are rerouted to a segment of intestine. Sometimes the old bladder is left in place. Some surgeons believe that in the case of IC/BPS patients it is preferable for every piece of the bladder and urethra to be removed in a cystectomy. Other surgeons prefer to leave the bladder in place and simply divert the urine. Outcomes vary greatly from patient to patient and there is no guarantee of complete symptom relief.

Ileal conduit urostomy

Ileal conduit diversion with simple cystectomy remains the gold standard approach for major surgical diversion. In this procedure, urine is rerouted to an external disposable bag attached to the outside of the body, for example using the Bricker technique. A segment of intestine is removed and fashioned into a tube. The ureters, that normally carry urine to the bladder, are connected to one end of this intestinal segment, while the other end is brought through the abdominal wall to create a stoma (an opening on the surface of the abdomen). An external urostomy pouch is then attached to the stoma to collect the continuously draining urine. The ileal conduit itself does not store urine but serves solely as a passageway for drainage into the pouch.

Continent diversion urostomy

A continent diversion, such as the Kock pouch or Indiana pouch, involves creating an internal reservoir or pouch from a section of the intestine. This pouch acts as a new bladder, storing

urine and allowing it to be drained at specific intervals through a stoma (an opening on the abdominal surface) using a catheter. While continent diversions—with their internal pouch and catheterizable stoma—may be more cosmetically appealing to some patients, they are associated with potential complications. These may include pouch inflammation, recurrent pain, nipple valve failure, and leakage, particularly in patients with interstitial cystitis/bladder pain syndrome (IC/BPS).

Additionally, a continent stoma is generally less suitable for patients with kidney dysfunction. All patients with a continent stoma must be physically capable of performing regular self-catheterization.

Neobladder

An alternative continent diversion is the neobladder, a bladder substitute constructed from segments of the intestine. It is placed at the site of the original bladder and connected to the urethra, allowing the patient to void through the natural passage. In many cases, catheterisation may still be required to empty the neobladder completely.

Urostomy associations will be able to provide patients with detailed information concerning the different surgical options and stoma care.

Denervation not recommended

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

Catheterization (indwelling) for surgery

When undergoing surgery, including non-urological procedures, IC/BPS patients may need to be catheterized for several days or longer, using an indwelling catheter which is held in place by 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 either a short or extended time. The urine is usually collected in a drainage bag.

However, an indwelling catheter can cause significant irritation and pain in the bladder of an IC/BPS patient. One potential solution is to use a 100% silicone catheter and only partially inflate the balloon. This may reduce discomfort.

TREATMENT FOR HUNNER LESIONS (formerly known as Hunner's ulcers)

Treatment specifically for **Hunner lesions** includes laser therapy, fulguration or electrocoagulation, transurethral resection or submucosal injection (such as triamcinolone which may also be added to an instillation cocktail for Hunner lesion patients). Selected treatments used for non-lesion patients can also be tried in lesion patients.

Hunner lesions, historically known as *Hunner's ulcers* (though ulcer is not medically correct), are also known as Classic IC and are now considered likely to be a separate disease entity from non-lesion IC/BPS.

In recent decades, Hunner lesions have been diagnosed with cystoscopy plus hydrodistension. However, office cystoscopy without hydrodistension is sometimes used instead. While some types of lesion can be seen without hydrodistension, others may be difficult to detect without it. Narrow Band Imaging (NBI) is a relatively new technique of detecting lesions, currently used in Japan.

Bladder pain caused by lesions can significantly improve following fulguration/ electrocoagulation, laser ablation (which burns and seals the lesion) or transurethral resection (TUR) which involves surgical removal of the lesion. These procedures may provide temporary relief from pain for several months or even years and 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 result in substantial improvement in both pain and frequency in many Hunner lesion patients.

A promising treatment for Hunner lesions is submucosal injection of the corticosteroid triamcinolone or triamcinolone instillation as part of a therapeutic cocktail.

VOIDING DIARIES

Voiding diaries or charts, now often available in electronic form, 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, during the day and night) can also be used periodically to monitor the success of treatment.

CHAPTER 5 - COMPLEMENTARY & ALTERNATIVE MEDICINE

What is Complementary & Alternative Medicine (CAM)?

- **Complementary:** generally refers to using a non-mainstream approach **together with** conventional medicine.
- **Alternative:** refers to using a non-mainstream approach **in place of** conventional medicine.
(see NIH fact sheet <https://nccih.nih.gov/health/integrative-health>].

When either or both of these approaches are combined with conventional healthcare, it is often termed **integrative care** and is similar to the concept of holistic care.

However, the CAM concept should be seen as fluid and continually evolving since many treatments once considered alternative have now shifted into the complementary category (e.g. acupuncture), while some former complementary approaches have now become more or less mainstream (e.g. cognitive-behavioural therapy).

There are many complementary therapies and self-help strategies that may alleviate symptoms, promote relaxation and contribute to a better quality of life. Due to the limited effectiveness of conventional treatments in many IC/BPS patients, these patients often seek alternative non-medical forms of therapy from which some patients report experiencing benefit and relief. One possible reason for this is that such therapies involve a more relaxed and interactive relationship between the practitioner and patient. In contrast, conventional medicine nowadays often resembles a fast-moving production line with little time for meaningful communication with patients.

This kind of alternative 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 in turn help to reduce 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.

Mind-Body interventions

The aim of mind-body interventions, also known as mindfulness-based stress reduction, is to reduce and manage stress levels and improve symptoms. IC/BPS can cause sufferers high levels of stress and anxiety, not helped by lack of proper deep sleep. Therefore, anything that can help to reduce stress levels will be beneficial and help patients to cope with the difficult situation in which they find themselves .

This includes the following:

- Hatha Yoga
- Tai Chi
- Guided imagery
- Hypnotherapy
- Mindfulness-based stress reduction
- Meditation
- Deep breathing
- Aromatherapy
- Reflexology

Manual physical therapy techniques

It is recommended that all patients should have a standardized pelvic floor examination and manual physical therapy should therefore be targeted to the individual patient's specific needs and findings from this examination. Specialized physiotherapists with training in this specific field should be involved. Basic therapy should include: avoiding pushing or straining with urination, preventing constipation, taking warm baths twice a day, using skeletal muscle relaxants, and engaging in physical therapy.

Complementary approaches may 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.

However, to achieve optimum results from either physical or relaxation therapy, it is essential to first bring the symptoms and particularly the pain under control using conventional medical therapy.

Kegel exercises and pelvic floor strengthening exercises are **not** recommended for IC/BPS patients. Instead, the goal of physiotherapy should be to **relax** the pelvic floor muscles, rather than strengthen them.

Topical heat or cold

Many patients feel benefit from either heating pads or cold compresses placed over the bladder or perineum and which can help to curb the pain. The hot pads can be either electric or pads that can be heated in a microwave. Some patients feel more benefit from an ice-pack.

Bladder training

Bladder training or re-education (timed voiding, gradually increasing the voiding interval) is likely to be more effective in selected patients where urinary urgency and frequency are the predominate symptoms. 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. However, if the patient experiences strong urgency sensations, 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 contracted, fibrotic bladder and it is not recommended for patients with ongoing pain.

HOMEOPATHY

Homeopathic remedies are used by some IC/BPS patients. However, there is little information or evidence regarding efficacy.

ACUPUNCTURE

Acupuncture has been a part of traditional Chinese medicine for more than 2000 years. Today, often in modified forms, it is used to treat many different diseases. Acupuncture includes placing thin needles into the skin at certain points. These are then activated by the provider's hands or through electrical stimulation. Patients who are interested in trying acupuncture should be advised to check that the acupuncturist is either a regulated healthcare professional

such as a doctor, nurse or physiotherapist or a member of a national acupuncture organisation.

Gao et al (2023) demonstrated that electroacupuncture can potentially be an effective management method for IC/BPS, with alleviation of lower urinary system symptoms and pelvic pain. Further research is required to assess the efficacy and safety of acupuncture for refractory IC/BPS.

SUPPLEMENTS, HERBAL REMEDIES, OVER-THE-COUNTER

Calcium Glycerophosphate (Prelief®),

Calcium Glycerophosphate, commonly known by its U.S. trade name “Prelief®”, is a mineral supplement and antacid that may help some patients manage their diet by preventing flares and reducing symptoms when consuming food or beverages that are likely to cause irritation or flare.

Super Strength Aloe Vera® (Desert Harvest SSAV):

Aloe vera extract is a herbal remedy with a long history in traditional medicine and is believed to possess antimicrobial, anti-inflammatory and immunomodulating properties. Previous studies have indicated that aloe vera has the ability to increase both sulphated and non-sulphated glycosaminoglycans (GAGs) which contribute to the protective layer of the bladder lining. It appears to be an effective means of significantly alleviating symptoms such as bladder pain, urinary frequency, urinary urgency, and urethral burning, thereby improving quality of life in some IC/BPS patients.

Studies and surveys have shown that aloe vera has the potential to reduce IC/BPS symptoms. Ongoing research is currently evaluating the efficacy of Super Strength Aloe Vera.

Although numerous aloe vera products are available in different countries, many contain only minimal amounts of the active ingredient. Patients should be aware that such low concentrations are unlikely to show any therapeutic benefit for IC/BPS patients.

CystoProtek

An open-label study evaluated an oral multicomponent nutraceutical preparation (CystoProtek™) in 252 IC/BPS patients, the symptom response rate was 65–85%. This supplement consists of a combination of glucosamine sulfate, chondroitin sulfate, hyaluronate sodium, quercetin dihydrate, rutin and olive kernel extract.

Cannabis and Marihuana

The term “**cannabis**” refers to the plant *Cannabis sativa*, a highly complex species that contains around 540 chemical substances. The term “**marijuana**” refers to parts of/or products derived from *Cannabis sativa* that contain substantial amounts of **tetrahydrocannabinol** (THC), the plant’s primary psychoactive compound.

IC/BPS patients have used cannabis for many years to alleviate symptoms and many have felt it to be beneficial for their symptoms.

Cannabinoids are medications derived from cannabis or marihuana and are used - where legally permitted and available - in forms such as atomizer sprays, vapours, oils or smoked products. While in some countries these treatments remain illegal, in others cannabidiol (CBD) oils and sprays can be purchased over the counter.

Treatment with cannabis-based medicines requires caution as they may cause central nervous system and psychiatric side effects.

Tetrahydrocannabinol (THC), the psychoactive component of cannabis, may be effective in relieving spasms and cramp-related pain.

Cannabidiol oil (CBD) is a non-psychoactive phytocannabinoid discovered in 1940. CBD is a popular natural remedy for many ailments and is available over the counter. Unlike THC, CBD does not produce a “high” or pose a risk of addiction. Potential benefits include pain relief, and relaxation.

It is also thought that CBD oil may help to reduce the inflammation and pain associated with IC/BPS. In addition, it may also reduce the pain associated with bladder spasms common in this condition. Furthermore, it can potentially also alleviate anxiety suffered by patients caused by the impact of IC/BPS. CBD's anti-inflammatory and pain-reducing properties have been investigated in numerous studies and surveys.

CBD oil can be administered in various forms including topical creams, tinctures, capsules, edibles and sublingual drops.

Quercetin

Quercetin is a flavonoid found in many plants and has been shown to have antioxidant properties. It is thought to have anti-inflammatory effects and to inhibit the activation of mast-cells. It is felt that these qualities may help to reduce the bladder irritation of IC/BPS. Quercetin has shown promising results and is available over the counter (OTC).

D-Mannose

D-mannose is a monosaccharide naturally produced by the body from glucose. It is found in body cells and in certain foods. Several studies, reviews and meta-analyses have documented that D-mannose use can reduce the risk of recurrent urinary tract infections (UTI). However, its role in the treatment of UTI/cystitis-related symptoms remains unclear. Nevertheless, observational studies and clinical trials consistently suggest that D-mannose may be beneficial in managing UTI/cystitis symptoms. D-mannose is widely available over the counter in tablet or sachet form and is commonly used by many IC/BPS patients, as it is thought to help reduce recurrent UTIs.

CHAPTER 6 – INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME & ASSOCIATED DISORDERS

Many patients with IC/BPS also have one or more non-bladder conditions or symptoms in addition to their bladder condition, including other chronic pain syndromes, allergies/hypersensitivities, chronic fatigue, rheumatic systemic autoimmune diseases, gastrointestinal or gastroesophageal disorders and vulvar pain conditions, as demonstrated by studies and patient surveys.

Since IC/BPS patients are generally treated by a urologist, some associated disorders may go undiagnosed and untreated. This highlights the need for a multidisciplinary approach. Associated disorders should always be taken into account when treating IC/BPS and often make treatment very complex and challenging. This once again emphasises the need for patients themselves to keep a personal record of their medical history.

Associated disorders

Studies have indicated that some diseases and disorders appear to occur more frequently in IC/BPS patients than in the general population. These conditions – referred to as associated disorders or comorbidities or non-bladder conditions - can be grouped as follows:

- allergies or intolerances,
- different chronic pain and fatigue syndromes,
- rheumatic systemic autoimmune diseases
- gastrointestinal or gastroesophageal disorders
- neurological disorders.

Examples include the following disorders:

- allergy
- multiple drug intolerance
- chronic fatigue (syndrome)
- endometriosis
- fibromyalgia,
- irritable bowel syndrome, inflammatory bowel disease
- kidney disorders (e.g. interstitial nephritis, distal renal tubular acidosis (dRTA))
- low back pain
- peripheral neuropathy, autonomic neuropathy
- migraine/headaches
- rheumatoid arthritis, arthritis
- Sjögren's disease
- systemic lupus erythematosus
- temporomandibular joint disorder
- vulvodynia

In addition, IC/BPS patients may experience psychological disorders such as anxiety, depression and stress as a consequence of their bladder condition and its impact on all aspects of their lives.

Both doctors treating IC/BPS patients and the patients themselves should remain vigilant for other symptoms that may indicate the presence of one or more other disorders, since this could influence the approach to treating the bladder condition. *See Table 3.*

Associated disorders currently play an important role in phenotyping systems currently being developed.

Autoimmune disease and IC/BPS

One of the prevailing theories regarding IC/BPS is that it may itself be an autoimmune disease. Examples of autoimmune diseases are rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's disease (formerly known as Sjögren's syndrome) and thyroid disorders.

In autoimmune diseases, the immune system mistakenly attacks the body's own tissues. Some autoimmune diseases are "organ specific", meaning they target a single organ in the body (for example thyroid disorders). Others may be "generalized" or "systemic", affecting multiple organs and systems throughout the body—including the urinary tract.

Patients diagnosed with both an autoimmune disease and IC/BPS should ensure that all relevant specialists are informed, especially if the autoimmune condition is diagnosed after the IC/BPS. This is important because it may necessitate changes in the treatment strategy, including the use of different medications for managing IC/BPS.

A significant challenge with IC/BPS patients with symptoms indicative of autoimmune disease is that in a group of these patients laboratory tests may show few or no abnormalities. The patients frequently do not quite meet the full criteria for any one specific disease. While strict criteria are created for the purpose of research, they are often rigorously applied clinically too. This can lead to many sick patients remaining 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/BPS patients who also shows symptoms of autoimmune diseases may benefit from "systemic" treatment, that is treatment targeting the whole body with a single medication. Examples include the antimalarial hydroxychloroquine and the anti-inflammatory sulphasalazine (commonly used to treat inflammatory bowel disease and rheumatic conditions) or corticosteroids such as prednisolone, dexamethasone or hydrocortisone. Some patients have reported a significant improvement in their IC/BPS symptoms following such treatment. However, here too treatment is highly individual and every patient is different. Side effects could be problematic in some patients.

Multiple pain syndromes

Certain IC/BPS patients suffer from multiple co-existing pain syndromes affecting different parts of the body and not limited to the pelvic organs. Common overlapping conditions include irritable bowel syndrome, vulvodynia, fibromyalgia, migraine, temporomandibular disorder, and other types of pelvic pain.

Many pain theories

Pain research continues to explore several theories behind the occurrence of multiple pain syndromes. These 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 so-called cross-sensitization or cross-talk with inflammation in one organ causing inflammation in another, abnormalities of autonomic function and more recently limbic system dysfunction.

IC/BPS patients may suffer from widespread pain. Ongoing research is investigating brain changes associated with chronic pain. Additionally, variations in bladder pain throughout the menstrual cycle suggest that hormonal factors may also influence pain perception in affected women.

A brief look at a selection of associated disorders

Allergy and Intolerance: Many IC/BPS patients suffer from allergy or intolerance. True allergies can be identified by standard allergy tests. Allergies can affect the skin, airways and sometimes internal organs. Examples include asthma, rhinitis, urticaria (nettle-rash or hives), eczema and anaphylaxis. Interestingly, some patients treated with antihistamines for allergies also report an improvement in their IC/BPS bladder symptoms.

However, not all adverse reactions are due to true allergies, some are cases of non-allergic intolerance. This type of non-allergic intolerance is challenging because reactions to drugs are often unpredictable and vary from person to person, typically involving trial and error, as standard allergy tests cannot detect non-allergic intolerances.

Non-allergic intolerance is still a relatively unexplored, unresearched field and particularly so in relation to the drug intolerance found in some IC/BPS patients.

Some IC/BPS patients may also have multiple chemical intolerance (MCI), experiencing symptoms such as dizziness or faintness when exposed to airborne chemicals or when perfumed products or chemical substances come into contact with their skin. The reasons why only some IC/BPS patients develop these sensitivities remain unclear. However, it is noteworthy that similar patterns of drug and chemical intolerance are also observed in patients with fibromyalgia.

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

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

Depression is experienced by many individuals in the general population, either occasionally or persistently. However, it may occur more frequently in patients with chronic conditions such as IC/BPS which can have a profound impact on quality of life. In IC/BPS patients, it may be a question of a temporary inability to cope which can be helped by good support and a compassionate approach from healthcare providers, patient support groups, and a supportive home environment. If more serious, it should be treated with medication combined with counselling.

While depression may be caused by psychological or emotional issues, it may also form part of a broader syndrome of symptoms associated with chronic diseases. This has been documented in conditions such as systemic lupus erythematosus (SLE) and may occur in any disease with a neurological component, including pain syndromes and especially chronic fatigue. It is also important to remember that depression can be a side-effect of many medications.

Distal Renal Tubular Acidosis (dRTA)

Distal renal tubular acidosis (distal RTA or Type 1 RTA) is a medical condition where the distal tubules of the kidney fail to properly excrete acid (hydrogen ions) into the urine. This leads to a buildup of acid in the blood, resulting in a condition called metabolic acidosis.

- Distal tubule dysfunction: The problem is in the final portion of the nephron, where acid should be secreted into the urine.
- Failure to acidify urine: Even in the presence of systemic acidosis, the urine remains inappropriately alkaline (pH > 5.5).
- Metabolic acidosis: The blood becomes too acidic due to poor acid excretion.
- Hypokalemia: Patients often have low blood potassium levels.
- Symptoms include muscle cramps, fatigue, muscle weakness, constipation or diarrhoea, tachycardia, numbness or tingling, feeling lightheaded or faint.

Distal RTA can be hereditary or acquired. Common causes include: autoimmune diseases (e.g., Sjögren's syndrome, lupus), medications (e.g., amphotericin B, lithium, NSAIDs), genetic mutations, hypercalciuria or nephrocalcinosis.

While the blood becomes more acid with loss of potassium (hypokalaemia), potassium may end up in the urine and cause flares of burning bladder pain in an IC/BPS patient.

Treatment of choice is potassium citrate and/or oral bicarbonate.

Information on dRTA:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4107275/>

<https://www.orpha.net/en/disease/detail/18>

<https://www.ncbi.nlm.nih.gov/books/NBK519044/>

Fatigue: many IC/BPS patients experience fatigue problems. This may be tiredness resulting from lack of sleep due to frequent nighttime trips to the bathroom or from the inability to relax due to constant pain. However, severe fatigue with memory and concentration difficulties - described by patients as 'brain fog' - or extreme fatigue after minimal physical exertion may suggest the presence of an autoimmune disease. If this seems possible, it may be worthwhile investigating whether an autoimmune disease is present in addition to IC/BPS.

The term *chronic fatigue syndrome* (sometimes also called *myalgic encephalomyelitis* or *ME*) should be reserved for cases where no underlying disease has been identified to explain the chronic fatigue. However, in practice, the terms *chronic fatigue* and *chronic fatigue syndrome* are often used interchangeably.

Fibromyalgia syndrome (FMS) is a chronic, debilitating multisystem pain syndrome of unknown cause characterised by 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. However, inflammation is not considered to be a defining feature of FMS.

Current theories concerning the cause focus on central sensitization, a condition in which the central nervous system becomes hypersensitive to stimuli.

FMS 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 may also experience tingling, numbness, dizziness and cognitive or memory disorders.

The severity of FMS varies widely among individuals. While some may experience mild discomfort, others may suffer from a severely disabling form with intense pain and extreme fatigue. Some researchers propose that FMS may encompass several distinct subgroups or phenotypes.

Like IC/BPS, the course of FMS is variable, often marked by periods of exacerbation and remission. For further information:

<http://www.fmaware.org/>

Gastro-intestinal disorders are frequently associated with IC/BPS.

- **Irritable bowel syndrome (IBS)**, a functional bowel disorder, is the most common gastrointestinal disorder in IC/BPS patients. Symptoms include abdominal pain or cramping, alternating diarrhoea and constipation, and a bloated feeling due to gas formation.
- **Inflammatory bowel disease (IBD)**, which includes Crohn's disease and ulcerative colitis, is also more prevalent in IC/BPS patients than in the general population. Symptoms typically include weight loss, blood in the stool, and nocturnal diarrhoea. IBD is commonly thought to have an autoimmune origin.

For further information about the digestive system and how it works, visit:

<https://www.niddk.nih.gov/health-information/digestive-diseases>

Gastro-esophageal disorders have also been linked with IC/BPS patients.

Gastroesophageal reflux (GER) occurs when your stomach contents come back up into your esophagus.

Gastroesophageal reflux disease (GERD) is a more severe, chronic condition in which GER causes repeated symptoms or leads to complications over time.

Both GER and GERD commonly cause heartburn and regurgitation. GERD may develop when your lower esophageal sphincter becomes weak or relaxes. These conditions can cause chest pain.

The National Digestive Diseases Information Clearinghouse (NDDIC) has useful information on IBS at:

<https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome>

on IBD at:

<https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis>

on GERD at:

<https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-adults>

also useful:

Colitis – StatPearls: Azer SA, Sun Y. Colitis. [Updated 2023 Aug 7]. In: StatPearls [Internet].

Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from:

<https://www.ncbi.nlm.nih.gov/books/NBK541037/>

Rheumatoid arthritis (RA) is a chronic systemic, autoimmune connective tissue disease that primarily affects the synovial membranes of joints. It is characterised by joint pain, swelling and stiffness, typically symmetrically. As the disease progresses, the ligament damage and

bone erosion occur, leading to joint deformities. This deformity of the joints is an important difference with other rheumatic diseases such as Sjögren's disease.

Sensitive skin: Many IC/BPS patients experience dry, itchy, sensitive skin. It is advisable to keep the skin well moisturized with cream or lotion formulated for sensitive skin, as this may help to reduce the dryness and may also alleviate some itchiness. IC/BPS patients should avoid exposure to irritants such as household cleaning products (wear protective gloves) and perfumes. They should also avoid using perfumed soaps or any other fragranced products around the vulvar/genital area. Caution is advised with contraceptive devices that contain chemicals, such as condoms and spermicidal creams. Whenever possible, clothing should be washed with products specially designed for sensitive skin that are free from fragrances. Patients are also encouraged to wear cotton underwear and loose-fitting clothing. They should avoid contact with garden plants that may cause skin reactions and be cautious in the sun if their skin is sensitive to sunlight.

Sjögren's disease (formerly known as Sjögren's syndrome) is a chronic, systemic autoimmune disease of unknown cause in which lacrimal (tear) and salivary glands malfunction causing dryness. Its hallmark symptoms are sore, irritated eyes and dry mouth, often accompanied by a need to drink when eating because dry food otherwise tends to stick in the mouth and cannot be chewed or swallowed properly (known as the "cracker sign").

Sjögren's is a systemic or "generalised" disease and may therefore affect many organs and systems of the body.

Approximately nine out of ten patients are women.

This disease has traditionally been classified into two types:

- **Primary Sjögren's** where the disease occurs alone and
- **Secondary Sjögren's** 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, others suffer significant impairment in quality of life due to debilitating symptoms and severe fatigue. Diagnosis can often be delayed for many years, particularly in patients who do not exhibit the typical combination of eye and mouth dryness, lack detectable autoantibodies, or have a normal erythrocyte sedimentation rate (ESR).

In recent years, clinical studies, observational data and patient surveys have led to an increased awareness of a potential association between IC/BPS and Sjögren's and that Sjögren's may be being underdiagnosed in IC/BPS patients.

Further information on Sjögren's:

<https://sjogrens.org/>

Sicca syndrome, also known as Sicca Complex, is a condition characterized by dryness of the eyes and mouth. It's most commonly associated with Sjögren's disease, an autoimmune disorder in which the body's immune system attacks the glands that produce saliva and tears. However, sicca syndrome can also occur independently or as part of other conditions.

Key Features of Sicca Syndrome:

- **Dry eyes (keratoconjunctivitis sicca):** Patients may feel like there's sand or grit in their eyes.

- Dry mouth (xerostomia): This can lead to difficulty swallowing, speaking, or an increased risk of dental decay.
- Sometimes includes dryness of other mucous membranes (e.g., nose, throat, skin, vagina).

However, Sicca Syndrome is sometimes also used (inaccurately) as a synonym for Sjögren's.

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, autoimmune connective tissue disease that can affect multiple organ and systems. It is characterised by unpredictable flares and remissions. It may commonly 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/BPS. The symptoms and severity of SLE can greatly vary from patient to patient and may also fluctuate over time in an individual patient. Similar to IC/BPS, there is a high predominance of women patients.

See: <https://ghr.nlm.nih.gov/condition/systemic-lupus-erythematosus>

Thyroid disorders: The thyroid gland is located at the front of the neck, just below the skin and muscle layers. Shaped like a butterfly, it consists of two lobes (right and left) that wrap around the trachea. The thyroid's primary function is to produce hormones that regulate the body's metabolism and are essential for both mental and physical development.

The thyroid gland is susceptible to two primary functional disorders:

- Hyperthyroidism: excessive production of thyroid hormone
- Hypothyroidism: insufficient production of thyroid hormone.

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

Vulvodynia (or chronic vulvar pain) is a distressing, painful and often debilitating 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 (more than three to six months) and encompasses several subtypes that cause chronic or intermittent pain, burning, rawness and pain during sexual intercourse. There are two main types of vulvodynia which may occur independently or together:

- **Provoked Vestibulodynia (PVD) (also known as vulvar vestibulitis)** is pain or burning sensation caused when the vestibule (entrance to the vagina) is touched. This may be triggered 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. Diagnosis is often made by applying gentle pressure to the vestibule with a Q-tip, which can cause significant discomfort.
- **Generalized Unprovoked Vulvodynia (GV) (formerly known as dysesthetic or essential vulvodynia)** involves spontaneous pain, burning, stinging or rawness on or around the vulva, labia, vestibule, clitoris or perineum regardless of activity or touch. Although not caused by direct contact, symptoms can be worsened by pressure. Pain

may also occur during urination. GV is diagnosed based on a consistent history of chronic pain in the absence of any visible abnormalities or identifiable medical conditions such as infections.

For further information on vulvodynia, see: www.nva.org (National Vulvodynia Association, USA)

Table 3. Questions to assess the possibility of an IC/BPS 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 or irritated 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/BPS PATIENTS: CAUSES, IMPACT & COPING

Fatigue is a potentially disabling condition that can cause mental and physical dysfunction, severely impacting a patient's relationships, home-life, employment and social life. It may lead to physical incapacity, brain fog, difficulty communicating to people around you, and an overwhelming sense of isolation.

Many IC/BPS patients suffer from fatigue, listlessness and lack of energy or motivation. 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 friends. This can create a very unsympathetic environment and make coping with the condition much more difficult.

As with many symptoms experienced by IC/BPS patients, fatigue can vary widely—from mild and intermittent to severe and debilitating, potentially paralyzing a patient's ability to function in daily life. In some cases, fatigue may be temporary, with an identifiable and treatable cause. In others, it may be persistent, unexplained, and resistant to treatment. Patients may experience purely physical fatigue, or a combination of physical and mental fatigue, often referred to as "brain fog."

One of the complexities of fatigue is that it can stem from multiple causes simultaneously. An individual patient may be affected by several contributing factors, all of which must be identified and addressed. Determining the root cause(s) is often challenging, as symptoms from different types of fatigue can be similar and may overlap.

A frequently overlooked cause of fatigue is peripheral neuropathy or polyneuropathy which can sometimes occur with autoimmune diseases, particularly small fibre neuropathy which often goes undiagnosed.

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
- Neurological disorders
- Psychological disorders
- Diseases without proven psychological or physical cause
- General

Sleep disruption

Lack of proper sleep is the first aspect to consider in relation to an IC/BPS patient. We know that IC/BPS patients vary greatly in their symptom levels, including night-time urination, and this can even fluctuate in an individual patient depending on whether the patient is in a flare or in remission. Even urinating only 2 or 3 times a night on a regular basis can lead to

considerable fatigue, especially for those who find it difficult to fall asleep again after getting out of bed. The most severe IC/BPS patients or patients in a flare may be out of bed every 20 minutes or worse, even sitting almost all night on the toilet, or wrapped up in a blanket on the bathroom floor.

However, many other factors 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 in the body; many IC/BPS patients may suffer from one or more additional pain syndromes that may cause pain at night.
- **Restless legs syndrome,** itching, burning, tingling: all of which can prevent sleep.
- **Medications:** various medication can cause insomnia.
- **Environmental disturbances:** such as noise from a snoring partner, crying babies, traffic.
- **Light exposure:** excessive light inside or outside the home, from streetlights or outdoor security lights.
- **Psychological stress:** anxiety, work-related stress, and the stress, worry and sometimes panic of coping with IC/BPS can all interfere with sleep.
- **Underlying health conditions:** many diseases and disorders, such as fibromyalgia and anaemia, are known to disrupt sleep or cause or insomnia.

Therefore, each patient should carefully think about whether it is solely the bladder pain and urge to urinate that is waking them (or keeping them awake), or whether something else has disturbed their sleep, after which they become aware of their bladder discomfort and get out of bed. It may be purely the IC/BPS 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 experts, proper, restorative sleep typically occurs during the first part of the night. This early phase of sleep is often the most disrupted in IC/BPS 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
- Impaired motor performance
- 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 IC/BPS patient

- Suitable treatment for the bladder pain, urgency and frequency and any other associated pain should be given absolute priority.
- If the distance to the bathroom is too far, it may be helpful for an IC/BPS patient to keep a commode or an old-fashioned chamber pot or a portable camping toilet in the bedroom. The further the distance to the bathroom, the more time the body has to fully wake up, making it harder to get off to sleep again when back in bed. A toilet facility close by can also reduce the risk of falls in the night.
- Patients should aim to reduce night-time urination as far as possible or advisable by limiting fluid intake in the evening and avoiding food or drinks known to irritate the bladder or to keep them awake. However, they should compensate for this by drinking plenty of fluids earlier in the day to avoid concentration of urine.
- If medication causes irritation in the bladder, it should be taken either early in the morning or very late at night just before sleeping. But preferably change the medication to something that does not irritate the bladder.
- Earplugs may help patients kept awake or woken by noise of any kind.
- If it is impossible to do anything about disturbing light, an eye-mask may help.
- If lack of sleep is partly due to anxiety or stress, counselling may be beneficial. IC/BPS patients can become very anxious and panicky about their bladder disorder and its impact on their life and of course about the fact that treatment may not be working. They worry continually about what the future may hold. Professional counselling could help manage these emotional challenges.

Medication causing daytime drowsiness

While some medication can cause insomnia, other drugs can cause drowsiness all day long. Unfortunately, many treatments used for pain in IC/BPS have sedative effects, leaving patients feeling like zombies. However, numerous other drugs can also have a sedative effect in some patients.

Some IC/BPS patients experience heightened sensitivity or intolerance to medications, reacting strongly even to very low doses. Therefore, it's important to recognize that any medication has the potential to cause either insomnia, daytime drowsiness, or to worsen existing chronic fatigue.

Physical (organ-based) diseases

Diseases that can cause tiredness include anaemia, hypothyroidism, heart failure, low blood pressure, infectious diseases such as glandular fever, and cancers. These conditions can all be investigated by the doctor. Any illnesses causing chronic daily pain are very exhausting.

Coping with a bladder disorder like IC/BPS is also particularly tiring because a patient can never fully relax. They are constantly aware of the pain or irritation in the bladder and become 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 disease in which true **chronic fatigue** can be a completely disabling symptom. Chronic fatigue is also common in fibromyalgia. When no underlying

disease or identifiable cause of the fatigue can be found, it is known as **chronic fatigue syndrome (CFS)**.

Chronic fatigue differs from ordinary tiredness. Unlike fatigue due to lack of sleep, autoimmune-related fatigue occurs regardless of whether a person has slept well or not. Chronic fatigue can fluctuate from week to week, month to month and year to year and it may wax and wane during the day. During flares, patients may feel flu-like symptoms, such as chills, headaches, severe exhaustion and inability to think (brain fog).

They no longer have the energy to take action, talk to people, answer the phone or take a decision. With chronic fatigue, patients lose their drive and motivation, they may have memory lapses, no concentration and experience confusion. Physically, they may feel unwell constantly and become exhausted after the slightest physical or mental effort. While rest may sometimes temporarily alleviate the fatigue, it soon returns when the patient becomes active again.

Advice to patients with chronic fatigue

Plan your daily routine according to how you feel each day. If necessary, restructure your life, adjust your lifestyle. Do not take on more commitments than you can cope with. Learn to say no. Recognize when you are overexerting yourself before you reach the point of collapse. Don't feel guilty about taking naps or siestas during the day. Discover how much exercise you need and your body 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. 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 impair your ability to drive or operate machinery, making it potentially dangerous.

Psychological disorders

While depression can cause fatigue, chronic fatigue can itself cause depression. Since the very nature of IC/BPS symptoms can make patients 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 entire family, often disrupting the lives of all family members, including children. It can prevent the patient from managing the household, maintaining routines, create a stable environment for the family, participating in social activities or having a normal relationship. The financial impact of chronic fatigue is also significant since people with chronic fatigue may not be able to hold down a job.

Table 4: SOME CAUSES OF FATIGUE

A. Sleep disruption

- night-time frequency
e.g. IC/BPS, 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
Neurological/neuropathy
Cancer

D. Psychological disorders

Depression
Burnout

E. Diseases without proven physical and psychological cause

Chronic fatigue syndrome
Fibromyalgia

APPENDIX

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AN 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.” (Howard Kelly, Operative Gynecology, 1912)

In 1808, Philip Syng Physick, a renowned surgeon from Philadelphia, was reported 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 earliest record of the term interstitial cystitis discovered so far can be found in *“A Practical Treatise on the Diseases, Injuries and Malformations of the Urinary Bladder, the Prostate Gland and the Urethra”* by Samuel D. Gross, Professor of Surgery in Philadelphia, 3rd Edition revised and edited by his son Samuel W. Gross and published in 1876. In the section Diseases of the Urinary Organs, Part I, Chapter I (Inflammation of the bladder and its results), he writes: *“When all the coats are implicated, it is termed interstitial, or parenchymatous cystitis...”*

Two years later, in 1878, the term interstitial cystitis appeared again in the first edition of 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.

This was echoed by Van Buren and Keyes in 1880 who explained:

“Inflammation of the bladder, according to the anatomical portion of its walls involved, is known as:

- *Cystitis mucosa – catarrh of the bladder*
- *Interstitial cystitis*
- *Peri-cystitis; epi-cystitis.*

These varieties, however, do not demand detailed and separate descriptions, since they follow one upon the other as grades of intensity of the same morbid process.”

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 shortly after his untimely death at the age of only 57 years.

By 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 - 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 series 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 by his contemporaries as a lesion. Hunner was using either the Nitze or Kelly cystoscope, but vision in those days was relatively poor and this may have been one of the reasons he thought he was seeing ulcers. However, his description of lesions remained the gold standard for many years.

Guy Hunner had deep empathy with his patients, describing their pain as follows: *“The pain is often of the most extreme grade, the patient complaining of a jabbing or stabbing knifelike pain or of a sensation of a jagged, sharp stick in the bladder.”* One of his patients *“often had such extreme urgency that she had to leave a streetcar in order to enter the nearest house and ask for permission to void.”*

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.

In 1946, on the other side of the world in New Zealand, Dr Patrick A. Treahy (1898-1963) published a remarkably detailed article on Interstitial Cystitis focusing on ulcers or lesions, noting that *“the chief complaints are intense urgency, pain and frequency”*. And while the condition may be suspected from the history, *“cystoscopy is necessary for confirmation.”*

While there were many more publications on this disorder on both sides of the Atlantic in English, French and German at 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 milder cases would eventually progress to lesions.

Although earlier writers – including Guy Hunner - were aware of a possible association with rheumatic diseases, Hand emphasized that *“allergies were more common among the patients with IC than among those from the general admission.”*

Like all of 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" 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 punctate red dots as "glomerulations" but questions the specificity of glomerulations since *"glomerulation is not absolutely pathognomonic since it has been seen after overdilation in patients with dyskenesia"*. However, despite Walsh's possible doubts, glomerulations mistakenly 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 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, in a landmark paper, Magnus Fall and colleagues described interstitial cystitis as a *"heterogeneous syndrome"*. They also reported observing marked clinical differences between ulcerative (classic) and nonulcerative interstitial cystitis: *"These 2 conditions appear to represent separate entities and should be evaluated separately in clinical studies"*. Unfortunately, this went unheeded and all patients with or without lesions continued to be bundled together.

Also in 1987, encouraged by the Interstitial Cystitis Association (ICA) founded in the United States of America 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. While the criteria were never intended as a definition for the clinician, 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.

An interesting aspect of the NIDDK criteria was that pain was not compulsory: it required either pain or urgency. However, this was likely because at that time urgency in a hypersensitive bladder was termed “sensory urgency”.

Although the name painful bladder (disease) 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 doctors found it difficult to understand what the distinction was supposed to be between IC and PBS, particularly in countries where it was not customary to perform cystoscopy and/or biopsy in all patients. This definition of PBS was shown by J. Warren to have only 64% sensitivity.

The same ICS paper redefined the term “urgency” – previously subdivided into motor urgency (sudden urgency) and sensory urgency in a hypersensitive bladder – now making all urgency “sudden” and “for fear of leakage”, so the term could only be used for overactive bladder syndrome. Urgency was then cut out of all IC definitions and consequently out of research.

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 was a new name taken from the urogenital pain taxonomy (classification) of the International Association for the Study of Pain (IASP), a taxonomy also used in EAU Guidelines for chronic pelvic pain.

In 2008, the NIDDK launched an initial 5-year multi-centre research programme, followed by a second research programme, entitled the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) with an innovative shift in research focus. This research project was to 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/BPS or CP/CPPS. The primary objectives of the MAPP included: 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 was to be the *phenotyping* (clinical characterization into types) of patients participating in the studies. The ultimate 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 introduced by the NIDDK: the Urologic Chronic Pelvic Pain Syndromes (UCPPS). For more information on the MAPP study, visit: <https://www.mappnetwork.org/>

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.*

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 was to classify patients with IC according to clinically relevant domains or subtypes (phenotypes) with the ultimate aim of optimizing therapy and improving outcomes. These UPOINT domains were: **U**rinary, **P**sychosocial, **O**rgan Specific, **I**nfection, **N**eurologic/Systemic, **T**enderness. However, in 2018 this was changed for IC/BPS to **INPUT**: **I**nfection, **N**eurologic/systemic, **P**sychosocial, **U**lcers and **T**enderness of muscles.

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. The HBS concept was slightly adjusted in 2013. They defined 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. They created the umbrella term of “frequency/urgency syndrome” characterized by frequency (frequent voiding) and urgency (strong desire to void). This is an inclusive term incorporating overactive bladder syndrome, hypersensitive bladder and other conditions associated with frequency and urgency.

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." In this AUA guideline, the terms IC and BPS are used synonymously. This guideline is regularly updated and can be accessed at:

[https://www.auanet.org/guidelines/guidelines/interstitial-cystitis-\(ic/bps\)-guideline](https://www.auanet.org/guidelines/guidelines/interstitial-cystitis-(ic/bps)-guideline)

In its 2012 updated Guidelines on Chronic Pelvic Pain, the European Association of Urology (EAU) used the term bladder pain syndrome with the following definition: "*bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy.*" The term IC is reserved for Hunner's lesion as a specific type of chronic inflammation of the bladder.

At the 1st Sensory Bladder Meeting held at Les Pensières, Fondation Merieux, Veyrier du Lac, France, 22-23 June 2012, J-J Labat from Nantes presented the French hypersensitivity proposal:

- *Non-painful visceral hyperactivity syndrome due to visceral hypersensitivity (bladder, bowel)*
- *Painful pelvic visceral hypersensitivity (bladder, bowel, vulva, urethra, prostate)*
- *Pelvic non-visceral hypersensitivity (musculoligamentous trigger points, bone (bone tenderness), skin, mucosa (hyperpathia, superficial allodynia)*

The book "Bladder Pain Syndrome, A Guide for Clinicians" by the ESSIC group was published in 2013.

The Joint meeting of the 3rd International Consultation on Interstitial Cystitis (ICICJ3) and the ESSIC Annual Meeting 2013, held in Kyoto Japan 21-23 March, 2013, recommended splitting off Hunner lesion and calling it by its historic name interstitial cystitis, reserving the term bladder pain syndrome for non/lesion patients. However, the East Asian countries did not like use of the pain term since they believe that patients do not necessarily interpret discomfort, pressure and unpleasant sensations as being pain and for this reason they use the term hypersensitive bladder. The meeting emphasised that glomerulations should not be considered diagnostic, they are not specific to IC/BPS and at present no-one knows what causes them or what their significance is.

In 2015, Wennevik and colleagues concluded that there are no convincing data to show that the presence of glomerulations is specifically related to BPS/IC in Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in Bladder Pain Syndrome – A review. *J Urol* 2016 Jan 01;195(1)19-25

In 2018, the book Bladder Pain Syndrome – an Evolution. Edited by P.M. Hanno, J. Nordling, D.R. Staskin, A.J. Wein, J.J. Wyndaele was published.

Meetings of ICICJ/SICJ in Kyoto and ESSIC in Florence in 2018 concluded that 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 and is essential for international research. But first we need to understand exactly what

disease (or diseases) it is that we are trying to communicate! Further phenotyping or subtyping should help to point the way to better treatment. In the meantime, for the sake of continuity and clarity for patients and for others seeking information, the patient organizations are mainly continuing to use the traditional name interstitial cystitis (IC), sometimes in combination with bladder pain syndrome (IC/BPS) or painful bladder syndrome (IC/PBS) and in East Asian countries hypersensitive bladder (HSB).

In 2019, several papers were published from different parts of the world recommending that Hunner Lesion Disease should be considered a separate entity from non-lesion IC/BPS. This continued into 2020 with a paper published by an ESSIC working group noting that “It is time to accept that classic IC with Hunner lesions and BPS always should be evaluated separately in science as well as in clinical routine.”

Also published in 2020 was a paper calling for the reinstatement of sensory urgency so as to help ensure that researchers and drug developers are actually researching the real disease suffered by real patients. *Meijlink J. An urgent case for sensory urgency: A patient perspective. Neurourol Urodyn. 2020 Sep;39(7):2008-2010. doi: 10.1002/nau.24457. Epub 2020 Jul 10. PMID: 32648972.*

Hanno *et al* published a comment in 2020 urging that “*It is time to move on with a new paradigm. The benefits to our patients’ now and future progress in drug development and knowledge beg for a separation of HLD from BPS. To do otherwise is to continue a prolonged disservice to patients.*”

To add to the global terminology confusion, the IASP ICD-11 task force for chronic pain recently introduced the term chronic primary visceral pain to include chronic primary bladder pain syndrome.

This classification system introduces chronic pain as a disease in itself for the first time (<https://icd.who.int/en>). This is echoed by the EAU’s revised chronic pelvic pain guideline which now refers to primary bladder pain syndrome (<https://uroweb.org/guideline/chronic-pelvic-pain/>).

The intention of ICD is that primary should be used when there is no identifiable cause of the disorder. However, Hunner lesion does not appear to have been explicitly excluded and that is indeed identifiable. A question is therefore: should it in fact be “primary” or should it come under “chronic secondary visceral pain”, or should it be split up between the two?

However, ICD-11 still has “interstitial cystitis” under Genitourinary Diseases:

GC00.3 Interstitial cystitis

A condition characterised by inflammation of the urinary bladder and ureters. This condition may be associated with a malformation of, or injury to, the bladder epithelium, infection with toxins, an autoimmune reaction, or an allergy. This condition may also present with Hunner ulcers diffuse glomerulations affecting all quadrants of the bladder mucosa, mild to severe chronic bladder pressure, bladder pain, urgency to urinate, and low volumes of urine.

While the description here is not entirely up-to-date, it is at least understandable for clinicians around the world.

In 2023, ICS and ICUD published the 7th Edition of the book Incontinence, with Chapter 18 providing a comprehensive history and update on diagnosis and treatment of Interstitial Cystitis/Bladder Pain Syndrome, compiled by an international committee chaired by Philip Hanno, MD.

Terminology issues had not been resolved internationally by 2024. Some countries and societies were now using IC exclusively for Hunner lesion, others IC/BPS for all patients, the EAU Primary BPS, Japan referring to Hunner lesion as HIC (Hunner IC), ESSIC preferring HLD (Hunner Lesion Disease), and the many patients without lesions who had originally been officially diagnosed as IC in the past now wondering where they stand. What will artificial intelligence (AI) make of this?

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By Dr Rajesh Taneja (India)
Published by Kontentworx
ISBN: 978-93-83988-00-6

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Editors: Alan W. Partin, Roger R. Dmochowski, Louis R. Kavoussi, Craig A. Peters, Alan J. Wein. See Chapter 57 Interstitial Cystitis/Bladder Pain Syndrome and Related Disorders
Robert M. Moldwin MD and Philip M. Hanno MD, MPH
Campbell-Walsh-Wein Urology, 57, 1224-1250.e16

Supplements: Open Access

-Translational Andrology & Urology, Focused Supplement on interstitial cystitis/bladder pain syndrome
Supplement Part I: Vol 4, No 5 (October 2015). **Read more...**
Supplement Part II: Vol 4, No 6 (December 2015). **Read more...**

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