

# Interstitial Cystitis (Bladder Pain Syndrome)



Interstitial cystitis (IC) is a chronic bladder disease characterized by symptoms of cystitis. These are pain, pressure or discomfort in or around the bladder, an urgent need to urinate and frequent urination both in the daytime and at night. The pain usually increases as the bladder fills. However, no urinary tract infection or other cause can be identified. The symptoms have serious consequences for the social and personal life of the patients. In the case of many patients, it may take many years before the diagnosis of IC is established.

During the past few years, there has been much international discussion concerning the name and definition of the disease. Other names that are used are *painful bladder syndrome* (PBS), *hypersensitive bladder*, and *bladder pain syndrome* (see below), each with or without the addition of IC.

## ESSIC diagnostic criteria

The *European Society for the Study of IC/PBS* (ESSIC) has recently proposed, in addition to the name *bladder pain syndrome* (BPS), a new definition (see box) and new diagnostic criteria.<sup>33</sup> ESSIC

### ESSIC definition of Bladder Pain Syndrome<sup>33</sup>

ESSIC agreed that BPS would be diagnosed on the basis of chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency.

Confusable diseases as the cause of the symptoms must be excluded.

Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies.

The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.

chronic: > 6 months  
ESSIC: <http://www.essic.eu>

defined types of BPS on the basis of findings used to document the diagnosis of BPS. BPS type indications consist of two symbols: first symbols 1, 2 or 3 indicate increasing grade of abnormal findings at cystoscopy with hydrodistension and second symbols A, B or C indicate increasing grade of abnormality of biopsy findings. X indicates that no cystoscopy with hydrodistension (first symbol) or no biopsy (second symbol) was done (see figure 11.1).

The name IC will be used here further as a synonym for painful bladder syndrome and bladder pain syndrome.

## Pain, pressure and discomfort

Many patients report a sensation of pressure or discomfort in the bladder/pelvic area and do not report this sensation as pain but rather as urgency. The IASP (International Association for the Study of Pain; [www.iasp-pain.org](http://www.iasp-pain.org)) definition of pain is: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Patients having microwave treatment for benign prostatic obstruction producing tissue damage at the bladder neck report the same sensation of pressure and discomfort in the bladder region. The sensation is therefore by definition a pain sensation, but not described as such by the patient.<sup>33</sup>

## Disease characteristics

Cystoscopy is an essential diagnostic procedure for IC because it allows the inside of the bladder to be examined and small samples of tissue to be taken. This enables many other diseases such as carcinoma *in situ* to be excluded as a cause of the symptoms. A number of findings are considered to be hallmarks of IC, despite not being specific. These are diffuse pinpoint haemorrhages (glomerulations) in the bladder wall when the bladder is filled with water, a bladder capacity of less than 350 ml and so-called Hunner's ulcers. None of these characteristics are found in all patients and the last two in only a small

The sensations of pressure and/or discomfort in the bladder/pelvic area are by definition pain sensations.

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		CYSTOSCOPY WITH HYDRODISTENSION			
		not done	normal	glomerulations <sup>1</sup>	Hunner's lesion <sup>2</sup>
BIOPSY	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive <sup>3</sup>	XC	1C	2C	3C

<sup>1</sup> cystoscopy: glomerulations grade II-III  
<sup>2</sup> with or without glomerulations  
<sup>3</sup> histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

**Figure 11.1** BPS types as proposed by the European Society for the Study of IC/PBS (ESSIC). <sup>33</sup> BPS type indications consist of two symbols: first symbols 1, 2 or 3 indicate grades of abnormal findings at cystoscopy with hydrodistension and second symbols A, B or C indicate grades of abnormality of biopsy findings. <sup>34</sup> X indicates that no cystoscopy with hydrodistension (first symbol) or no biopsy (second symbol) was done.

percentage of IC patients.

Hunner's ulcer is not in fact a true ulcer but a red lesion in the bladder mucosa with blood vessels radiating towards a central scar. The lesion is covered with a fibrin deposit or coagulum and ruptures as the bladder is distended, causing blood to ooze. After distension, edema can be seen. ESSIC no longer uses the term Hunner's ulcer, preferring instead the term *Hunner's lesion*.<sup>33</sup>

The typical histological finding in IC is submucosal edema, vasodilatation and an inflammatory infiltrate of lymphocytes and mast cells. <sup>2</sup> The number of mast cells is particularly elevated in the detrusor muscle layer and to a lesser extent in the mucosa and submucosa.<sup>3</sup> Immunofluorescence may show strong diffuse or focal colouring of IgA throughout the urothelium. IgE can sometimes be seen on mast cells.<sup>4</sup> In some patients the bladder is fibrotic.

**Prevalence**

IC occurs 5-10 times more frequently in women than in men. Prevalence differs per study, in part due to the use of different definitions. In the Netherlands, prevalence is estimated at 8-16 cases per 100,000 women.<sup>5</sup> Recently, however, far higher figures were found in the USA: varying from 197 cases per 100,000 women and 41 per 100,000 men to 10% of third year women medical students.<sup>6-7</sup> IC is also found in children.<sup>8</sup> Due to the fact that the NIDDK criteria (*National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of*

*Health*, Bethesda, MD, USA) exclude the diagnosis of IC in persons under the age of 18 years, there are no figures in the literature concerning the prevalence of IC in children.

**Pathogenesis and etiology**

There are various theories concerning the cause of IC, none of which have been scientifically proven. It is consequently often suggested that IC may be multicausal. A number of these theories will be briefly discussed below.

**Increased permeability of the bladder mucosa**

The bladder wall is covered with a mucin layer which includes glycosaminoglycans (GAGs). GAGs are hydrophilic and maintain a stable layer of water between the urothelium and bladder lumen. The theory is that the defect in the GAG causes inflammation of the urothelium through contact with bacteria and toxic agents in the urine. This hypothesis is the rationale for treating IC with drugs aimed at replacing the GAG layer, such as pentosan polysulfate, heparin, hyaluronic acid and glucosamines.

**Mast cells**

Detrusor mastocytosis is defined as more than 28 mast cells per mm<sup>2</sup> tissue; fewer than 20 are considered to be normal.<sup>9</sup> While there is no correlation between the number of mast cells and the severity of the symptoms, there is a correlation, however, with

the degree of inflammation in the submucosa and the presence of "ulcers".<sup>10</sup> Most of the mast cells are degranulated due to IgE or other isotypes binding to their Fc receptors.

The vasoactive and proinflammatory mediators hereby released, such as histamine, prostaglandins, leukotrienes and tryptases, may possibly play a role in the pathogenesis. The urine may contain elevated concentrations of methylhistamine and tryptase.

Mast cells can also release mediators without degranulation under the influence of anaphylatoxins, neuropeptides and cytokines.<sup>11</sup> In patients with spina bifida and fibrosis of the bladder, it has been shown that mast cells stimulate the synthesis of collagen, leading to fibrosis.<sup>12</sup>

Mast cells also occur in the bladder wall in healthy people and in people with bacterial cystitis and bladder carcinoma, albeit in lower numbers.<sup>13,14</sup> There is no consensus concerning the significance of mast cells in the bladder in IC.

**Neurogenic factors**

The presence of degranulated mast cells at nerve endings has led to the hypothesis of neurogenic inflammation.<sup>15</sup> It is believed that stimulation of sensory nerves could lead to the release of neuropeptides and mediators from mast cells. This concept could explain inflammation limited to the bladder without direct damage to or infection of the bladder.<sup>16</sup> It has been demonstrated that mast cells in the bladders of mice can only provoke antigen-induced inflammation in the presence of neurokinin-1.<sup>17</sup>

**Infection**

One condition for the diagnosis of IC is the exclusion of any urinary tract infection. However, certain bacteria such as *Ureaplasma urealyticum* and *Mycoplasma hominis* require special culture methods and are therefore easily missed. There are various publications on the positive effects of antibiotics in some IC patients.<sup>18,19</sup> A possible role of bacteria in initiating and perpetuating IC cannot be entirely excluded since the relationship between diseases and microorganisms is a complex one, for example because the consequence of an infection depends on the genetic properties of individuals.

**Toxins in the urine**

In some patients, bladder symptoms may improve following surgical diversion of urine so that the urine no longer enters the bladder. This has led to the theory that the urine of IC patients contains toxic substances that cause inflammation. Support has been found for this hypothesis in animal experiments.<sup>20</sup> The improvement after urinary diversion could also be due to the absence of the mechanical effects

of bladder volume changes due to filling and emptying of the bladder.

A peptide, the antiproliferative factor (APF), has been found in approximately 95% of IC patients. APF is produced by the bladder epithelium but inhibits its proliferation and could consequently play a role in pathogenesis.<sup>21</sup>

**Genetic factors**

In a study with 8 monozygote twins and 26 dizygote twins, concordance was found in the monozygote twins varying from 37.5% (confirmed IC in the co-twin) to 62.5% (probable IC in the co-twin). In the dizygote twins, concordance was 0%.<sup>22</sup> Genetic factors may therefore have an influence on the likelihood of developing IC.

**Association with other diseases**

IC often occurs in association with other diseases (table 11.1). This concerns allergies, fibromyalgia, irritable bowel syndrome, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome.

**Allergy**

In a survey study in the United States, 40.6 % of the patients with IC stated that they suffered from allergy and in a Swedish study 41-47%.<sup>23,24</sup> In a Japanese study, young IC patients (20-39 years) were studied in more detail and compared with an older IC group (50-69 years). The study looked at the number of allergies, the type of IC symptoms ("painful type" or "frequency and urgency type"), skin tests, blood tests and the course of the IC following hydrodistension.<sup>25</sup> In two patients from the young group, IC was

diagnosis	prevalence (%)	
	IC	general population
allergy	40.6	22.5
irritable bowel syndrome	25.4	2.9
sensitive skin	22.6	10.6
vulvodinia	10.9	15.0
fibromyalgia	12.8	3.2
chronic fatigue syndrome	7.7	8.5
migraine	18.8	18.0
asthma	9.2	6.1
Crohn's disease/ulcerative colitis	7.3	0.07
rheumatoid arthritis	4-13	1.0
systemic lupus erythematosus	1.7	0.05
Sjögren's syndrome	8.0	0.5

considered to be part of generalised allergic diseases. In 25 patients an association was assumed between IC and the allergy and in 15 of these the symptoms of allergy and IC alternated or ran parallel. Eleven patients had multiple allergies. In the young patients, 86% had one or more allergies, in the older patients this was 19%.

### **Irritable bowel syndrome**

Irritable bowel syndrome (IBS) is a disorder of the function of the intestines and not an inflammatory condition. In questionnaires, 25-43% of IC patients mentioned they had IBS, 2-4x more than the normal prevalence.<sup>23,35</sup> IBS is clinically important as abdominal bloating may be responsible for pressure on the stomach (dyspepsia) and bladder. Inflammation is not part of IBS and this is a marked difference with IC. Further information can be found in chapter 8.

### **Fibromyalgia**

Fibromyalgia occurs in 3% of the population and more commonly in women than in men. The main symptom is pain all over the body, followed by fatigue, morning stiffness and sleep disturbances. In the USA survey 12.8% of IC patients stated that they suffered from fibromyalgia, 4x more frequent than in the general population.<sup>23</sup> Further information on fibromyalgia can be found in chapter 6.

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

Crohn's disease and ulcerative colitis are inflammatory bowel diseases of unknown cause. Some consider them to be autoimmune diseases. They are often combined under the term inflammatory bowel disease (IBD). This was also the case in the USA survey where 7.3% of IC patients stated that they suffered from IBD. This is 100x more frequent than in the general population.<sup>23</sup> Further information on Crohn's disease and ulcerative colitis can be found in chapter 8.

### **Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a systemic disease characterised by the specific way in which joints are affected by chronic inflammation. The disease is associated with systemic lupus erythematosus and particularly with Sjögren's syndrome.

RA occurs in 1-2% of the population. Peeker *et al* mentioned that RA occurred in 13% of their classic IC patients (with "ulcers") and in 4% of IC patients without ulcers.<sup>24</sup> This is about 10x more frequent than in the general population.

### **Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is the autoimmune disease which has been known for many years

to have a relationship with IC. IC in SLE patients was often called *lupus cystitis*.

In the USA survey 1.7% of IC patients stated that they suffered from SLE, this is 34x more frequent than in the general population.

SLE is a generalised autoimmune disease that occurs more frequently in women (10x) and non-whites. Symptoms and signs that occur most frequently are arthritis, red skin lesions after sun exposure such as a red butterfly lesion of the face, pericarditis and pleuritis (inflamed membranes around the heart and lungs), glomerulonephritis and increased lysis of red blood cells (*haemolytic anaemia*), white cells (*leukopenia*) and platelets (*thrombocytopenia*).

Antinuclear antibodies (ANA) can be found in all untreated patients. In addition, in many SLE patients it is possible to detect one or more other auto-antibodies such as anti-DNA and anti-Sm.

Antiphospholipid antibodies may cause venous and/or arterial thrombosis and a wide variety of complications in pregnancy.

Criteria for the diagnosis of SLE are summarised in Table 11.2. A patient may be said to have SLE if 4 out of 11 items are present at any time.

### **Sjögren's syndrome**

In 1992, as a consequence of the similarity observed between IC and Sjögren's syndrome, we began a clinical study of IC patients to investigate whether the presence of a second autoimmune disease could be demonstrated.<sup>27,28</sup> We recently presented data on 100 patients with IC who were investigated for the presence of Sjögren's syndrome.<sup>29</sup> The IC patients had characteristic irritative urinary voiding symptoms, no evidence of infection or other bladder disease, typical cystoscopic appearance demonstrable with maximal bladder distension, bladder biopsies ruling out other diseases and showing inflammation in the mucosa and submucosa with lymphocytic infiltrate

**Table 11.2 Summary of the criteria for the diagnosis of systemic lupus erythematosus (American Collega of Rheumatology 1997)**

1. malar rash
2. discoid rash
3. photosensitivity
4. oral/nasopharyngeal ulcer
5. arthritis
6. pleuritis or pericarditis
7. proteinuria > 0.5 g/day
8. neurologic/psychiatric disorder
9. haematologic disorder
10. anti-DNA, anti-Sm, or antiphospholipid antibodies
11. antinuclear antibodies (ANA)

and increased numbers of mast cells.

The diagnosis of Sjögren's syndrome was made according to the recent version of the European criteria for Sjögren's syndrome.<sup>30</sup> These consist of six defined items and can be summarized as follows:

1. ocular symptoms
2. oral symptoms
3. ocular signs
4. salivary gland histopathology
5. salivary gland involvement demonstrated by radiology, scan or salivary flow
6. auto-antibodies to SSA/Ro and/or SSB/La

The criteria allow a diagnosis of Sjögren's syndrome if four out of items 1-6 or three out of items 3-6 are present. This latter situation did not occur in our patient group as we did not further investigate patients for Sjögren's syndrome if both ocular and oral symptoms were absent. Item 3 was only tested if item 1 was present, item 4 was only tested if item 2 was present. Item 5 was never tested because of lack of reproducibility or sensitivity.

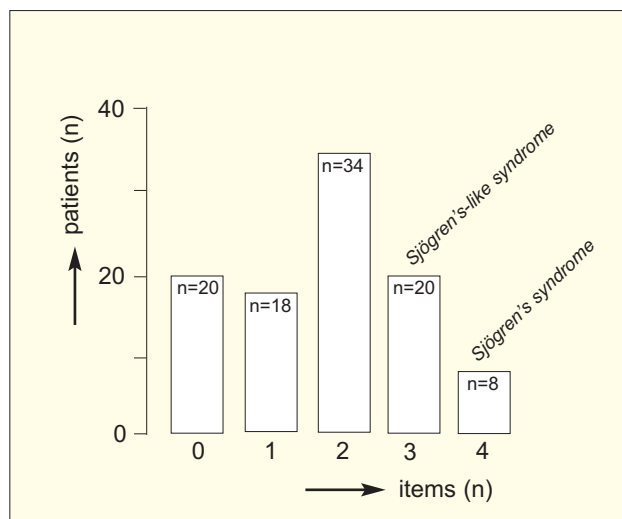
Table 11.3 shows the prevalence of each of the investigated items in the IC patients. Figure 11.2 shows the frequency distribution of the number of items present.

We concluded that in 8% of our patients with IC a diagnosis of Sjögren's syndrome according to the European classification criteria could be made. In addition, 20% of the patients had three items of these criteria and no other disease was found that could account for the present items. In a clinical situation, a diagnosis of Sjögren's syndrome (Sjögren's-like syndrome) is justified in these 20% too.<sup>27,29</sup>

This finding of a relationship between IC and Sjögren's syndrome has led to a hypothesis in which auto-antibodies against the muscarinic M3-receptor, which is present on exocrine cells and the detrusor muscle, play a role in causing early symptoms as well as causing local inflammation later on.<sup>31</sup>

Unfortunately, it is not yet possible to reliably demonstrate M3-receptor stimulating and blocking auto-antibodies.

<i>item</i>	<i>prevalence (%)</i>
ocular symptoms	68
oral symptoms	60
abnormal ocular test	16
abnormal salivary histology	16
antibodies to SSA/Ro or SSB/La	12



**Figure 11.2** Frequency distribution of the number of items of the European criteria for Sjögren's syndrome present in 100 patients with IC

Several authors have also studied the relationship between IC and Sjögren's syndrome. Peeker *et al* surveyed the clinical records of 222 patients with IC for diagnoses of autoimmune disorders. 43% of the IC patients had some type or degree of hypersensitivity/allergy. Rheumatoid arthritis occurred in 10% and inflammatory bowel disease (Crohn's disease and ulcerative colitis) in 1% but no diagnoses of Sjögren's syndrome were found.<sup>24</sup> Using a questionnaire, Leppilahti *et al*, on the other hand, recently found IC-like urinary symptoms in 5% of 870 patients with Sjögren's syndrome.<sup>32</sup>

**Conclusion**

The clinical relevance of the findings is that a high index of suspicion for Sjögren's syndrome is indicated in IC patients and *vice versa*. The findings also support the possibility of a common pathogenic mechanism such as has recently been proposed.<sup>31</sup>

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