published at: AWMF online
Das Portal der wissenschaftlichen Medizin

S2K guideline
Diagnosis and Treatment of Interstitial Cystitis (IC/BPS)

Long version

1st edition, version 1, last updated: September 30, 2018

AWMF register no.: 043/050

Publishing information

PUBLISHER

This guideline "Diagnosis and Treatment of Interstitial Cystitis (IC/BPS)" was initiated and written as a S2K guideline by the *Deutsche Gesellschaft für Urologie*.

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PERIOD OF VALIDITY AND UPDATING

Period of validity: 5 years

ICA-Deutschland e.V. is responsible for monitoring and updating this guideline.

VERSIONS OF THE GUIDELINE

The S2K guideline "Diagnosis and Treatment of Interstitial Cystitis (IC/BPS)" is published with the following components:

- Long version (this document) for doctors and therapists
- Short version for doctors and therapists
- Information for patients and their relatives

Please cite as follows:
Guideline group S2K guideline for interstitial cystitis (IC/BPS) long version, 1st edition, version 1, 2018.

Professional associations and organizations involved

Deutsche Gesellschaft für Urologie (DGU)
Deutsche Gesellschaft für Innere Medizin (DGIM)
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)
Deutsche Gesellschaft für Schmerzmedizin e.V. (DGS)
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ICA-Deutschland e. V., Interstitial Cystitis Association
Multinational Interstitial Cystitis Association (MICA)
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Reference was made to the following AWMF guidelines:

- *Brennen beim Wasserlassen* (Burning sensation when passing water), AWMF register no. 053/001
- *Harnwegsinfektionen bei Erwachsenen, unkompliziert bakteriell ambulant erworben: Epidemiologie, Diagnostik, Therapie und Management* (Uncomplicated, bacterial, community-acquired urinary tract infections in adults: epidemiology, diagnosis, treatment and management), AWMF register no. 043/044
- *Enuresis und nicht-organische (funktionelle) Harninkontinenz bei Kindern und Jugendlichen* (Enuresis and non-organic (functional) urinary incontinence in children and adolescents), AWMF register no. 028/006.
- *Chronischer Unterbauchschmerz der Frau* (Chronic lower abdominal pain in women), AWMF register no. 016/001
- *Langzeitanwendung von Opioiden bei nicht tumorbedingten Schmerzen – "LONTS"* (Long-term use of opioids for non-tumour associated pain), AWMF register no. 145/003

Special note:

Medicine is continuously developing, so that all information in this S2K guideline (particularly information relating to diagnostic and therapeutic procedures) can only reflect the current state of knowledge at the time of printing. Utmost care has been taken with respect to recommendations on treatment, as well as the selection and dosage of medicines. Users are nonetheless urged to consult the manufacturer's package leaflet and summary of product characteristics and. if in doubt, to consult an IC/BPS specialist.

These recommendations are based on the evidence identified, clinical expertise and patient preferences. They therefore explicitly include elements of subjective judgment. In this consensus-based (S2K) guideline, the strength of the recommendations has been determined and agreed upon via an online consensus process. We do not intend to indicate levels of recommendation (or levels of evidence). The strength of each recommendation will be expressed in a purely linguistic manner. In addition, the strength of the consensus (percentage of the guideline group agreeing with the consensus) will be given for each recommendation. The results of the voting procedure are presented in an easily digestible form, in a summary table in the Guideline Report.

The user retains full responsibility for each diagnostic or therapeutic application, medicine and dosage.

Registered trademarks (protected product names) are not specifically identified in this S2K guideline. The absence of a note to this effect cannot therefore be taken to mean that a name is an unregistered product name.

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I. Introduction

This S2K guideline has been developed as the result of a joint project initiated by the *Deutsche Gesellschaft für Urologie* to develop an S2K guideline. It has been developed by representatives of relevant professional associations and organizations. It is the first attempt to produce a guideline on this condition in the German language.

II. Objective

Although research into treatment options has made significant progress in recent years, there remains room for improvement in all aspects of the care given to IC/BPS patients.

Specifically, the new S2K guideline has the following aims:

- The detection, diagnosis and treatment of interstitial cystitis in German-speaking countries
- To agree upon key recommendations on high-priority problems in the care of people with IC, recommendations made by all groups involved in delivering this care, who at the same time have taken into consideration the views of patient and relative representatives
- To formulate and update recommendations in accordance with the current state of scientific knowledge, taking into account medical considerations
- To ensure an effective dissemination and implementation of these recommendations by having reached a broad consensus, achieved by the participation of patients and all professions and organizations involved in delivering care
- To give specific recommendations on coordinating care and reaching an agreement on that care between all disciplines and other healthcare professions involved in delivering it
- To identify barriers to the implementation of the new recommendation – and routes to overcoming these barriers
- To see that the recommendations made are systematically taken into consideration during education and training

III. Those at whom this guideline is aimed and area of application

This guideline is aimed at all professions that are involved in identifying, diagnosing and treating patients with interstitial cystitis (IC/BPS), including GPs, abdominal surgeons, proctologists, psychosomatic medicine specialists, gynaecologists, internal medicine specialists, physiotherapists, psychiatrists, pain therapists and urologists.

IV. Handling of conflicts of interest

All authors had disclosed any conflicts of interest in writing at the beginning of the guideline process. It was then determined that the risk that the group's judgment would be biased was negligible and that no special management of this issue would be necessary.

V. Literature selection

Literature searches in the existing EAU, AUA, Japanese and Canadian urology association guidelines were analysed and evaluated. The literature is broadly covered by the search strategies used by these guidelines. The literature searches for the above guidelines were followed by a systematic literature search. A systematic approach to expanding the literature was then taken. The cut-off date for the literature search was July 5, 2018.

Schlüsselwörter (D): Zystitis, Interstitielle Cystitis, Blasenschmerzsyndrom, IC, BPS
Keywords (E): Interstitial Cystitis, Bladder Pain Syndrome, Painful Bladder Syndrome, Pelvic Pain

1. Principles

1.1. Interstitial cystitis (IC/BPS): definition and terminology

Interstitial cystitis (IC/BPS) is a non-infectious chronic bladder disease characterized by pain, pollakiuria, nocturia and urgency, to varying degrees and in various combinations, where other conditions have been ruled out. A diagnosis of IC/BPS does not require a specific bladder volume or persistent pain.

There is to date no uniform global definition of the disease [1–3].

The terms bladder pain syndrome (BPS) and painful bladder syndrome (PBS) present too narrow a picture of IC/BPS, as they place the primary focus on pain [4–7].

Numerous factors have been posited as being potentially responsible for the aetiology of the condition. In view of the diversity of the aetiology and symptoms, various alternative terms to classify this condition have been proposed in recent years [8–10].

History and nomenclature [11]

1808	Philip Syng	An inflammatory condition of the bladder with an "ulcer" producing the same symptoms as a bladder stone.
1836	Joseph Parrish	A painful tic of the urinary bladder
1887	Skene	An inflammation that has destroyed the mucous membrane, partly or wholly, and has spread to the muscles.
1915	Hunner	A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).
1978 [12]	Messing and Stamey	The finding of multiple petechiae-like haemorrhages (glomerulations) on the second distention of the bladder is the hallmark of interstitial cystitis, and a reduced bladder capacity and Hunner's ulcers represent a different (classic) stage of this disease. In all stages, the characteristic histology finding is submucosal oedema and vasodilation.
1990	NIDDK	Unexplained urgency or frequency (seven or more voids per day), or pelvic pain of at least six months duration in the absence of other definable aetiologies.
2008 [4]	ESSIC	The authors agreed to name the disease bladder pain syndrome (BPS).
2015 [9]	Hanno	American Urological Association (AUA): "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."
2016 [1]	Homma	East Asian IC-Guideline: "A disease of the urinary bladder diagnosed by three conditions: lower urinary tract symptoms, Hunner lesions or mucosal bleeding after distension, and exclusion of confusable diseases. The characteristic symptom complex (hypersensitive bladder) includes bladder hypersensitivity, usually associated with urinary frequency, with or without pain."

Numerous other terms have been used in connection with IC/BPS (see figure 1)

Hypersensitive bladder (HSB) is an umbrella term used to describe a disease of the bladder with symptoms such as increased bladder sensitivity and increased urinary frequency. This may or may not be accompanied by pain. These symptoms can be caused by hyperactivity of sensory nerves [7]. Overactive bladder (OAB) is a complex of symptoms which similarly describes a disease of the bladder; characterized in this case by a strong urge to urinate, with increased urinary frequency and nocturia, possibly being accompanied by urge incontinence. It can in some cases be triggered by detrusor overactivity [7, 13, 14]. There is some overlap between the symptoms of these conditions. IC/BPS mirrors some of the symptoms of HSB but can also exhibit symptoms of OAB (see figure 1) [1, 7, 15–19].

Bladder pain syndrome (BPS) is a symptom complex in which, in the absence of an infection or another underlying disease, the sufferer experiences chronic bladder-associated pelvic pain, pressure or discomfort, and at least one other specific symptom (e.g., a frequent or persistent urge to urinate).

IC is a chronic inflammatory disease of the bladder in which, in addition to the BPS symptom complex, the bladder exhibits characteristic cystoscopy and/or histology changes. IC is divided into two subtypes:

1. Hunner type, in which Hunner's lesions are clearly visible on cystoscopy. This type is significantly more rare than non-Hunner type.
2. Non-Hunner type, in which no Hunner's lesions are observed during/after bladder distension [7].

Under the World Health Organization international classification of diseases, IC has the ICD code N30.1 [7, 15, 20–23].

Hypersensitive bladder

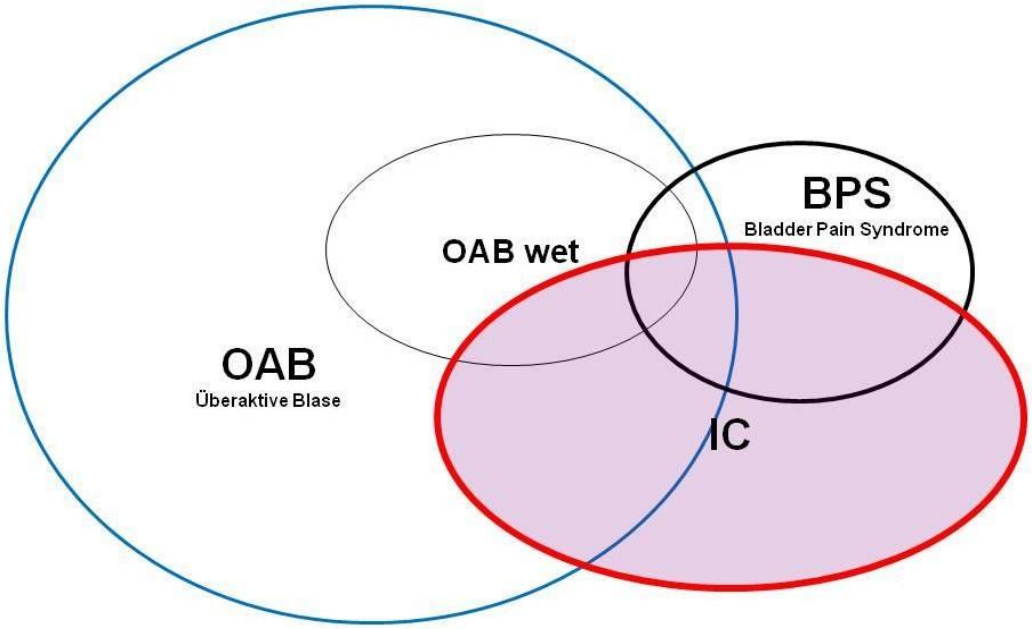


Figure 1 Overlapping frequency and urgency symptoms result in intersections between the individual conditions/symptom complexes and some overlap between the symptoms of individual conditions/symptom complexes. HSB (hypersensitive bladder) as an umbrella term, wet OAB (overactive bladder with incontinence); OAB (overactive bladder), BPS (bladder pain syndrome), IC (interstitial cystitis) [23].

1.2. Epidemiology

IC/BPS is a disease which can occur at any age. Even young children and adolescents can exhibit the IC/BPS symptoms described above [24]. Prevalence is highest in middle age. Women are nine times more likely to be affected than men. Prevalence in women is 52–500/100000 and in men 8–41/100000 [18, 25, 26].

Estimates of prevalence vary depending on how it is measured and being defined. The various epidemiological studies carried out have not always used the same diagnostic criteria [17, 27–34].

In Germany, IC/BPS is a rarely-diagnosed condition. The number of cases which remain undiagnosed is unknown.

1.3. Pathogenesis

The pathogenesis of IC/BPS remains unclear. The following pathogenetic factors have been proposed:

1.3.1 Urothelial dysfunction

Changes in urothelial cell differentiation and disorders of urothelial homoeostasis generally manifest themselves as damage to the glycosaminoglycan (GAG) layer and often to the urothelium, in some cases including complete denudation. The starting point is therefore probably damage to the urothelium. This induces damage to the GAG layer, allowing irritant substances in the urine or produced by urothelial cells to penetrate the submucosa and deeper layers of the bladder wall [3, 35–37].

A reduction in interleukin 8 expression leads to urothelial cell dysfunction. This can range from alterations in function to apoptosis, therefore affecting normal urothelium function. A significant increase in the rate of cell apoptosis, reduced cell proliferation, increased mast cell activation and reduced E-cadherin expression have been observed in people suffering from IC/BPS [38]. There is a statistically significant correlation between mast cell activation, increased urothelial cell apoptosis, reduced E-cadherin expression and pain scores measured on a visual analogue scale. This suggests that damage to the bladder mucosa leads to an increase in bladder sensitivity and pain [39]. Dysregulation of urothelial function with increased permeability of the bladder mucosa can cause IC/BPS symptoms. Potassium leakage into the bladder interstitium through the damaged urothelium particularly results in the above IC/BPS symptoms [40].

Various studies have shown that antiproliferative factor (APF), a glycopeptide, can cause anomalies in urothelial cells (reduced proliferation, reduced tight junction formation, and increased paracellular permeability) [37, 41–44].

1.3.2. Inflammation

People with IC/BPS have been found to have high concentrations of immunoglobulins and inflammatory markers in tissue and urine samples. High expression of B cell and T cell markers associated with focal lymphoid aggregates in the submucosa has been demonstrated. These observations apply to people with Hunner-type IC/BPS. Nerve growth factor (NGF) is also raised in people with IC/BPS, as well as in other conditions such as OAB. NGF concentration correlates with pain severity in IC/BPS. The growth factor brain-derived neurotrophic factor (BDNF) has also been observed to be elevated in people with IC/BPS [45–48].

People with IC/BPS have also been shown to have elevated levels of proinflammatory cytokines (IL-6, IL-10 and IL-17A) [49] and leukotrienes [49]. One study investigated urine cytokine concentrations, where levels of proinflammatory chemokines and cytokines (CXCL1, CXCL10 and IL-6) were generally 10–100 times higher in people with both types of IC/BPS than in a control group [50].

These results demonstrate that, in addition to mast cell activation and histamine secretion, other inflammatory processes are also involved [49-52]. It has been shown that activation of the leukotriene D4 receptor leads to sensitization of detrusor muscle cells to histamine.

People with Hunner-type IC/BPS have been shown to have an increase in inflammation and over-expression of proinflammatory genes. Gene expression differs between IC/BPS sufferers with small bladder volumes and IC/BPS sufferers with normal bladder volumes. This may point to a difference in pathophysiology. In addition, gene expression in urine samples from people with Hunner-type IC/BPS differs from that in a control group and in patients with non-ulcerative IC/BPS [5, 6, 35, 53–55].

1.3.3. Neuronal hyperactivity

Neuropathic pain can be caused by injury to or dysfunction of the nervous system. Whereas nociceptive pain is caused by harmful stimuli, neuropathic pain is characterized by spontaneous pain and hypersensitivity to harmless stimuli. Causes of this neuronal dysfunction include neuronal hyperexcitability. Changes in afferent excitability are primarily the result of changes in various ion channels. A large peripheral input is generally necessary to trigger neuropathic pain [56-59].

Bladder inflammation induces hyperactivity of the afferent nerves [60]. The TRPV1 receptor is overexpressed in the mucosa and muscle tissue of the bladder in people with IC/BPS. Increased NGF, ATP and prostaglandin secretion are also observed. Prostaglandin is significantly elevated in people with Hunner-type IC/BPS, but not in people with the other subtypes [6, 51, 61–63].

Urine NGF levels appear to correlate with pain levels and response to treatment. Patients who respond to treatment and have reduced pain (on a visual analogue scale) are also found to have a reduction in urine NGF levels [51].

Increased sympathetic nervous system activity has been postulated in IC/BPS. In this sense, there are parallels with diseases such as fibromyalgia, chronic fatigue syndrome (CFS) and irritable bowel syndrome [64–66]. Elevated levels of urine noradrenalin in IC/BPS also point in this direction. Noradrenalin is primarily present in sympathetic nerve fibers and the central nervous system.

In 2000, Jasmin et al. [67] demonstrated that mast cell-mediated inflammation of the bladder could be provoked in an animal model by infecting the central nervous system with pseudorabies virus. They observed mast cell degranulation and an increase in urine histamine. Cystitis did not occur in any animals given a mast cell degranulator for five days, starting on the date of viral infection. Neurogenic inflammation was solely mast cell-mediated. CNS activation, because of factors such as virus infection or immobilization stress [68], enables CRF-induced mast cell degranulation to trigger cystitis. This may explain the mechanism of action of the therapeutic approach of stabilizing mast cells and blocking inflammatory mediators [69].

The autonomic function of the sympathetic nervous system appears to be altered in people with IC/BPS, resulting in their having abnormal nerve self-regulation. In patients with abnormal findings on endoscopy (glomerulations and/or Hunner’s lesions), abnormal heart rate and blood pressure responses are observed – even when anesthetized. Hydrodistension of the bladder leads to an increase in blood pressure and heart rate [24, 70–72]. A segmental increase in pain sensitivity with spinal sensitization has also been observed in people with IP/BPS [73]. They can also exhibit higher levels of mental stress and the magnification of various sensitivities. This situation is probably also induced by systemic or central neuronal hyperactivity [74].

1.3.4. Microcirculatory impairments

People with IC/BPS have raised expression of angiogenic growth factors in the bladder and endothelial cell death. Increased, dysregulated angiogenesis causes mucosal haemorrhages during hydrodistension. High levels of vascular endothelial growth factor (VEGF) induce immature angiogenesis, resulting in microvessels with insufficient coverage of pericytes, leading to haemorrhagic vessels. VEGF expression is associated with the degree of pain described by patients. It is also possible that the imperfectly formed microvessels contribute to glomerulations (petechiae-like haemorrhages) [75, 76].

1.3.5. Exogenous substances

Nearly 90% of people with IC/BPS report intolerances to a broad spectrum of foods. Pathological mechanisms appear to be responsible for the association between food consumption and the occurrence or worsening of symptoms. These include peripheral and/or central neuronal hyperexcitability, bladder epithelium dysfunction and signal transduction between various organs.

Recent survey data suggests that the consumption of citrus fruits, tomatoes, horseradish, vinegar, pepper, glutamate, artificial sweeteners, tea, coffee, carbonated and alcoholic beverages and Indian or Thai food can increase the severity of IC/BPS symptoms. On the other hand, both calcium glycerophosphate and sodium bicarbonate appear to improve symptoms [77–80].

In 1993, Gillespie published a comparison of 237 women and 13 men with IC with 10 healthy control subjects. Compared to the control group, the IC group was found to have lower blood prolactin and serotonin levels over a 24-hour period after consuming high-tryptophan foods, and higher histamine and urea levels, due to impaired conversion of tryptophan to serotonin. There was no difference in tryptophan levels. The IC group, in comparison to the control group, was also found to have raised urine levels of indicans, kynurenic acid and xanthurenic acid and raised urine pH-values. 83% of people in the IC group experienced increased pain and urinary frequency, bladder spasms and a noticeable odor to their urine. 10 members of the IC group were monitored following a further change in diet. In these subjects, histamine and urea levels and urine indican, kynurenic acid and xanthurenic acid levels all returned to normal. Blood prolactin and serotonin levels, however, remained abnormal [81].

1.3.6. Histamine intolerance

IC/BPS may be an expression of histamine intolerance. Histamine intolerance is a food intolerance. Its precise pathophysiology has yet to be fully clarified, and there is no scientifically recognized test method. Depending on the histamine receptor involved, the disease can give rise to a wide range of symptoms, ranging from irritable bowel syndrome to flushes, urticaria, rhinitis, dyspnoea and migraines to tachycardia.

Histamine intolerance is defined as an intolerance to dietary histamine. It is caused by a deficiency in the enzyme diamine oxidase (DAO), which breaks down histamine, or an imbalance between histamine and DAO. Most foods known to trigger IC/BPS symptoms contain histamine, release histamine or inhibit DAO. Histamine, however, is also formed by some gut bacteria, enterocytes and immune cells. At 1% of the population, the prevalence of histamine intolerance is comparable to that of IC/BPS. Similarly, 80% of its sufferers are middle-aged women [82–84]. A retrospective study found that 65% of 97 people with IC/BPS had elevated levels of histamine in their stool [85].

1.3.7. Infections

A possible link between IC/BPS and a bacterial or viral infection (e.g., uropathogenic Escherichia coli, BK polyoma viruses) of the bladder is the subject of ongoing debate and some amount of controversy in the literature [86]. Nonetheless, women with recurrent urinary tract infections have an increased rate

of urothelial cell apoptosis, an increased mast cell count and a reduction in E-cadherin. These factors could explain their hypersensitivity symptoms [87]. It should be noted that IC/BPS symptoms could also occur in conjunction with bacterial infections [88].

1.3.8. Pelvic floor dysfunction

Pelvic floor dysfunction can affect genitourinary and anorectal function. The prevalence of pelvic floor hypertonia in people with IC/BPS ranges from 50% to 87% [89]. Musculoskeletal abnormalities are a common finding. Relaxation is delayed or absent and other muscle functions, such as strength, endurance and coordination, are often reduced [15]. Myofascial pain, trigger points and muscle spasms are common findings in people with a hypertonic pelvic floor [90].

1.3.9. Visceral organ crosstalk between the gut and bladder

Irritable bowel syndrome is one of the most common comorbidities in IC/BPS. In a rat model, it has been shown that inducing intestinal inflammation with trinitrobenzene sulphonic acid leads to increased bladder permeability within 24 hours. Conversely, intravesical instillation of protamine sulphate, which increases bladder permeability, causes an increase in intestinal permeability within 24 hours [91].

This “leaky gut syndrome” – damage to the tight junctions in the intestinal epithelium – appears to be capable of triggering autoimmune diseases, as well as food allergies and sensitivities [92].

1.3.10. Endometriosis

Around one-third to one-half of people with endometriosis are also likely to suffer from IC/BPS. A large epidemiological study involving over 9,000 people found an elevated hazard ratio of 4.4 for developing IC/BPS in women with endometriosis, compared to women without endometriosis [93]. A systematic review found that endometriosis was diagnosed concomitantly with IC/BPS in 48% of patients [94].

Consequently, co-occurrence of endometriosis and IC/BPS is very common. People with IC/BPS should therefore be asked about endometriosis when having their medical history taken. In situations where required (involving disabling dysmenorrhea, sterility, dyschezia, etc.), additional diagnostic steps should be taken to detect and treat endometriosis. Patients with endometriosis should be asked whether they have any bladder problems and, if required, further steps to diagnosis of IC/BPS should be taken.

1.3.11. Non-bladder associated factors

People with IC/BPS frequently have co-morbidities such as irritable bowel syndrome, autoimmune disorders, general exhaustion, chronic fatigue syndrome, fibromyalgia and functional somatic syndrome or neurological, rheumatological or mental health conditions.

The presence of non-bladder conditions correlates with the severity of IC/BPS symptoms. One study looked at the prevalence of non-bladder conditions in 2,185 women with IC/BPS and it found that all had at least one non-bladder condition [70, 88, 95–100].

Previous pelvic operations (e.g., hysterectomy and other non-bladder operations) appear to increase the risk of IC/BPS [96].

People with IC/BPS were at significantly greater risk of developing coronary heart disease than controls. People with IC/BPS should therefore be tested for modifiable risk factors for CHD [101].

1.3.12. Somatic symptom disorders

Pain receptors and pain-experiencing structures in the nervous system are extremely modulatory, especially when subjected to chronic stimulation. This can cause pain perception to be amplified, developing into chronic pain syndrome [102].

Various brain regions are involved in experiencing and modulating pain, but each is also involved in other functions. This implies that other skills (concentration, memory, etc.) can also be adversely affected by pain [103].

It has also been reported that strong feelings (of stress, anxiety, anger, defensiveness, etc.) can lead to muscle tension, producing various somatic symptoms [104].

Because IC/BPS is a long-lasting clinical picture, people with the condition can also develop somatic symptom disorder. Somatic symptom disorder places ever-greater restrictions on many aspects of the quality of life. Three criteria can be used to determine the presence of somatic symptom disorder [105]:

Criterion A
One or more somatic symptoms that are distressing or result in a significant disruption of daily life.

Criterion B
Psychological features related to the somatic symptoms: disproportionate and persistent thoughts about the seriousness of one's symptoms (cognitive dimension), a persistently high level of anxiety about one's health or symptoms (emotional dimension), and excessive time and energy devoted to these symptoms or health concerns (behavioral dimension).

Criterion C
The state of being symptomatic is persistent (typically, lasting more than six months).

According to DSM-5, criteria A, B (at least one of three psychological dimensions) and C must be met for a diagnosis of somatic symptom disorder [105].

1.3.13. Microbiome

Recent progress and insights in the field of microbiome research may give rise to new diagnostic and therapeutic approaches, and these may be relevant to IC/BPS.

DNA sequencing of urine from people with IC/BPS showed reduced bacterial diversity and an increase in lactobacilli species, compared to healthy women [106]. DNA sequencing and PCR of stool DNA in people with IC/BPS showed reduced levels of these bacterial species: *Eggerthella sinensis*, *Collinsella aerofaciens*, *Faecalibacterium prausnitzii*, *Odoribacter splanchnicus* and *Lactonifactor longoviformis* [107].

These observations do not allow, at present, any specific proposals regarding treatment.

1.3.14. Genetics

Genetic factors may play a role, but this has not yet been unambiguously demonstrated [34, 108].

1.4. Disease progression

IC/BPS is a chronic recurrent to chronic progressive condition affecting the bladder. It involves chronic inflammation of all layers of the bladder wall [109]. There is some discussion concerning the possibility of spontaneous remission [110]. In late stages, patients often have a shrunken bladder with only a small capacity [111].

The range of symptoms in IC/BPS is similar to that of other common urological conditions – such as recurrent urinary tract infection – and gynecological conditions (e.g., endometriosis) [112]. As a result, misdiagnosis is common, especially in the early stages of the condition. This explains why a substantial proportion of people with IC/BPS have large numbers of visits to the doctor and undergo multiple diagnostic and surgical interventions in the years prior to diagnosis [88, 113–115].

Many patients experience tightness and tenderness in the muscles of the pelvic floor and other somatic tissues [116–123]. Also common are anomalies such as muscle tenderness and connective-tissue restrictions relating to the muscles, fascia and subcutaneous tissue of the pelvic floor, hips and abdominal wall. These somatic anomalies may contribute to painful symptoms in people with IC/BPS [124].

During a flare up, there is often a constant feeling of needing to urinate, which focuses the sufferer's attention to their bladder and makes it impossible for them to focus on normal, everyday activities. Often, they are only able to pass only a few drops of urine at a time. Patients often support micturition by exerting abdominal pressure, which only worsens the pain.

Over a one-year period, 48% of 56 patients with chronic pelvic pain (IC/BPS or chronic prostatitis) experienced at least one exacerbation of their symptoms (44.4% once, 29.6% twice, 25.9% more than three times). These exacerbations lasted from two days to more than two weeks [125].

A variety of psychopathological personality factors and behaviors appear to play a major role in determining the progression of the condition. These include: ineffective coping strategies, indecisiveness, behaviors characteristic of type A somatic symptom disorder [105] and high sensitivity to sensory stimuli [126].

Research on chronic pain disorders in general (of which IC/BPS is one example) has found that social stress factors in childhood and adolescence appear to play an important role. It was discovered that children who had experienced a disruption in their early-childhood emotional attachment to their caregivers had failed to develop systems for dealing with stress properly. There is some discussion of whether lack of coping strategies for dealing with stressful situations can have a negative effect on disease progression [127].

1.4.1. Effects and consequences of IC/BPS

80% of people with IC/BPS report problems in their day-to-day life, with 40% of them reporting severe problems, including a repeated or permanent inability to work. Additionally, the majority of female sufferers report that they experience symptoms and reduced libido during sexual intercourse [128, 129]. Partnership conflicts, leading in some cases to psychiatric treatment, can also occur. The result is a significant impact on quality of life with psychosomatic changes [88, 114, 115, 130–132].

1.4.2. Miscellaneous

A cohort study found a 52% increase in the risk of ischaemic stroke in people with IC/BPS, compared to a control group [133].

1.4.3. Tumors

0.36% of people with IC/BPS developed bladder carcinoma and 0.22% upper urinary tract cancer after three-to-nine years (control group 0.06% and 0.10%, respectively). This significant increase in cancer risk in people with IC/BPS may be explained by inflammatory changes in the bladder wall [134].

2. Diagnosing IC/BPS

2.1. Medical history

Diagnosis should start with a detailed medical history. The person taking the history should inquire about current symptoms and their effects, acute and chronic diseases, previous operations and non-surgical treatments, previous and current medication and any complementary medical interventions. In addition, the person taking the history should inquire about any addictions and any physical or mental ill-treatment or abuse [109, 135–137].

Recommendation:	we recommend	Strong consensus	100 %

2.2. Differential diagnosis

It is important to rule out other confusable disorders.

Table 1: Confusable disorders
(After the guideline *Chronischer Unterbauchschmerz der Frau* [138])

Diseases of the musculoskeletal system and connective tissue	Pelvic floor dysfunction Chronic back pain Fibromyalgia Hernias Malignant disorders of the musculoskeletal system and connective tissue Myofascial pain, trigger points Scar tissue pain
Gastrointestinal disorders	Inflammatory bowel disease Chronic constipation Chronic intestinal pseudo-obstruction Small or large intestine stenosis Malignant diseases of the intestine Irritable bowel syndrome
Gynecological disorders	Endometriosis/adenomyosis Malformations (e.g., accessory ovary and uterus didelphys) Malignant gynecological diseases Ovarian remnant syndrome/residual ovary syndrome Ovulation pain Pelvic inflammatory disease (PID) and its consequences Radiation-related disorders Pelvic congestion syndrome (pelvic varices) Cervical stenosis with hematometra

Neurogenic conditions	Genital herpes Nerve compression syndrome Neuralgia/neuropathic pain Varicella zoster
Mental health disorders	Mood (affective) disorders Adjustment disorders Schizophrenia, schizotypal disorder and delusional disorders Somatoform disorders
Urological disorders	Functional disorders of the bladder Chemical cystitis Chronic urinary tract infections (especially bacterial and parasitic) Chronic prostatitis Malignant urological disorders Radiation cystitis Urethral syndrome Urolithiasis

Recommendation:	We recommend	Strong consensus	100 %

2.3. Questionnaires and record sheets (see appendix)

The following questionnaires are available for advanced pain diagnostics:

- O'Leary-Sant interstitial cystitis problem and symptom indices (ICPI/ICSI)
- Pelvic Pain and Urgency/Frequency patient symptom scale (PUF)
- Bladder Pain/IC Symptom Score (BPIC-SS)

The ICSI/ICPI has high sensitivity but low specificity; therefore, it should not be used for a differential diagnosis of IC/BPS [139]. The ICPI/ICSI is excellent for recording symptoms such as increased frequency and bladder discomfort. Use of this questionnaire after treatment can also be helpful in assessing treatment outcomes. One disadvantage of this questionnaire is that it does not record general symptoms, such as dyspareunia and pelvic pain [140].

The PUF questionnaire (see appendix) includes additional questions on dyspareunia and the presence and location of pelvic pain. A score of 12 or above is considered significant [141]. The PUF is excellent for evaluating and assessing treatment outcomes in patients with IC/BPS [142]. There is, however, no correlation between PUF questionnaire scores and cystoscopy findings. Consequently, the questionnaire does not appear to be a reliable predictor of the presence of IC/BPS or for the severity of the condition [143]. In combination with a potassium sensitivity test, however, this questionnaire does seem to be suitable for identifying patients with chronic pelvic pain with bladder involvement [144].

The Bladder Pain/IC Symptom Score (BPIC-SS) is primarily used in clinical research [145].

Record forms can be used to record pain and micturition resp. their course over time (e.g., pain dairy and voiding/drinking diary; see appendix).

The Female Sexual Function Index can be used to measure sexual function in women with IC/BPS. A validated German version is available (FSAFI-d) [146].

* There are no validated German-language versions of the ICPI/ICSI, PUF or BPIC-SS (see appendix for a German translation of the PUF).

Recommendation:	We recommend	Strong consensus	100 %

2.4. Biomarkers

There are, at present, no internationally-recognized biomarkers for diagnosis of IC/BPS.

There is ongoing research into many biomarkers, including APF, urine and/or serum NGF and proinflammatory cytokines or chemokines. An increase in chemokines or receptors involved in pronociceptive inflammatory reactions in the tissues has been reported. Research is also being carried out on a metabolic urine biomarker – etiocholan-3α-ol-17-one sulphate (Etio-S) – and studies to date have shown 90% sensitivity and specificity in differentiating between IC/BPS and other conditions. In addition, urinary Etio-S levels correlate with known symptom scores and they may be able to be used to distinguish between high- and low-symptom subgroups [6, 19, 46, 47, 50, 52, 147–150].

A further study investigated the general presence of various metabolites in urine. 200 known and 290 unknown metabolites were detected, using gas chromatography-mass spectrometry. Most of the metabolites present at different concentrations in the control group fell into the category of unknown metabolites. The level of histidine and erythronic acid was upregulated in people with IC/BPS, compared to that of the control group, whereas the level of tartaric acid was downregulated. Histidine is a precursor of histamine, which could point to an increase in the mast cell population [151].

No recommendation made	Strong consensus	95 %

2.5. Physical examination

A physical examination should be carried out. It should, in particular, involve an examination of the genitalia in women and the penoscrotal area in men. Pain mapping in the genital area should also be performed. A digital rectal examination should be carried out on both sexes, with special attention being paid to musculofascial dysfunction (see appendix for record sheet).

Recommendation:	We recommend	Strong consensus	100 %

2.6. Urine testing

Urinalysis using test strips and a urine culture should be performed. The urine culture is usually normal, unless the patient is suffering from an acute urinary tract infection. Urine cytology should be performed where sterile leukocyturia and/or microhaematuria are detected.

Recommendation	We suggest	Strong consensus	85 %

2.7. Additional investigations

Urosonography should be performed.

Recommendation	We suggest	Strong consensus	90 %

In men, uroflowmetry (including measurement of residual urine volume) should be performed.

Recommendation	We suggest	Strong consensus	100 %

Cystoscopy should be performed. Hunner's lesions can be recognized as red mucosal lesions lacking a normal capillary structure (associated with convergent vessels), not covered by fibrin clots and with no nearby scarring. It is essential that the mucosa of the bladder be observed from the earliest stage of filling, as Hunner's lesions are easily overlooked after bladder distension. These lesions are more easily observed using narrow-band imaging during cystoscopy [18, 152].

Recommendation	We suggest	Strong consensus	90 %

Hydrodistension is carried out under general or spinal anesthesia. A standardized method should be used to record observations from the procedure. A bladder that appears normal before hydrodistension can exhibit glomerulations, cracking or waterfall-like hemorrhages during or after hydrodistension [1, 153].

Recommendation	May be considered	Strong consensus	80 %

A flow EMG or urodynamic testing with filling cystomanometry and pressure uroflowmetry can be useful where required, allowing an evaluation of bladder sensation and maximum cystometric capacity [154].

Recommendation	May be considered	Strong consensus	100 %

2.8 Potassium chloride (KCl) test

A potassium chloride test can also be performed, carried out on an awake patient. The test provides information on elevated-pain sensitivity. A bladder capacity of less than 350 ml and a positive potassium chloride test have a positive predictive value for IC/BPS of 91.2%. The KCl test is based on the assumption that IC is the result of a change in epithelial permeability in the bladder [155–157].

This epithelial dysfunction allows soluble urinary products (urea and potassium) to penetrate the bladder wall. Potassium causes depolarization of nerves, muscles and tissue damage, resulting in urgency and pain. This test is positive in 80% of people with IC, but it is also positive in people with OAB, HSB, prostatitis, gynecological CPPS, radiation cystitis and acute urinary tract infections (sensitivity for LUDE – lower urinary dysfunctional epithelium). It is negative in 98.3% of healthy people (specificity) [158, 159].

Another study found that a KCl test with 40 ml of a 0.4 M solution had a specificity of 81.6% and a sensitivity of 85.5% in people with IC [160].

The test is also predictive for the success or failure of GAG therapy. Patients with a more positive than negative KCl test result are significantly more likely to benefit from instillation therapy [148].

A modified version of the test uses a 0.2 M solution to reduce the pain experienced during the

procedure. The authors demonstrated a 30% reduction in maximum bladder capacity in IC/BPS patients. The test was pain-free in all the control subjects and 82% of people with IC, compared to filling with a physiological saline solution [161].

As an alternative, a small number of papers propose intravesical instillation of lidocaine for diagnostic purposes. This may allow identification of the bladder as the source of symptoms. Various procedures have been described. In some cases, lidocaine (200 mg/10 ml) is combined with 8.4% sodium bicarbonate. Procedures ranging from one-off instillation for one hour to continuous administration over a period of two weeks have been described. To date, there is no uniform, standardized procedure [162, 163].

Recommendation	May be considered	Strong consensus	90 %

2.9. Biopsy of the bladder wall

A biopsy of the bladder wall, including the detrusor muscle, may be performed if required [164]. A bladder biopsy is not essential for diagnosis of IC/BPS. Hunner-type IC exhibits epithelial erosions and thick layers of inflammatory infiltrate in the bladder, which differ markedly from non-Hunner-type IC and HSB [35].

Mast cell counts in bladder biopsies could be a criterion for diagnosing IC/BPS in principle, since mast cell activation also plays a role in this condition and may be involved in pain production (mast cell activation leads to the sensitization of peripheral nociceptive nerve fibers).

Other factors, however, are also involved in pain production; NGF is one example. Various studies use mast cell counts (< 28 mast cells/mm²) in detrusor tissue samples as a marker for identifying IC/BPS, as do the diagnostic criteria of the International Society for the Study of Bladder Pain Syndrome [8, 165, 166].

This diagnostic criterion presents some difficulties, as mast cells are involved in many different inflammatory processes; therefore, they are also found in people who do not have IC/BPS. They are particularly involved in the development of allergies, which are especially common in the industrialized world.

Where a urologist suspects IC, they should inform the pathologist of this suspicion, so that the biopsy can be subjected to extended morphological diagnosis with van Gieson's stain, to visualize any fibrotic changes [167].

Hunner-type and non-Hunner-type IC can be distinguished based on lymphocyte infiltration and evaluation of urothelial integrity. There is, however, no difference in mast cell populations [8, 87, 165].

Another approach is immunohistological investigation of neurotransmitter receptors in the detrusor muscle. Using the increased immunoreactivity of the muscarinic acetylcholine receptor M2, the P2X1 and P2X2 purinergic receptors and the histamine H1 receptor, it was possible to differentiate between people with IC/BPS and normal controls with an accuracy of 89.46%. Patients with this receptor profile had a 9.25-times enhanced risk for IC/BPS [150].

Recommendation	May be considered	Strong consensus	85 %

2.10. Stool diagnostics

In complementary medicine, it is customary to identify gut microorganisms (in the past, exclusively by culturing – today, increasingly using sequencing) in patients with gastrointestinal symptoms, as well as in diseases involving disorders of the immune system and the barrier function of the intestinal mucosa – which can certainly be the case in IC/BPS.

Recommendation	May be considered	Strong consensus	95 %

3. Treatment

Preamble

For all treatment options, the current approval status in relation to IC/BPS or off-label use must be considered.

3.1. Conservative treatment

3.1.1. Lifestyle changes

Clothing, sexual activity and sporting activities should be individually adapted so that they do not lead to a worsening of symptoms [168–171]. Sufferers should avoid getting too cold and avoid stress [172, 173]. Bladder training with controlled-fluid intake can reduce the intensity and frequency of the need to urinate [174].

Recommendation:	We recommend	Strong consensus	100 %

3.1.2. Diet

Since IC/BPS is often associated with food intolerances, a food-and-symptom diary combined with an individually-tailored elimination diet followed by gradual re-exposure can play an important role in patient management [168]. Citrus fruits, tomatoes, horseradish, vinegar, pepper, glutamate, artificial and nutritive sweeteners, plus tea, coffee, carbonated drinks, liquor and spicy foods cause a worsening of symptoms in many people with IC/BPS. Foods not fermented or matured through microbial action are to be preferred, as they have a lower histamine content. A low-carbohydrate, low-FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet may be helpful. Such a diet improves symptoms in people with irritable bowel syndrome, a disease in which it is known that histamine release from intestinal mast cells is one of the main pathogenetic mechanisms [77–80, 175, 176].

Recommendation:	We recommend	Strong consensus	100 %

3.1.2. Psychological/psychiatric support

In view of the persistent nature of the condition, depression and exhaustion are common findings. Symptoms such as general malaise, pain with no clear cause, feeling cold and feeling bunged up are often observed. Depression and/or exhaustion can be treated by a psychotherapist. Such therapy can reduce depression and/or exhaustion [9, 43, 177].

Social support or support from an IC/BPS patient support group is an essential therapeutic instrument for people with IC/BPS. Use of the biopsychosocial model was also successful in improving quality of life [170, 177, 178].

Recommendation:	We recommend	Strong consensus	100 %

3.1.3. Physiotherapy

IC/BPS is often associated with an overactive pelvic floor [90]. Physiotherapy from a specialist, a pelvic-floor physiotherapist, is recommended as the first treatment option for pelvic floor dysfunction

(level of evidence 1a) [179]. Relaxation techniques, such as the contraction-relaxation technique (with or without the use of biofeedback), and myofascial techniques such as trigger point therapy can reduce pelvic floor tightness, improve muscle function and reduce myofascial pain in both women and men [119, 180–182]. See appendix for muscle-function examination record sheets (vaginal and anal pelvic floor function examinations).

Studies by Fitzgerald have found that results from treating IC/BPS with myofascial physical therapy are significantly better than with global massage [124]. Massage following the recommendations of Dresden physiotherapist Stefan Thiele (also known as Thiele massage) and pelvic floor stretches resulted in a moderate-to-good improvement in pollakiuria, nocturia and urgency [120].

Vibration therapy using a special vibration plate (5–10 Hz) has very positive effects on pelvic floor relaxation. Other treatment options include connective tissue and foot reflexology massage. These methods have not been evaluated with respect to IC/BPS.

Recommendation:	We recommend	Strong consensus	100 %

3.2. Oral drug therapy

3.2.1 Pentosan polysulphate

Pentosan polysulphate (PPS) is the best-studied drug for treating IC/BPS. By repairing the GAG layer of the urothelium, PPS can provide significant relief of IC/BPS symptoms. This, in turn, prevents the passage of substances dissolved in the urine, which have a toxic or irritant effect on the bladder wall. In addition, PPS improves bladder perfusion, which counteracts any deficits in the bladder microcirculation [183]. Where there are relevant pathological findings, however, the anticoagulant effect of PPS should be considered in assessing the potential risks and benefits.

Overall, side effects are comparable both quantitatively and qualitatively to a placebo. It can take from three to six months for the drug to take effect. Symptoms of IC/BPS can be controlled with this drug in many cases. A long-term effect and tolerance have been described.

Efficacy is also dependent on how soon after diagnosis treatment is commenced. The sooner treatment is started, the more effective it is. In addition, it has been shown that there is a significant positive correlation between a reduction in the O'Leary-Sant Interstitial Cystitis Symptom Index score and satisfaction with treatment with PPS. In terms of efficacy, the duration of treatment with PPS appears to be more important than the dose. 300 mg of PPS per day in three equal doses was as effective as a higher dose [88, 184–191].

These findings contrast with the results of a 2015 placebo-controlled double-blind study. However, patient selection in this study differed from the previous studies in key respects and this study had a high placebo dropout rate. Because no initial cystoscopy was performed, it is not clear what type of patients had been investigated. The study was terminated early, following an unplanned interim analysis [192].

Since 2017, pentosan polysulphate is the only oral drug approved for the treatment of IC/BPS with glomerulations or Hunner’s lesions in Europe.

Recommendation:	We recommend	Strong consensus	100 %

3.2.2. Amitriptyline

As a tricyclic antidepressant, amitriptyline alters pain transmission in the central nervous system by

inhibiting serotonin and noradrenaline reuptake. In addition, by binding to H1 receptors, it also inhibits mast cell activation. In non-controlled clinical studies, it was found that the frequency and intensity of bladder pain was reduced in 26–73% of patients [193–195]. The reduction in pain and discomfort and change in O'Leary-Sant interstitial cystitis problem and symptom indices were statistically significant, compared to a placebo [196].

A randomized, placebo-controlled study from 2004 found a statistically significant improvement in pain and urgency symptoms in the amitriptyline group, but no statistically significant improvement in frequency or bladder capacity [196]. By contrast, a larger, multicenter, randomized, placebo-controlled trial from 2010 found no statistically significant improvement in symptoms with amitriptyline treatment. Retrospective re-analysis of the data showed a possible effect in those patients taking amitriptyline at a dose of 50 mg or more [197].

Anticholinergic side effects constitute a limitation when taking amitriptyline; they have led to some patients to stop taking the drug. A long-term study found that side effects were experienced by 86% of patients [198].

Non-controlled and double-blind studies have shown moderate efficacy. The response rate in a group treated with at least 50 mg as a single dose was significantly higher than in the placebo group [197]. Amitriptyline alters metabolism and satiety, which can lead to weight gain. Central nervous system and cardiovascular side effects can also occur [199]. Amitriptyline can inhibit diamine oxidase (DAO), thus inhibiting histamine breakdown. Treatment with amitriptyline should start with an initial dose of 10 mg in the evening, before being gradually increased.

Recommendation	We suggest	Strong consensus	80 %

3.2.3. Mirtazapine

One alternative to amitriptyline is the tetracyclic antidepressant mirtazapine. Because it does not bind to synaptic muscarinic acetylcholine receptors, it does not exhibit any anticholinergic side effects. In addition, it has no effect on serotonin, dopamine or noradrenaline re-uptake, as it does not bind to the membrane transport molecules. The dose should be between 15 and 45 mg per day [18, 88, 193, 195–200]. Treatment with mirtazapine should start with an initial dose of 15 mg in the evening, before being gradually increased. No results from trials on its use for the treatment of IC/BPS are available.

Recommendation	May be considered	Strong consensus	100 %

3.2.4. Hydroxyzine

Hydroxyzine can inhibit mast cell activation triggered by neurological stimuli. In combination with its anticholinergic, anxiolytic and analgesic effects, this may explain the reduction in symptoms when used to treat people with IC/BPS. A 2x2 factorial trial compared the efficacy of a placebo, hydroxyzine only, PPS only and a combination of hydroxyzine and PPS. It was found that it was not sufficiently effective in most IC/BPS patients. The dose used was between 25 and 75 mg per day [69, 199, 201].

Another study showed that histamine receptors are expressed on detrusor muscle cells [202]. It was found that H1 receptor expression was elevated in people with IC/BPS [150].

Recommendation	May be considered	Strong consensus	100 %

3.2.5. Cimetidine

Molecular histopathology analysis of bladder wall biopsies from people with IC/BPS has found increased expression of H1 and H2 receptors, P2X purinergic receptors (P2X1, 2 and 3) and cholinergic muscarinic receptors (M2, M3) [150]. This suggests that inhibition of these overexpressed

receptors might represent one approach to treatment.

The histamine H2 receptor antagonist cimetidine was first used to treat IC/BPS by Seshadri et al. in 1994. With a dose of 2 x 300 mg orally (no control group), six of nine patients (66%) showed an improvement within one month. Four of six patients experienced complete remission of symptoms for two years. No side effects were observed [203].

Improvement with cimetidine treatment is rapid [204]. The overall response rate with cimetidine in uncontrolled studies was between 57% and 100%. Complete remission was reported, on average, in 46% of cases [203–206]. A prospective, double-blind, placebo-controlled trial involving 36 patients over a period of three months (2 x 400 mg cimetidine) found a statistically significant improvement in the treatment arm (symptom score, suprapubic pain, nocturia). No major changes were observed in bladder biopsies performed before and after treatment [207].

In a survey by the British IC Support Group, 36% had been offered cimetidine [208].

Despite a lack of data, cimetidine has also been recommended for IC/BPS in children, as it has been successfully used on them in gastro-esophageal reflux disease. With regard to side effects, particular consideration should be given to neurotoxicity [209].

Recommendation	May be considered	Strong consensus	90 %

3.2.6. Leukotriene receptor antagonists

Montelukast is the only leukotriene receptor antagonist approved in Germany for the treatment of asthma.

Montelukast can reduce the mast cell-mediated inflammatory response. However there has been only one pilot study on its use for the treatment of IC/BPS, involving ten patients. An improvement was seen in eight of the ten patients [210].

Recommendation	May be considered	Strong consensus	95 %

3.2.7. Phosphodiesterase-5 (PDE5) inhibitors

Phosphodiesterase-1 and 5 inhibitors have been shown to have a muscle-relaxant effect and phosphodiesterase-4 inhibitors, an anti-inflammatory effect [211–213]. To date, the muscle-relaxant effect of phosphodiesterase-5 inhibitors has primarily been used for relaxation of the erectile tissue in erectile dysfunction, but it has also been used for male lower urinary tract symptoms [213].

PDE5 inhibitors can relax smooth muscle cells in the bladder. The reason for their efficacy has not yet been clarified.

A dose of 25 mg of the phosphodiesterase 5 inhibitor sildenafil over a period of three months resulted in a statistically significant improvement in O'Leary-Sant IC symptom and problem indices and in a urodynamic index as well, all in comparison to placebo, during the trial period and for three months afterwards. Only mild-to-moderate, temporary side effects were experienced [214].

Recommendation	May be considered	Strong consensus	90 %

3.2.8. Nifedipine

The calcium channel antagonist nifedipine has shown some effect in the treatment of interstitial cystitis [215]. The optimal daily dose of nifedipine should be titrated. The clinical and local immune response to nifedipine was investigated in an open-label study involving ten women with IC [216]. In a pilot

study, ten women with IC/BPS were given 30 mg per day. Four women who did not experience any relief from their symptoms were titrated up to 60 mg per day. Five women experienced a reduction in symptoms of at least 50% within four months and three of those five were subsequently symptom-free.

Urine interleukin-2 inhibitor activity prior to treatment with nifedipine indicates the presence of cell-mediated inflammation. After four months of treatment, urine interleukin-2 inhibitor activity was normal in seven of nine patients. This effect was not dependent on the severity of symptoms. This suggests that nifedipine exerts an immunosuppressant effect [216]. The authors recommend giving nifedipine for at least three months. Patients who did not respond well to nifedipine were those with pelvic floor muscle spasm [215]. Other than the above two studies, no other data has been published on this topic.

Although nifedipine is an effective, well-tolerated oral drug, the true value of nifedipine in treating patients with IC/BPS still needs to be confirmed in a prospective, randomized clinical trial [215].

Recommendation	May be considered	Strong consensus	95 %

3.2.9. Pain therapy

The effects of pain therapy can be achieved via changes in peripheral nociception and central neuronal excitation patterns. Sections 3.2.2, 3.2.3 and 3.2.11 discuss the potential efficacy of amitriptyline, mirtazapine, muscle relaxants and anticonvulsants. While the first priory must be to relieve the patient's severe pain, it is equally important that the patient is not harmed by uncritical use of poorly-effective or ineffective painkillers [217]. There have been no high-quality studies on the efficacy of these drugs for the condition under discussion.

Because there is at present no standard treatment concept for pain therapy in IC/BPS, we can only refer to the individual drug groups, which can be used in combination where necessary. Depending on the severity of the pain symptoms and the individual patient response, oral selective and non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), metamizole and opioids may be used. Consideration should be given to the fact that NSAIDs and morphine also cause histamine release – which can worsen or perpetuate symptoms.[88, 131, 218, 219]. In principle, treatment with opioids is considered an off-label "individual therapy trial" (*individueller Therapieversuch*) and should only be performed where there is a proven clinical effect, the treatment is well/adequately tolerated and in accordance with LONTS recommendations. Instillation of local anesthetics and specific local anesthesia or nerve block procedures can be used for acute pain, which cannot be controlled by other means.

Recommendation:	We recommend	Strong consensus	100 %

3.2.10. Immunosuppressants

Cyclosporin A, azathioprine and methotrexate are immunosuppressants which can be used in IC. There is a severe lack of studies in this area, however. Immunosuppressants do not play a major role in treatment of IC/BPS in practice [220–226].

No recommendation made	Strong consensus	100 %

3.2.11. Muscle relaxants

Tizanidine is an alpha-2 agonist and acts on alpha-2 receptors (subtypes A, B, and C). Alpha-2 receptors inhibit noradrenaline release from presynaptic neurons. This results in centrally-mediated pain modification via the dorsal horn. Tizanidine is used for muscle spasms and cramps resulting from

disorders of the central nervous system, and for myofascial neck and back pain. Tizanidine is a hepatotoxin and, used in combination with fluoroquinolone and other cytochrome P450 inhibitors, it can lead to elevated serum tizanidine levels [227].

Alpha-2 agonists have been used in combination with analgesics for the treatment of chronic pelvic pain syndrome [228]. Tizanidine is also used in a variety of diseases associated with symptoms of spasticity. The dose should be between 2 mg/day and 6 mg/day [229].

Recommendation	May be considered	Strong consensus	95 %

3.2.12. Alpha blockers

The alpha blocker tamsulosin blocks adrenergic receptors. It has a high affinity for class α1A-AR receptors, found primarily in the blood vessels. The antagonistic effect of this drug results in increased relaxation of the smooth muscles of the urethra, the bladder neck and the prostate. Tamsulosin is used primarily for the treatment of benign prostatic hyperplasia. The dose should be 0.4 mg/day.
Depending on the dosage, the drug may need to be discontinued due to significant side effects [230]. The most commonly-observed side effects are dizziness, followed by ejaculations, heart palpitations, rapid fatigability, headache, a fall in blood pressure with retrograde circulatory insufficiency, nausea, vomiting, diarrhoea, constipation, skin rash, itching, urticaria and rhinitis [199]. No data from controlled studies on treatment of IC/BPS is currently available.

No recommendation made	Strong consensus	95 %

3.2.13. Anticonvulsants

The anticonvulsant pregabalin is also used for neuropathic pain and anxiety disorders. Pregabalin reduces calcium release in the nerve endings, resulting in a reduction in glutamic acid, substance P and noradrenaline release. Side effects of pregabalin should be considered when assessing its risks and benefits [231, 232]. With a gradually increasing dose, side effects are manageable. The potential for dependence is low. When discontinuing use, the dose must be reduced gradually. No controlled studies on the use of pregabalin in IC/BPS have been published to date.

Recommendation	May be considered	Strong consensus	90 %

3.3. Complementary medicine

3.3.1 Acupuncture

Acupuncture is a standard therapy in traditional medicine. The exact mechanism of action remains unclear. Needles are inserted at specific points on the body, with the aim of relieving an illness and the underlying disturbance.

A basic principle of acupuncture therapy is a detailed medical history and a physical examination. The medical history should consider the progression of the illness, previous treatments, specific symptoms, personal environment, lifestyle, social situation, mental state, diet, sexual practices, and physical and sporting activities [173, 233]. This history is used to develop aids and opportunities for lifestyle improvement with and for the patient.

Acupuncture points are selected on an individual basis, taking into account the medical history and physical findings of the patient and their constitution and symptoms. Fixed combinations of points for

specific illnesses are used only rarely. There are constellations of established points for specific groups of symptoms, from which the therapist selects appropriate points. To these are added other individual points that are determined by the patient's current state and current symptoms.

Results of studies on acupuncture are hard to interpret since the results generally relate to non-individualized, one-off treatment series and to a diagnosis with no further presentation of the case. A large placebo effect and contradictory results with limited and time-limited effectiveness have been reported. To produce clarity, larger randomized clinical trials are needed [171, 234–237].

A case study using the same combination of acupuncture points (SP6, SP9, BL33, ST36, LI3, LI4, KI3 and CV4) on 12 women with refractory IC/BPS found that 10 twice-weekly sessions produced a statistically significant reduction in visual analogue pain score, PUF, O'Leary-Sant Symptom Score (ICSI), Patient Health Questionnaire (PHQ9) and maximum voided volume (MVV). The reduction in pain score was still observable 12 months after the one-off course of treatment. This effect was not observed in the other assessment scores [238].

Recommendation	May be considered	Strong consensus	100 %

3.3.2. Microbiological therapy

Administration of bacteria (probiotics) such as lactobacillus, bifidus species, Escherichia coli and enterococci can improve functional disorders of the mucous membranes and immune system. This treatment is effective for conditions including irritable bowel syndrome and other disorders of the intestinal mucosal barrier [239–242]. No studies on the efficacy of this procedure in IC/BPS have been published to date.

Recommendation	May be considered	Strong consensus	85 %

3.3.3. Neural therapy

According to the theory of neural therapy, the therapy resolves disorders which are expressed as IC symptoms [173, 243]. Specifically, this is postulated:

- It suppresses scarring
- It eliminates trigger points in the muscles which form part of a regulatory circuit with the bladder
- It blocks nerves, which stops pain without modifying pain thresholds
- "Injecting" organs (tonsils, thyroid, ovaries, appendix) disrupts "interference fields"

No studies evaluating its efficacy in IC/BPS have been published to date.

Recommendation	May be considered	Strong consensus	95 %

3.3.4. Orthomolecular therapy

Where the intestinal mucosal barrier is impaired, micronutrient deficiencies can occur; so that, in addition to microbiological therapy, orthomolecular therapy with vitamins, minerals and trace elements may be useful. It is posited that a high-fiber diet is helpful, as phytochemicals have a probiotic effect and serve as a nutrient source for bacteria, which can preserve the integrity of the mucous layer of the intestinal mucosa and produce short-chain fatty acids [244]. No studies on the efficacy of this procedure in IC/BPS have been published to date.

Recommendation	May be considered	Strong consensus	80 %

3.4. Intravesical therapy

Intravesical therapy has the advantage of introducing high concentrations of a drug directly into the bladder, thereby largely avoiding systemic side effects. Consideration, though, must be given to the fact that this is an invasive procedure that comes with the risk of infection. Furthermore, it should be noted that some forms of this therapy are relatively high in cost.

Active substances that may be considered for instillation into the bladder include heparin, hyaluronic acid (hyaluronan), chondroitin sulphate, lidocaine, dimethyl sulphoxide (DMSO), ropivacaine, sodium bicarbonate, cortisone and liposomes (liposomal formulations that protect a drug from premature metabolism) [88, 245]. Intravesical instillation of pentosan polysulphate was used for a long time as a therapy for IC, but it is currently no longer available on the European market.

3.4.1. Heparin

Heparin is thought to function as a GAG when instilled into the bladder. The heparin adheres to the bladder urothelium [18]. This is posited to restore the integrity of the bladder mucosa. More than 50% of patients reported an improvement in symptoms – even one year after treatment [246–248].

Recent clinical studies have shown an effect with heparin and with heparin in combination with alkalized lidocaine. Weekly instillation of heparin, lidocaine and sodium bicarbonate for 12 weeks produced an improvement in symptoms in 60% of patients after the fourth treatment and in 76.7% of patients after the final treatment. The effect was observable for a period of six months. This effect was seen in both Hunner-type and non-Hunner-type IC/BPS. In addition, treatment with heparin and alkalized lidocaine produced an improvement in pain and urgency symptoms lasting 12 hours [249, 250].

Recommendation	May be considered	Strong consensus	100 %

3.4.2. Hyaluronic acid/hyaluronan

Hyaluronic acid/hyaluronan, a GAG, is a connective tissue component that plays an important role in cell proliferation and migration. It is believed that hyaluronan can repair the GAG layer of the bladder mucosa [18, 251].

A number of studies have shown intravesical hyaluronic acid therapy to have a moderately enduring effect (56%). Furthermore, no significant hyaluronic acid toxicity was observed. A treatment success rate of 80% was observed in patients with IC/BPS and a positive potassium chloride test [252–259].

A systematic review and meta-analysis of the efficacy of intravesical hyaluronic acid, both alone and in combination with chondroitin sulphate, found a statistically significant improvement in pain symptoms after treatment, measured by using a visual analogue pain scale, and ICSI and ICPI scores. This showed that intravesical administration of hyaluronic acid alone or in combination with chondroitin sulphate is a promising therapeutic option for improving pain symptoms and quality of life in people with IC/BPS [260].

Recommendation	We suggest		Strong consensus	100 %

3.4.3. Chondroitin sulphate

A trial of intravesical administration of chondroitin sulphate found a statistically significant improvement in symptoms in almost all forms of chronic cystitis. Like heparin and hyaluronic acid, chondroitin sulphate also regenerates the GAG layer. The effectiveness of chondroitin sulphate was greater in patients with a positive KCl test [261–264].

In persistent IC/BPS, it has been reported that instillation of hyaluronic acid combined with chondroitin sulphate led to a statistically significant improvement in symptoms [264]. These results were contradicted by a multi-center, randomized, double-blind parallel group trial, which found no statistically significant differences between the individual groups. This study used a different concentration than previously published studies. In addition, the high-dose chondroitin sulphate in this study was administered in a phosphate buffer, which was not the case for the low doses used in the other studies [265, 266].

Recommendation	We suggest	Strong consensus	100 %

3.4.4. Lidocaine

Lidocaine can reduce pain by temporarily blocking sensory nerve fibers. Alkalizing the lidocaine with sodium bicarbonate is posited to result in a faster absorption of the active substance. Lidocaine is quick to take effect, its effect lasting up to 12 hours.

A combination of lidocaine and dexamethasone achieved a statistically significant increase in bladder volume. This was administered using the EMDA® method (see below) to achieve better penetration of the drug into the mucosa of the bladder and underlying tissues. Administration using this method can be repeated if symptoms reoccur. The efficacy of repeat treatments bears similarities to that of the first treatment [249, 267–270]. Lidocaine is suitable for use as a component of rescue instillations.

Recommendation	May be considered	Strong consensus	100 %

3.4.5. Dimethyl sulphoxide (DMSO)

Intravesical treatment with DMSO has anti-inflammatory, analgesic, muscle-relaxant and collagenolytic effects, which stimulate the release of NO from the dorsal root ganglia and bladder. This may represent the initial phase of desensitization of nociceptive signalling pathways. This treatment does not increase bladder capacity [271].

Randomized and non-randomized trials have found DMSO to have some efficacy in people with IC/BPS. Up to 80% of patients reported an improvement in their symptoms. Patients with Hunner-type IC, in particular, responded positively to DMSO treatment in combination with hydrodistension. Hydrodistension in combination with DMSO treatment was more effective than hydrodistension alone. Many patients reported a garlic-like smell and some patients reported bladder spasms.

Treatment usually involves instilling 50% DMSO diluted in physiological saline into the bladder. The solution is typically retained in the bladder for 10 to 20 minutes. The interval between treatments varies from several times a week to monthly [272–276].

One study found that treatment with DMSO caused a reduction in pain but had more side effects than would be expected with intravesical treatment with a combination of hyaluronic acid and chondroitin sulphate. In addition, treatment with hyaluronic acid and chondroitin sulphate produced a greater reduction in pain than treatment with DMSO [277].

Another study compared the efficacy of DMSO therapy and treatment with chondroitin sulphate. The dropout rate with DMSO was very high and efficacy low compared to chondroitin sulphate [278]. DMSO is not currently available in sterile form for instillation.

Recommendation	We suggest	Strong consensus	100 %

3.5. Transurethral procedures

3.5.1. Onabotulinum toxin A (Botox)

Possible mechanisms of action in IC/BPS:

- Inhibition of presynaptic acetylcholine release
- Reduced expression of P2X3 and TRPV1 receptors in afferent nerves
- Inhibition of stretch-induced ATP release from the urothelium
- Reduced NGF and BDNF production

Single-arm and randomized trials have found that IC/BPS symptoms were reduced after an injection of botulinum toxin (100 units) into the bladder wall. This has been reported for both one-off and repeat administration; in each, there was a reduction in pain and an increase in bladder capacity. A 74–86% improvement after three months was reported. No improvement was observable one year after receiving a dose of 100 units [9].

The efficacy of botulinum toxin was increased if the treatment was combined with hydrodistension [279, 280]. The average duration of effect of botulinum toxin was 5.2 months. The injection was repeated when symptoms recurred [9].

The success rate was 63% for patients treated with botulinum toxin, compared to 15% in the control group [279].

A randomized placebo-controlled double-blind trial involving 21 patients examined the efficacy of 10 intratrigonal onabotulinum toxin A injections of one millilitre. 60% of patients in the onabotulinum toxin arm and 22% in the placebo arm experienced a 50% or greater reduction in pain (VAS). In week 12, four patients in the onabotulinum toxin A arm (40%) had a VAS pain score of 0 or 1. The maximum residual urine was 80 ml, and urinary retention was not observed [281].

It is not clear to what extent the efficacy of treatment is affected by the presence of Hunner's lesions. One study found that treatment had no effect on symptoms in patients with Hunner-type IC, while 50% of patients with non-Hunner type IC reported a significant improvement in their symptoms.

Similarly, another study investigated the effect of botulinum toxin on symptoms in Hunner-type and non-Hunner-type IC. In this study, both IC types responded to treatment and showed an improvement in symptoms.

In view of the contradictory results produced by these two studies, it is worth noting that the concentration and method of administration of the botulinum toxin differed one from the other (trigonal vs. intravesical, broadly submucosal vs. intramuscular injection), so that the results are not comparable. Patients must be carefully chosen since urinary retention can occur and persist for up to six months. This situation requires self-catheterization four-to-five times daily [282, 283].

A systematic review found that botulinum toxin could achieve a significant improvement in symptoms in refractory IC/BPS patients [284].

Recommendation	May be considered	Strong consensus	100 %

3.5.2. Corticosteroids and local anaesthetics

Endoscopy-supported injection of corticosteroids (triamcinolone 10 ml, 40mg/ml; in 0.5 aliquots) into the submucosal space of the center and periphery of the ulcers and bupivacaine (0.5%; 10 ml) into the bladder wall improved symptoms in patients with Hunner's lesions [285, 286].

Recommendation	May be considered	Strong consensus	95 %

3.5.3. Hydrodistension

Cystoscopy with hydrodistension is a non-standardized but established diagnostic and therapeutic procedure for interstitial cystitis/bladder pain syndrome. The literature on hydrodistension of the bladder includes descriptions of the procedure with or without urethrocystoscopy and under general or local anesthesia (one or multiple short instillations lasting a few minutes and longer instillations lasting up to several hours). The pressure used also varies between 10 cm and 100 cm H2O [9, 18, 153, 287–289].

Most studies found an improvement in symptoms in 50% of cases, with the effect continuing for several months.

The underlying mechanism is regeneration of afferent nerve fibers, an anti-inflammatory effect and a reduction in NGF. Urine NGF levels appear to correlate with pain levels and response to treatment. NGF concentration is raised in people with IC/BPS, compared to a control group. Patients who respond to treatment and have reduced pain (as measured on a visual analogue pain scale) are also found to have a reduction in urine NGF levels [51].

The efficacy of hydrodistension was reduced in patients with spinal stenosis or irritable bowel syndrome [234].

Hydrodistension can be performed as follows [10, 18, 153, 287]:

- Under a general or spinal anesthetic.
- The bladder is filled with physiological saline or resection solution at a pressure of 60–80 cm H_2O until full. To quickly detect any pathological events, such as bladder rupture, the bladder is continuously monitored via an endoscope during this process.
- If the volume infused reaches 800–1000 ml before the intravesical pressure reaches 60–80 cm H_2O, the procedure should be stopped.
- The pressure should be maintained for one to three minutes.
- It is recommended that image documentation of the procedure be obtained.
- The filling medium should then be allowed to drain, while monitoring the bladder mucosa for hemorrhages.
- The volume filled should be recorded.
- The bladder should be refilled and Hunner's lesions fulgurated where required.
- An indwelling catheter should be used until all hematuria has ceased or until the patient has regained control of voiding after the anesthetic.

Hydrodistension can lead to bladder rupture and gross hematuria, which may lead to the development of bladder tamponade. Persistent distension can also lead to bladder necrosis. It is therefore important that the procedure be carried out with care and under controlled pressure. The bladder should be visually monitored throughout the procedure [1, 18, 153, 290–294]. The pressure used should not exceed 80 cm H_2O and the pressure should not be maintained for more than ten minutes.

The procedure can be repeated, though the therapeutic value of repeating the procedure is unclear. An indwelling urinary catheter can be left in place overnight [18, 153].

Recommendation	We suggest	Strong consensus	100 %

3.5.4. Electromotive drug administration (EMDA®)

The EMDA® method is based on the principle of iontophoresis and electrophoresis. It allows ionized or, using a hydrated carrier molecule, non-ionized drugs to be delivered to deeper layers of the bladder wall electrochemically. Compared to the passive diffusion used in conventional instillation, this represents a controlled way to transport drugs administered via intravesical instillation into the deeper bladder wall layers [267, 295–297].

When used in the bladder, it involves the use of a transurethral anode and a suprapubic skin cathode. In one trial, lidocaine and adrenaline were administered to six people with IC/BPS using EMDA® at maximum bladder distension. The treatment resulted in a statistically significant increase in bladder capacity and a reduction in pain and urinary frequency. 66% of subjects treated stated that the effect was persistent [270].

21 women with IC/BPS were treated with lidocaine and dexamethasone using EMDA®. Treatment showed good efficacy in 85% of those treated two weeks after treatment. This effect continued for two months in 63% of these patients. 25% of these patients were completely pain-free six months after treatment [268].

The same technique was used in another study, one in which 13 people were treated. 62% of these patients reported that their symptoms had resolved completely. In addition, an increase in bladder capacity was observed in 66% of those treated [298].

A study in Germany on care for people with IC/BPS found that 180 of its 270 participants had undergone treatment using the EMDA® technique. When asked to assess the success of invasive treatment methods, more than 60% of those treated said that the treatment had been successful. EMDA® was the most effective invasive therapy in this study [3, 88, 296].

The application solution and electrical parameters are specified in the manufacturer's data sheet.

Recommendation	We suggest	Strong consensus	100 %

3.6. Surgical treatment

3.6.1. Transurethral resection and fulguration

A number of studies have found that electrical or laser fulguration for Hunner's lesions is effective and that the procedure leads to a reduction in pain, lasting between several months and two years after treatment. In Hunner-type IC, hydrodistension combined with fulguration of the lesions was more effective than either treatment alone. Fulguration does not reduce bladder capacity [299–302]. Resection of Hunner's lesions has also been reported to be a successful treatment. Here again, combining this treatment with hydrodistension appears to be more effective [234].

No recommendation made	Strong consensus	80 %

3.6.2. Sacral neuromodulation

Sacral neuromodulation (SNM) involves inserting an electrode dorsally through the S3 foramen, so that it is in close proximity to the S3 sacral nerve and can be used to continuously stimulate. Test stimulation is initially performed using either a simple electrode or the 4-pin, tined lead, permanent stimulation electrode. After a test phase of about four weeks and an evaluation of any changes, (if proven successful) the neurostimulator can be implanted permanently. SNM can be performed on

either one or both sides. In patients with voiding disorders, the treatment is eligible for reimbursement by health insurers.

SNM modifies transmission in afferent nerves, reducing pain, suppressing the overactive detrusor and stabilizing the pelvic floor musculature. There is currently some debate over other of its effects.

SNM should be considered in IC/BPS if conservative therapy is unsuccessful. SNM should particularly be used before considering more major surgery. It is currently unclear which patient groups gain the most benefit from this treatment method [303-311].

In a care evaluation study, Jacobs et al. found that six of 13 patients (46%) described the effect as having “helped a great deal” or had “noticeably helped” [88]. Srivastava has published a review of all publications between 1950 and 2011 [312]. He found that 70.8% of patients (170/244) responded well during the test phase. Nine studies found a reduction in long-term pain and one study showed global improvement in 80% of patients. To date, however, only one randomized controlled trial has been published. After six months of SNM, the success rate was 49%, with the visual analogue pain score falling from 7.9 to 4.0.

No recommendation made	Strong consensus	75 %

3.6.3. Pudendal neuromodulation (PNM)

A prospective, single-blind, crossover study of sacral nerve stimulation (SNS) versus pudendal nerve stimulation (PNM) for people with IC/BPS (n = 22) found that PNM improved a total of 59% of symptoms, whereas SNS improved a total of 44% (p = 0.05). Most patients who underwent testing with both sacral and pudendal electrodes chose PNM as the better method. Follow-up showed significant improvements in micturition variables and validated BPS symptom questionnaire scores. More than 90% of patients treated with neuromodulation said that they would undergo the procedure again [311].

No recommendation made	Strong consensus	80 %

3.6.4. Percutaneous tibial nerve stimulation (PTNS)

Percutaneous tibial nerve stimulation (PTNS) has also been used to treat IC/BPS. There is, however, little data on its efficacy available at present [313, 314].

No recommendation made	Strong consensus	90 %

3.6.5. Hyperbaric oxygen therapy

A study involving 11 people with IC/BPS found that multiple sessions (10-20) of hyperbaric oxygen therapy led to a reduction in ICSI, a statistically significant reduction in pelvic pain, urgency and urinary frequency, and an increase in bladder capacity. These effects were observable for at least one year after therapy [315].

A case study involving two people with IC/BPS found that hyperbaric oxygen therapy caused a reduction in symptoms [316]. Specifically, a beneficial effect was found in Hunner-type IC [315] and people who had undergone DMSO treatment [317]. By contrast, a randomized, double-blind trial found that the effect of hyperbaric oxygen therapy was not statistically significant. Hyperbaric oxygen therapy is an option when results from other conservative treatments have proven unsatisfactory. It should also be mentioned that the beneficial effects from this treatment last for at least 12 months, but that the treatment is very expensive and it is not universally available [315–318].

No recommendation made	Strong consensus	90 %

3.5.6. Cystectomy, augmentation and urinary diversion

The last resort in refractory cases with high levels of patient distress is surgical intervention, in the form of bladder augmentation, orthotopic bladder substitution (neobladder) or non-continent/continent urinary diversion. Although surgical intervention relieves symptoms completely in 80%–100% of cases, in view of the perioperative and postoperative complications and the possibility that symptoms may persist despite the surgery, a critical view should be taken before selecting this option [319–323].

This is especially true in instances where the urethra is to be preserved and bladder augmentation is to be carried out or a neobladder is to be created. The literature suggests that 85% of patients with augmentation or a neobladder undergo secondary cystectomy, due to pain. Pain is a contraindication for supratrigonal cystectomy or bladder augmentation.

Depending on the circumstances, primary complete cystourethrectomy with creation of an ileal conduit or pouch with catheterizable umbilical stoma is an appropriate surgical intervention for resolving pain – permanently and reliably. Patients must always have the various types of urinary diversion explained to them, particularly the option of continent urinary diversion, even after urethrectomy (umbilical pouch). Continent urinary diversion carries with it a risk of problems with the continence mechanism.

Distal urinary diversion is reserved for patients with lives blighted by pain and pollakiuria and for whom results from less invasive treatments have been unsatisfactory.

No recommendation made	Strong consensus	80 %

4. Rehabilitative measures

Various outpatient therapy options are available for IC/BPS patients. Evaluated in various studies, these treatment options do not help all sufferers to control the symptoms of IC/BPS. Another option is inpatient rehabilitation, which can be carried out in the clinics of urology specialists. Patients are offered there a multimodal therapy, which addresses many different aspects of the condition.

In instances where symptoms do not improve with outpatient procedures (treatment with mucosal protective agents, muscle relaxants, analgesics, etc.) and the patient is at the point of being unable to work, before considering invasive procedures such as neuromodulation or cystectomy, the patient should apply to their pension insurer (for employees) or health insurer (retirees) for inpatient rehabilitation [324].

Inpatient rehabilitation achieved an improvement in pain in 61.9% of people with IC/BPS and, in 47.6%, this improvement continued for 1–17 months. The picture is similar for pollakiuria (66.7%, 47.6%). 71.4% of patients saw an improvement in their nocturia and this improvement persisted [325]. Inpatient urology treatment/rehabilitation with a specialist should be offered following cystectomy with urinary diversion.

Recommendation:	We recommend	Strong consensus	100 %

5. Summary

Interstitial cystitis (IC/BPS) is a non-infectious, chronic bladder disease characterized by BPS symptoms (to varying degrees and in various combinations), where other conditions have been ruled out. There is no uniform global definition of the disease at present [2, 10, 12, 23, 89]. A diagnosis of IC/BPS does not require a specific bladder volume or persistent pain. The condition can occur in people of any age or gender. IC/BPS occurs in two subtypes [3, 12, 18, 89]:

- Hunner type, in which Hunner lesions are clearly visible on cystoscopy. This type is significantly rarer than non-Hunner type.
- Non-Hunner type, in which no Hunner's lesions are observed during/after bladder distension.

The condition can be misdiagnosed, especially in its early stages. This explains why a substantial proportion of people with IC/BPS have made a large number of doctor's visits in the years prior to their diagnosis. The causes for misdiagnosis are variable and often multitudinous [88]. A detailed history and further diagnostic tests can help direct the choice of treatment options, particularly where characteristic changes to the bladder are visible on cystoscopy and/or histology (see figure 2) [85, 170, 245, 324, 326, 327].

Treatment of IC/BPS is often beset with difficulties, both for the therapist and for the patient. Treatment should therefore be comprehensive, interdisciplinary and multimodal, taking into account the extended biopsychosocial model (see figure 3). All parties should aim to ensure that there is close coordination between non-hospital practitioners and specialist centers [135, 170, 173, 177, 178, 328].

Figure 2: Individual treatment ladder

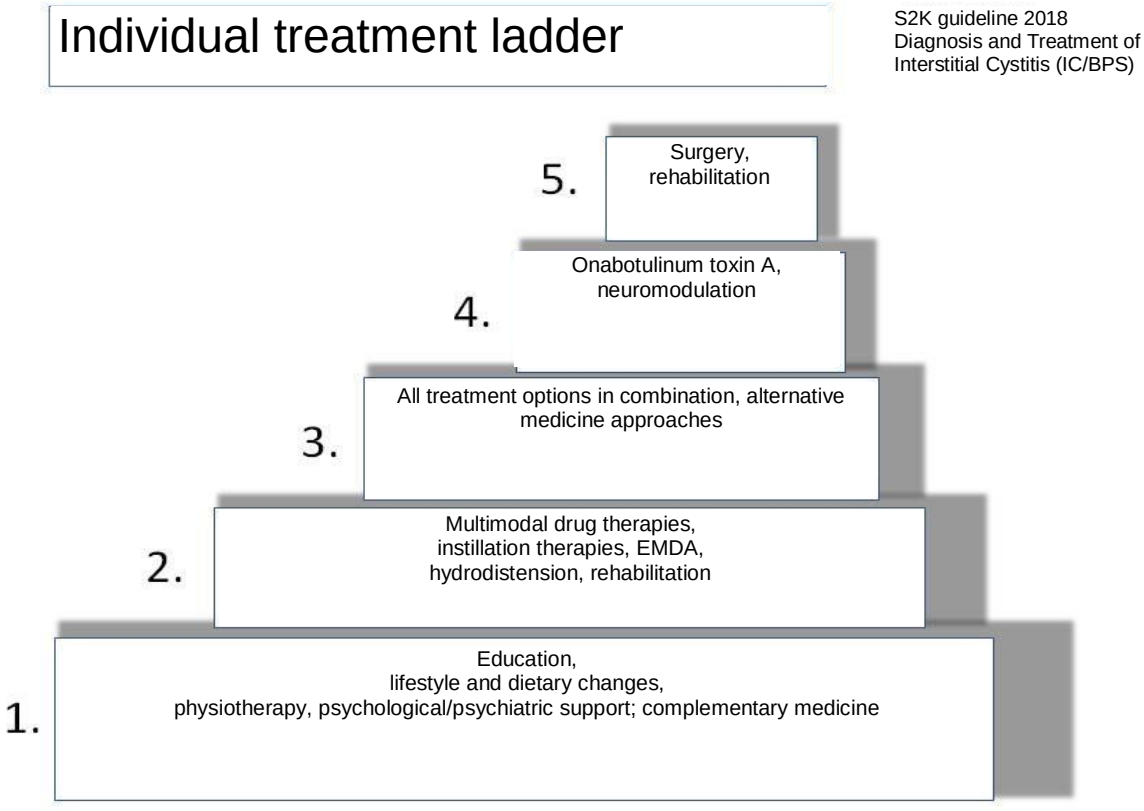
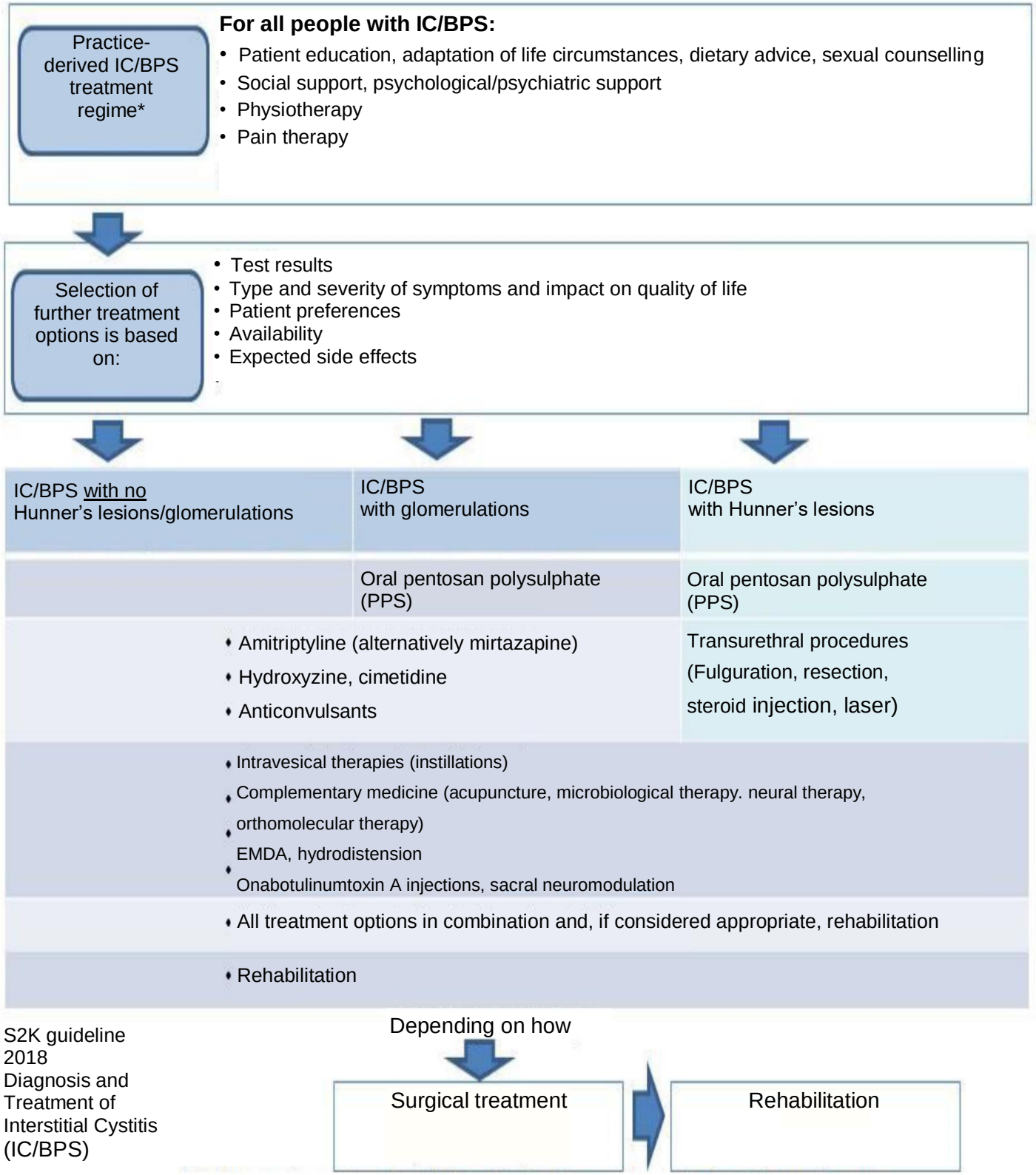


Figure 3: Practice-derived IC/BPS treatment regime



Results of voting on the recommendations:

Page	Section	**Diagnostics**	We recommend	We suggest	May be considered	Weakly against	Strongly against	No recommendation	Votes	Abstentions	Strength of consensus and recommendation
14	2.1.	Medical history	20						20	3	100% “Strongly in favour”
14	2.2.	Differential diagnosis	20						20	3	100% “Strongly in favour”
15	2.3.	Questionnaires and record sheets	20						20	3	100% “Strongly in favour”
15	2.4.	Biomarkers	1					18	19	4	95% “No recommendation”
16	2.5.	Physical examination	20						20	3	100% “Strongly in favour”
16	2.6.	Urine testing	3	17					20	3	100% “Weakly in favour“
16	2.7.	**Additional investigations**									
		Urosonography	2	18					20	3	90% “Weakly in favour”
		Uroflowmetry		20					20	3	100% "Weakly in favour"
		Cystoscopy	2	18					20	3	90% “Weakly in favour”
		Hydrodistension		3	16			1	20	3	80% “Can”
		Flow-EMG/urodynamic testing			20				20	3	100% “Can”
16	2.8.	Potassium chloride (KCl) test			18		1	1	20	3	90% “Can”
17	2.9.	Biopsy of the bladder wall	1	1	17			1	20	3	85% “Can”
18	2.10.	Stool diagnostics		1	19				20	3	95% “Can”

Page	Section	Treatment	We recommend	We suggest	may be considered	Weakly against	Strongly against	No recommendation	Votes	Abstentions	Strength of consensus and recommendation
18	**3.1.**	**Conservative treatment**									
	3.1.1.	Lifestyle changes	20						20	3	100% “Strongly in favour”
	3.1.2.	Diet	20						20	3	100% “Strongly in favour”
	3.1.3.	Psychological/psychiatric support	19	1					20	3	95% “Strongly in favour”
	3.1.3.	Physiotherapy	19	1					20	3	95% “Strongly in favour”
20	**3.2.**	**Oral drug therapy**									
	3.2.1.	Pentosan polysulphate	20						20	3	100% “Strongly in favour”
	3.2.2.	Amitriptyline		17	2		1		20	3	80% “Weakly in favour”
	3.2.3.	Mirtazapine			20				20	3	100% “Can”
	3.2.4.	Hydroxyzine			20				20	3	100% “Can”
	3.2.5.	Cimetidine			19		1		20	3	90% “Can”
	3.2.6.	Leukotriene receptor antagonists			19			1	20	3	95% “Can”
	3.2.7.	Phosphodiesterase-5 (PDE5) inhibitors			19		1		20	3	90% “Can”
	3.2.8.	Nifedipine			19			1	20	3	95% “Can”
	3.2.9.	Pain therapy	20						20	3	100% “Strongly in favour”
	3.2.10.	Immunosuppressants						18	18	5	100% “No recommendation”
	3.2.11.	Muscle relaxants			18			1	19	4	95% “Can”
	3.2.12	Alpha blockers			1			19	20	3	95% “No recommendation”
	3.2.13	Anticonvulsants	1		18		1		20	3	90% “Can”
23	**3.3.**	**Complementary medicine**									
	3.3.1.	Acupuncture	1		19				20	3	100% “Can”
	3.3.2.	Microbiological therapy	1		16			2	19	4	85% “Can”
	3.3.3.	Neural therapy	1		17			1	19	4	95% “Can”
	3.3.4.	Orthomolecular therapy	1		15			1	17	6	80% “Can”

Page	Section	Treatment	Strongly in favour	Weakly in favour	Can be considered	Weakly against	Strongly against	No recommendation	Votes	Abstentions	Strength of consensus and recommendation
24	**3.4.**	**Intravesical therapy**									
	3.4.1.	Heparin		1	19				20	3	100% “Can”
	3.4.2.	Hyaluronic acid/hyaluronan	1	19					20	3	100% “Weakly in favour“
	3.4.3.	Chondroitin sulphate	1	19					20	3	100% “Weakly in favour“
	3.4.4.	Lidocaine		1	19				20	3	100% “Can”
	3.4.5.	Dimethyl sulphoxide (DMSO)				17	1		18	5	100% “Weakly against“
	3.5.	**Transurethral procedures**									
	3.5.1.	Onabotulinum toxin A		1	19				20	3	100% “Can”
	3.5.2.	Corticosteroids and local anaesthetics			19	1			20	3	95% “Can”
	3.5.3.	Hydrodistension		19					19	4	100% “Weakly in favour“
	3.5.4.	Electromotive drug administration (EMDA®)		20					20	3	100% “Weakly in favour“
29	**3.6.**	**Surgical treatment**									
	3.6.1.	Transurethral resection and fulguration		1	3			16	20	3	80% “No recommendation”
	3.6.2.	Sacral neuromodulation			5			15	20	3	75% “No recommendation”
	3.6.3.	Pudendal neuromodulation (PNM)			3			16	19	4	80% “No recommendation”
	3.6.4.	Percutaneous tibial nerve stimulation (PTNS)				1		19	20	3	90% “No recommendation”
	3.6.5.	Hyperbaric oxygen therapy			1	1		18	20	3	90% “No recommendation”
	3.5.6.	Cystectomy, augmentation and urinary diversion			3	1		16	20	3	80% “No recommendation”
30		**Rehabilitative measures**	20						20	3	100% “Strongly in favour”

6. Appendix

List of abbreviations

APF	Antiproliferative factor
ATP	Adenosine triphosphate
AWMF	*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.*
BDNF	Brain-derived neurotrophic factor
BL33	Zhongliao acupuncture point
BMG	*Bundesministerium für Gesundheit*
BPIC-SS	Bladder Pain/IC Symptom Score
BPS	Bladder pain syndrome
CFS	Chronic fatigue syndrome
CPPS	Chronic pelvic pain syndrome
CRF	Corticotropin releasing factor
CV-4	Guanyuan acupuncture point
DMSO	Dimethyl sulphoxide
EMDA	Electromotive drug administration
ESSIC	International Society for the Study of Bladder Pain Syndrome
Etio-S	Etiocholan-3α-ol-17-one sulphate
GAG	Glycosaminoglycan
H1	Histamine H1 receptor
H2	Histamine H2 receptor
HSB	Hypersensitive bladder
IC	Interstitial cystitis
ICHL	Interstitial cystitis/Hunner's lesion
ICNHL	Interstitial cystitis/non-Hunner's lesion
ICPI	Interstitial Cystitis Problem Index
ICSI	Interstitial Cystitis Symptom Index
ICPI/ICSI	O'Leary-Sant interstitial cystitis problem and symptom indices
KCl	Potassium chloride
KI3	Taixi acupuncture point
LI4	He Gu acupuncture point
LIV3	Taichong acupuncture point
LUDE	Lower urinary dysfunctional epithelium
MVV	Maximum voided volume
$NaHCO_3$	Sodium bicarbonate
NAMSE	*Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen*
NBI	Narrow-band imaging
NGF	Nerve growth factor
NSAID	Non-steroidal anti-inflammatory drugs
NO	Nitrogen monoxide
OAB	Overactive bladder
PBS	Painful bladder syndrome

PNS	Pudendal nerve stimulation
PHQ9	Patient Health Questionnaire-9 (a depression questionnaire)
PPS	Pentosan polysulphate
PTNS	Percutaneous tibial nerve stimulation
PUF	Pelvic pain and urgency/frequency questionnaire
S3/4	Sacral root 3/4
SP6	Sanyinjiao acupuncture point
SP9	Yinlingquan acupuncture point
ST36	Zusanli acupuncture point
STD	Sexually transmitted diseases
TRPV1	Transient receptor potential cation channel subfamily V member 1
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
α1A-AR	α1A adrenergic receptor

List of tables

List of figures

Questionnaires and record sheets

Questionnaires and record sheets

No. 1: Voiding and pain diary

Voiding and pain diary for one day and one night

	Day: ……	**Drinks**		**Passing water**	**Urgency** Scale 1 to 10	**Pain** Scale 1 to 10	**Comments**
	Time	What?	How much? (ml)	How much? (ml)	0 – no urgency 10 – maximum urgency	1 – no pain 10 – maximum pain	e.g. light breakfast, ate an apple, cold feet, nice weather (hot), etc.
1					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
2					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
3					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
4					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
5					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
6					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
7					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
8					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
9					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
10					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
11					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
12					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
13					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
14					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
15					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
15					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
17					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
18					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	

	Day: ……	**Drinks**		**Passing water**	**Urgency** Scale 1 to 10	**Pain** Scale 1 to 10	**Comments**
	Time	What?	How much? (ml)	How much? (ml)	0 – no urgency 10 – maximum urgency	1 – no pain 10 – maximum pain	e.g. light breakfast, ate an apple, cold feet, nice weather (hot), etc.
19					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
20					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
21					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
22					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
23					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
24					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
25					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
26					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
27					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
28					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
29					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
30					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
31					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
32					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
33					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
34					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
35					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	
36					1 2 3 4 5 9 7 8 9 10	1 2 3 4 5 9 7 8 9 10	

Questionnaire and record sheet no.2
Pelvic pain and urgency/frequency patient symptom scale (PUF)

Name des Patienten:
_____Tagesdatum_____

Unterleibs-und Blasenschmerz, Harndrang und Harnfrequenz
SYMPTOMEN SCALA

Bitte geben Sie die Punktzahl ein, die bei jeder Frage Ihren Zustand am besten beschreiben.

		Punkte 0	1	2	3	4	Symptom Punkte	Belastungs Punkte
1	Wie oft müssen Sie am Tag Wasserlassen?	3-6 mal	7-10 mal	11-14 mal	15-19 mal	über 20		
2	a) Wie oft müssen Sie in der Nacht Wasserlassen?	0 mal	1 mal	2 mal	3 mal	über 4		
	b) Wenn Sie nachts Wasser lassen, wie belastet es Sie?	Nie	ein wenig	ja	Ja, sehr			
3	Sind Sie normal sexuell aktiv? ja _____ nein _____							
4	a) Wenn Sie sexuell aktiv sind, haben oder hatten Sie Schmerzen während oder nach dem Geschlechtsverkehr	Nie	manchmal	meistens	immer			
	b) wenn Sie Schmerzen haben, veranlasst Sie der Schmerz, Sex zu vermeiden?	Nie	manchmal	meistens	immer			
5	Empfinden Sie die Schmerzen gezielt in der Blase oder im Unterleib (Vagina, Enddarm, Harnröhre, Damm, Hoden, oder Hodensack)?	Nie	manchmal	meistens	immer			
6	Haben Sie Harndrang nach dem Wasserlassen?	Nie	manchmal	meistens	immer			
7	a) Wenn Sie auch Schmerzen nach dem Wasserlassen haben, sind die Schmerzen dann...?		gering	erträglich	stark			
	b) Belastet Sie der Schmerz?	Nie	manchmal	meistens	immer			
8	a) Wenn Sie Harndrang haben, ist der Drang in der Regel...?		gering	erträglich	stark			
	b) Belastet Sie der Harndrang?	Nie	manchmal	meistens	immer			

Summe der Symptomenpunkte Zählen Sie hier die Punkte zusammen, die Sie für die Fragen 1, 2a, 4a, 5, 6, 7a, 8a vergeben haben	
Belastungspunkte Zählen Sie hier die Punkte zusammen, die Sie für die Fragen 2b, 4b, 7b, 8b	
Gesamtpunkte (Symptomenpunkte + Belastungspunkte)	

0-4 = Normal
10-14 = 56% chance epitheliale Dysfunktion positiv
15-19 = 76% chance epitheliale Dysfunktion positiv
20+ = 92% epitheliale Dysfunktion positiv

Quelle:
Parsons, C.L., P. Zupkas, and J.K. Parsons,
Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome
Urology, 2001

Questionnaire and record sheet no. 3

Pelvic floor function examination: vaginal							
Patient name:			**Date of birth:**				
Examination at rest							Comments
Skin		Normal					
Scars		No	Yes	Clock position			
Perineal length		Normal	Short	Long			
Mucosa		Trophic	Atrophic				
Prolapse		No	Yes				
Hiatus		Normal	Large	Small			
Examination on movement							Comments
Voluntary contraction Inward movement of the perineum			Yes	No			
Voluntary relaxation Outward movement of the perineum			Yes	No			
Involuntary contraction (cough) No outward movement of the perineum			Yes	No			
Involuntary relaxation (pushing) Outward movement of the perineum			Yes	No			
Palpation at rest							Comments
Palpation	1 finger	2 fingers					
Tone	Normotonic	Hypotonic	Hypertonic				
Sensitivity	Normal	Hyposensitive	Hypersensitive				
Pain	No	Yes	NRS (0–10)				
Where?							
Trigger points							
Left/right symmetry	No	Yes					
Prolapse	Apical	Ventral	Dorsal				
Palpation on movement							Comments
Palpation		1 finger	2 fingers				
Voluntary contraction Oxford grading scale 0–5		0	1	2	3	4	5
Left/right symmetry contraction		Yes	No				
Repeat 15x		Yes	No				
Endurance max. 10 seconds		Yes	seconds				
Voluntary relaxation		Complete	Delayed	Absent			
Involuntary contraction (cough)		Yes	No				
Involuntary relaxation (pushing)		Yes	No	Paradoxical			
Prolapse		Ventral	Apical	Dorsal			
Urethral lift		Yes	No				
Pain		No	Yes	NRS			
Where?							

Questionnaire and record sheet no. 4

Pelvic floor function examination: anal							
Patient name:				**Date of birth:**			
Examination at rest							Comments
Skin		Normal					
Haemorrhoids		No		Yes	Clock position		
Marisca		No		Yes	Clock position		
Examination on movement							Comments
Voluntary contraction Inward movement of the perineum				Yes	No		
Voluntary relaxation Outward movement of the perineum				Yes	No		
Involuntary contraction (cough) No outward movement of the perineum				Yes	No		
Involuntary relaxation (pushing) Outward movement of the perineum				Yes	No		
Palpation at rest							Comments
Tone	Normotonic	Hypotonic		Hypertonic			
External anal sphincter							
Levator ani							
Sensitivity	Normal	Hyposensitive		Hypersensitive			
Pain	No	Yes		NRS (0–10)			
Where?							
Trigger points							
Left/right symmetry	No	Yes					
Rectocele	No	Yes					
Palpation on movement							Comments
External anal sphincter							
Voluntary contraction (Oxford grading scale 0–5)		0	1	2	3	4	5
Voluntary relaxation		Complete		Delayed		Absent	
Left/right symmetry contraction		Yes		No			
Levator ani							
Voluntary contraction (Oxford grading scale 0–5)		0	1	2	3	4	5
Voluntary relaxation		Complete		Delayed		Absent	
Left/right symmetry contraction		Yes		No			
Repeat 15x		Yes		No			
Endurance max. 10 seconds		Yes		seconds			
Voluntary relaxation		Complete		Delayed		Absent	
Involuntary contraction (cough)		Yes		No			
Involuntary relaxation (pushing)		Yes		No		Paradoxical	
Pain		No		Yes		NRS	
Where?							

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First published: **September 2018**

Next review scheduled: **September 2023**

authorized for electronic publication: AWMF online