

Interstitial cystitis: an enigmatic disorder of unclear aetiology

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Introduction

Interstitial cystitis (IC) is an enigmatic chronic disorder characterized by vague bladder pain of variable severity accompanied by urinary symptoms. Although it was initially thought to be a rather rare disorder, its prevalence has increased over years for various reasons including greater awareness by physicians and unclear diagnostic criteria.

Definition and epidemiology

In 1990, the National Institute for Diabetes and Diseases of the Kidney (NIDDK) recommended the use of criteria for IC diagnosis [1] (Table 1). These criteria were soon recognized to be useful for scientific purposes but to be strict for clinical practice [2]. The International Continence Society (ICS) proposed the term 'Painful Bladder Syndrome' [3] (PBS). It was defined as the syndrome consisting of 'suprapubic pain related to bladder filling accompanied by other symptoms, such as increased daytime and nighttime frequency in the absence of proven infection or other obvious pathology' [3]. Using a similar definition, the European Society for the Study of Interstitial Cystitis (ESSIC) proposed the term 'Bladder Pain Syndrome' (BPS) [4].

Due to multiple definitions and diagnostic criteria used, the prevalence of IC varies widely throughout the world. This variation may also reflect racial/ethnic differences. Older series report the prevalence of IC much lower than recent studies (18.1/100 000 women and 10.6/100 000 men and women [5], 52–197/100 000 women [6,7] and 40–70/100 000 men [6,7], respectively). Using self-report of a previous IC diagnosis, the prevalence was much higher (865/100 000 women and 501/100 000 men and women)

[8]. When questionnaires without clinical evaluation were used, the prevalence of symptoms was 30- to 50-fold higher in women and 60- to 100-fold higher in men [9]. In Europe, the reported prevalence is lower (8–16/100 000 women) [10], but when questionnaires were used [11] it increased to 450 cases per 100 000 women.

IC affects more often women, with a female/male ratio ranging from 5:1 to 10:1 [5,10]. People older than 50 years are at higher risk for IC [8]. Mean age at diagnosis is 40–50 years [12]. Women are diagnosed in younger age in comparison with men [6]. There may be genetic susceptibility in IC: prevalence is significantly increased in first-degree relatives of patients with IC and among monozygotic twins pairs [13].

Pathophysiology

The aetiology of IC is unknown. Several pathophysiological mechanisms have been proposed including uroepithelial dysfunction, mast cell activation, neural inflammation and immunological mechanisms.

In healthy individuals, the protective bladder lining is relatively impermeable to urinary solutes. However, this protective lining is damaged in IC leading to increased permeability. Toxic urine substances with potassium being the most important penetrate the epithelium and activate sensory nerve endings [14]. Mast cells may play an important role in IC pathogenesis [13]. Patients have twice as many bladder mast cells [13] with >70% being activated compared with 10% in healthy subjects [13]. Activated mast cells act through secretion of several vasoactive and inflammatory mediators [13].

Neurogenic inflammation may also be a possible pathogenetic mechanism [13]. Upregulation of receptors and increased nerve fibre density occur in both peripheral nerves and central nerves (sacral reflex arc), whereas the progression of the disease is characterized by activation of the bladder sensory nerves [15]. The increased prevalence of autoimmune diseases in IC patients suggests a possible underlying immunological mechanism. Interestingly, Sjogren syndrome and SLE [13,16] are reported with increased frequency in IC patients.

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Table 1. NIDDK [13] criteria for interstitial cystitis (adapted from reference [2])

For diagnosis of interstitial cystitis patients should have:

- Bladder pain or urinary urgency
- Glomerulations or Hunner's ulcers during cystoscopy/hydrodistention
- None of the following: awake cystometric capacity >350 ml using a fill rate of 30–100 ml/min, absence of intense urge to void at 100 ml gas or 150 ml liquid, involuntary detrusor contractions on cystometry, urinary frequency <8 voids per day, absence of nocturia, duration of symptoms <9 months, age <18 years, cystitis (bacterial, chemical and post-irradiation), prostatitis, vulvitis (herpes) or vaginitis, cancer (bladder, uterine, cervical, vaginal or urethral), bladder or lower ureteral calculi and urethral diverticulum

Clinical presentation

Clinical presentation can be variable, but there are many common clinical features. Patients have symptoms several years before diagnosis [13]. The most common symptoms include urinary frequency, urinary urgency, nocturia and pain [17]. In the early phase, patients present with few, mild and intermittent symptoms, which become worse as time passes [12,17,18] and tend to stabilize after several years [16].

Frequency is a common initial symptom. Urgency and pain usually develop next [17]. Voiding to avoid urine leakage is common in overactive bladder syndrome (OBS), whereas in IC voiding to relieve pain is typical [19]. ESSIC [18] did not include urgency in the description of patients needing further evaluation for IC since it is the main symptom of OBS, which is more common than IC. NIDDK [4] used the absence of nocturia as an exclusion criterion for IC. However, in the early phase it is not always present, but tends to appear later [1].

Pain is the most common and bothersome symptom [17] at diagnosis and a prerequisite for diagnosis according to ESSIC [18]. However, in the early phase many patients report pressure sensation or discomfort on the bladder, but not pain [4], whereas over time they report more intense pain. Pain typically is temporarily relieved by voiding [19]. Nevertheless, pain is not always present on bladder filling [18]. It is classically localized to the suprapubic area [20] although both location and character of pain are highly variable; pain may often be localized in lower abdomen, urethra, vaginal area, lower back, scrotum and rectum [13]. It often presents as pressure, aching and burning [19]. It is usually associated with sexual activity [16]. Dyspareunia is a common finding in IC patients [19].

IC tends to occur in flares and remissions. Flares may be provoked by stress, allergy symptom exacerbation [16,19], smoking [13], consumption of food rich in potassium and beverages containing biogenic amines and caffeine [13]. Exacerbations of symptoms also occur frequently during the premenstrual week [13].

Diagnosis

IC remains a diagnosis of exclusion after ruling out other obvious pathology and overlapping syndromes. There are no definitive diagnostic tests.

History and physical examination

The first step is a comprehensive medical history and a thorough physical examination [18]. There are no specific physical findings [21]. However, bimanual examination in women and rectal examination in men are mandatory. It is important to exclude pelvic floor dysfunction [18]. Variable tenderness is usually present in abdominal wall, pelvic floor, urethra and bladder neck.

Laboratory tests

There are no specific diagnostic laboratory tests. Urinalysis with microscopy and urine culture should be performed in all patients to exclude haematuria and infection. Urinary cytology should be reserved in patients over 40 years of age and in patients with a history of smoking, haematuria or increased risk for bladder cancer [21]. Patients with significant haematuria should undergo cystoscopy. Many urinary markers were tested such as interleukin-6 [21], but none was shown to be valuable for diagnosis. Anti-proliferative factor [22], which is increased in urine of IC patients, appears to be the most promising marker.

Questionnaires and voiding diaries

Two surveys are commonly used to assess symptoms: the O'Leary Sant Symptom Index and Problem Index [13] and the pelvic pain and Urgency/Frequency symptom scale [23]. These scales are mainly helpful for monitoring disease progress, but both have been used as screening tools [24]. Voiding diary can be extremely useful for screening urinary frequency and documenting symptoms. Moreover, it can be used to monitor response to treatment [11,25].

Optional diagnostic procedures

Cystoscopy. Until recently, cystoscopy with/without hydrodistention (see the 'Treatment' section) was essential for diagnosis according to NIDDK criteria [21]. However, this is considered by some experts to be too restrictive [1] and currently cystoscopy is not mandatory for diagnosis [26]. In the United States, cystoscopy is usually performed at physician's discretion. It is also performed when there is haematuria or other bladder pathology must be ruled out [27]. In contrast, in Europe, cystoscopy with hydrodistention is considered to be important, if not essential, for diagnosis [21]. It is a prerequisite for ESSIC and it is also used for disease classification [28]. When combined with a bladder biopsy, it can be useful in prognosis and treatment choice, e.g. patients with markedly reduced bladder capacity are unlikely to benefit from pharmacological treatment. Cystoscopy allows visualization of Hunner's ulcers (patches) and glomerulations (pin-point petechial haemorrhages), which were initially thought to be pathognomonic for IC, but they are present mainly in severe cases [4]. Moreover, symptoms may not be significantly correlated with bladder glomerulations at cystoscopy since these are also seen in many asymptomatic healthy women [2].

Biopsy. Whereas a bladder biopsy is still used widely in Europe [29], it is not essential for diagnosis since there are no specific findings contributing to diagnosis [28]. However, it is often necessary to exclude malignancy or other pathology. Biopsy may be helpful in choosing treatment modality e.g. when mastocytosis is seen, patients may benefit from antihistamine treatment [27].

Potassium sensitivity test (PST) and urodynamics. In PST [13], 40 ml of sterile water and 40 ml of a potassium chloride solution are instilled in the bladder sequentially. Increased pain with the potassium solution is considered indicative of bladder hypersensitivity and IC. PST is not recommended for diagnostic purposes [30]; it is positive in only 75% of IC patients [13] and gives false negative results in severe disease or after treatment and false positive in detrusor instability and urinary tract infections [13]. However, it detects the subgroup of patients who are likely to benefit from suitable treatment (see below). Although urodynamics are not essential for diagnosis, they can be helpful in excluding detrusor instability, a common overlap between OBS and IC [31].

Treatment

There is no consensus regarding the treatment of IC, which remains mainly empiric. Most of the data regarding the efficacy of the therapies are derived from uncontrolled studies or case series. Treatment plan includes supportive therapies and specific therapeutic modalities; the latter aim to proposed underlying pathophysiological mechanisms.

Supportive therapies

These modalities include general measures that can improve symptoms or prevent exacerbations. Psychosocial support is essential. Comorbid conditions should also be treated aggressively. Factors associated with symptom exacerbation, such as certain foods and activities, should be avoided. Behavioural therapy including avoidance of the triggering factors and timed voiding protocol leading to increased bladder capacity can also be effective [13]. Physical therapy by resolution of tender and trigger points [32] can alleviate symptoms.

Specific therapies

Intravesical treatments

Hydrodistention consists of bladder distention over regular capacity under general or epidural anaesthesia, and may also offer short-lived symptom relief [33]. Dimethyl sulphoxide (DMSO) is approved by FDA for intravesical use in IC. It is believed to inhibit mast cell activation and to have analgesic and anti-inflammatory actions. There are small studies favouring its use. Intravesical administration of heparin (usually combined with lidocaine and sodium bicarbonate to increase analgesia and absorption, respec-

tively) in various mixtures has been used with good remission rates [13].

There are limited studies reporting good response to the intravesical instillation of sodium hyaluronate and chondroitin sulphate [13], [34]. Although the first is approved for IC treatment in Canada, data are scarce. Intravesical Bacillus Calmette–Guerin (BCG) was shown to be effective in the past, but it was not recently found to be beneficial over placebo in refractory IC.

Oral treatments

Pentosan polysulphate (PPS) is the only oral medication approved by FDA for IC. PPS is a branched polysaccharide that is excreted in urine, where it is supposed to repair damaged bladder lining. There are studies suggesting that PPS 100 mg three times per day is effective and well tolerated [13]. However, only 6% of PPS is excreted in urine and in a recent study it was not shown to be effective over placebo.

Only one study supports the effectiveness of doxepin and piroxicam [13]; relapse was noted soon after drug discontinuation. Montelukast, that is used for asthma treatment, has been shown in one small study to be effective. Quercetin, a flavonoid with anti-allergic and anti-inflammatory actions, has been reported to alleviate symptoms.

Prednisone was suggested to improve symptoms in severe IC [13]. Cyclosporine has also been suggested to improve symptoms in refractory IC although relapse occurred after cyclosporine discontinuation. In another study, methotrexate diminished pain severity in women with refractory IC.

Hydroxyzine is used as a first-line treatment at 50–75 mg/day [13]. However, a recent clinical trial showed no effectiveness over placebo. Amitriptyline has been suggested to improve symptoms at dosages between 12.5 and 125 mg/day.

Other treatments

Sacral nerve stimulation has been used with good results, based on older reports that direct sacral nerve stimulation treated voiding dysfunction [13]. An implantable neuroprosthetic device approved by FDA for urinary urgency and frequency is used for this purpose. Disadvantages of the procedure include high cost, need for frequent surgical revisions and risk for surgical site infection and pain.

Agents with analgesic action have been used including dextroamphetamine, resineferatoxin, botulinum toxin, gabapentin and pregabalin [35]. Reasonable administration of analgesics, including narcotics, may be appropriate in refractory cases.

We believe that a chronic multifactorial disease like IC needs a holistic approach. Supportive therapies are important as a first step. Bearing in mind ‘to treat and not to harm’, we suggest that starting with treatments that are less invasive, have lower adverse events and broader clinical experience is advisable. Treatments with significant adverse events should be reserved for severe, refractory cases. With these rules in mind we propose the algorithm presented in Figure 1.

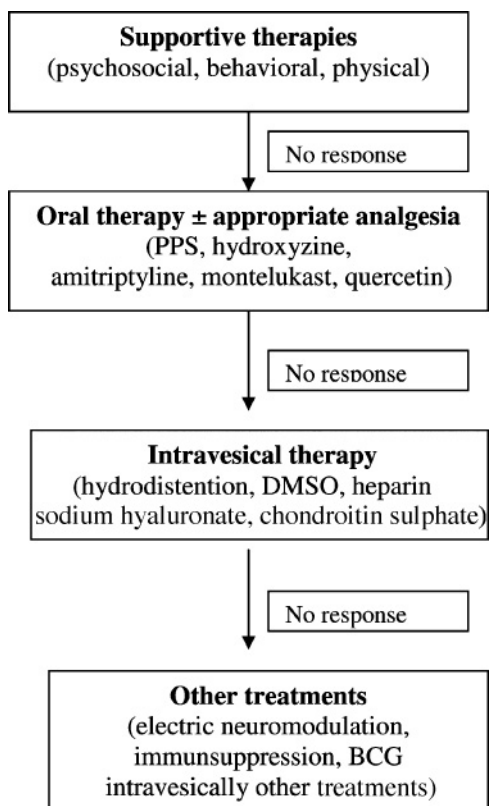


Fig. 1 Treatment algorithm for IC.

Teaching points

- (i) IC is an enigmatic chronic disorder of unclear aetiology characterized by vague bladder pain of variable severity and urinary symptoms. Although initially thought to be a rather rare disorder, its prevalence has increased over years. It occurs mainly in middle-aged women affecting significantly the quality of life.
- (ii) IC diagnosis is a diagnosis of exclusion. Therefore, it is crucial to exclude other more common disorders with worse prognosis (i.e. bladder cancer) but similar clinical presentation.
- (iii) Since there is no consensus for treatment, it is prudent to start with treatments that are less invasive, have lower adverse events and broader clinical experience reserving treatments with significant adverse events for severe, refractory cases.

Conflict of interest statement. None declared.

References

1. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28–29, 1987. *J Urol* 1988; 140: 203–206
2. Hanno PM, Landis JR, Matthews-Cook Y *et al.* The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol* 1999; 161: 553–557
3. Abrams P, Cardozo L, Fall M *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Am J Obstet Gynecol* 2002; 187: 116–126
4. van de Merwe JP, Nordling J, Bouchelouche P *et al.* Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol* 2008; 53(1): 60–67
5. Oravisto KJ. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn* 1975; 64: 75–77
6. Roberts RO, Bergstralh EJ, Bass SE *et al.* Incidence of physician-diagnosed interstitial cystitis in Olmsted county: a community-based study. *BJU Int* 2003; 91: 181–185
7. Clemens JQ, Meenan RT, Rosetti MC *et al.* Prevalence and incidence of interstitial cystitis in a managed care population. *J Urol* 2005; 173: 98–102 discussion
8. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. *Urology* 1997; 49: 2–9
9. Clemens JQ, Meenan RT, O’Keeffe Rosetti MC *et al.* Prevalence of interstitial cystitis symptoms in a managed care population. *J Urol* 2005; 174: 576–580
10. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in the Netherlands: prevalence, diagnostic criteria and therapeutic preferences. *J Urol* 1995; 154: 2035–2037, discussion 7–8.
11. Leppilahti M, Tammela TL, Huhtala H *et al.* Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. *J Urol* 2002; 168: 139–143
12. Koziol JA, Clark DC, Gittes RF *et al.* The natural history of interstitial cystitis: a survey of 374 patients. *J Urol* 1993; 149: 465–469
13. Theoharides TC. Treatment approaches for painful bladder syndrome/interstitial cystitis. *Drugs* 2007; 67: 215–235
14. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol* 1991; 145: 732–735
15. Letourneau R, Pang X, Sant GR *et al.* Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. *Br J Urol* 1996; 77: 41–54
16. Simon LJ, Landis JR, Erickson DR *et al.* The interstitial cystitis data base study: concepts and preliminary baseline descriptive statistics. *Urology* 1997; 49: 64–75
17. Driscoll A, Teichman JM. How do patients with interstitial cystitis present? *J Urol* 2001; 166: 2118–2120
18. Rosenberg MT, Newman DK, Page SA. Interstitial cystitis/painful bladder syndrome: symptom recognition is key to early identification, treatment. *Cleve Clin J Med* 2007; 74(Suppl 3): S54–S62
19. Parsons CL. Interstitial cystitis: epidemiology and clinical presentation. *Clin Obstet Gynecol* 2002; 45: 242–249
20. Warren JW, Meyer WA, Greenberg P *et al.* Using the International Continence Society’s definition of painful bladder syndrome. *Urology* 2006; 67: 1138–1142, discussion 42–43.
21. Evans RJ, Sant GR. Current diagnosis of interstitial cystitis: an evolving paradigm. *Urology* 2007; 69: 64–72
22. Lotz M, Villiger P, Hugli T *et al.* Interleukin-6 and interstitial cystitis. *J Urol* 1994; 152: 869–873
23. O’Leary MP, Sant GR, Fowler FJ Jr *et al.* The interstitial cystitis symptom index and problem index. *Urology* 1997; 49: 58–63
24. Parsons CL, Dell J, Stanford EJ *et al.* Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002; 60: 573–578
25. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. *J Urol* 2005; 174: 2231–2234
26. Erickson DR, Tomaszewski JE, Kunselman AR *et al.* Do the National Institute of Diabetes and Digestive and Kidney Diseases cystoscopic criteria associate with other clinical and objective features of interstitial cystitis? *J Urol* 2005; 173: 93–97
27. Nickel JC. Interstitial cystitis: the paradigm shifts: international consultations on interstitial cystitis. *Rev Urol* 2004; 6: 200–202

28. Nordling J, Anjum FH, Bade JJ *et al.* Primary evaluation of patients suspected of having interstitial cystitis (IC). *Eur Urol* 2004; 45: 662–669
29. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol* 1998; 160: 1663–1667
30. Parsons CL, Stein PC, Bidair M *et al.* Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. *Neurol Urodyn* 1994; 13: 515–520
31. Parsons CL, Greenberger M, Gabal L *et al.* The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998; 159: 1862–1866, discussion 6–7
32. Parsons CL, Koprowski PF. Interstitial cystitis: successful management by increasing urinary voiding intervals. *Urology* 1991; 37: 207–212
33. Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency-frequency syndrome. *J Urol* 2001; 166: 2226–2231
34. Iavazzo C, Athanasiou S, Pitsouni E *et al.* Hyaluronic acid: an effective alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis? *Eur Urol* 2007; 51: 1534–1540, discussion 40–41
35. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. *J Urol* 2003; 169: 1369–1373

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