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Review Article

Surgery Section

Painful Bladder Syndrome's Diagnostic and Therapeutic Controversies: A Review

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ABSTRACT

Painful Bladder Syndrome (PBS) is a controversial disease with no consensus on its nomenclature, diagnostic criteria, or aetiology. Interstitial Cystitis (IC), PBS, chronic pelvic pain syndrome, and Hypersensitive Bladder Syndrome (HBS) are closely related clinical diseases. Hence, underdiagnosis or misdiagnosis of PBS and consequent failure of disease management may occur. This review aims to explore the established and emerging controversies regarding the epidemiology, aetiology, pathogenesis, pathophysiology, clinical presentation, diagnostic criteria, workup and management strategies of PBS. A literature search was carried out in the following electronic databases, PubMed, Scopus, Embase, Google Scholar, Directory of Open Access Journals and Cochrane electronic databases from starting of May to first week of June 2020. Keywords including Bladder Pain Syndrome (BPS), aetiology, histopathology, management and diagnosis were used to search these various databases. Accurate data on the prevalence of PBS is scarce, primarily as there is no standardised definition. Furthermore, there are there no fixed criteria for diagnosis, leading to variability in the reported prevalence of PBS in the literature. Management approaches in patients with PBS must be individualised and tailored to each case in terms of aetiology, diagnosis, and treatment.

Keywords: Aetiology, Clinical presentation, Interstitial cystitis, Management, Misdiagnosis

INTRODUCTION

The IC is a disease of an intricate nature that is rife with controversies, beginning with the fact that no scientific consensus on its naming, diagnostic criteria, aetiology, or management exists. IC, PBS, BPS, chronic pelvic pain syndrome and HBS [1,2] are all diagnoses that share many characteristic storage symptoms: urgent urination, nocturia, frequent urination and painful or unpleasant bladder sensations that improve with emptying. There is a wide variety of diagnostic criteria, depending on which organisation's definition of the disease is used. One primary difference in these criteria is the duration of symptoms: six weeks is specified in the American Urological Association (AUA) guidelines and six months in European Association of Urology (EAU) guidelines. In addition, cystoscopy is optional according to the AUA, but not according to the EAU [3-5]. Another difference is in the strictness of the criteria; the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has the strictest guidelines, with 18 exclusionary criteria [Table/Fig-1] [4]. The NIDDK definition of IC as intended for research purposes states that the patient should not have any of the exclusionary criteria [Table/Fig-1], and must have either glomerulations that appear during cystoscopy, bladder distention to 80-100 cm of water pressure for two minutes under regional or general anaesthesia, petechial haemorrhaging appearing in three to four quadrants of the bladder, or Hunner's ulcers on cystoscopy, in addition to urgency or bladder pain with filling [4].

NIDDK Exclusion Criteria

Automatic exclusions:

1- Age, <18 years
2- Benign or malignant bladder tumours
3- Radiation cystitis
4- Tuberculous cystitis
5- Bacterial cystitis
6- Vaginitis
7- Cyclophosphamide cystitis
8- Symptomatic urethral diverticulum
9- Uterine, cervical, vaginal, or urethral cancer
10- Active genital herpes
11- Lower ureteral calculi
12- Wakeful frequency <5 times in 12 hour
13- Nocturia <2 times
14- Relief by antibiotics, urinary antiseptics, or urinary analgesics (for example, phenazopyridine hydrochloride)
15- Duration <12 months
16- Involuntary bladder contractions (urodynamics)
17- Capacity >400 cc

[Table/Fig-1]: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) exclusion criteria [4].

The International Society for the Study of BPS defines IC as chronic pelvic pain, discomfort, or pressure related to the bladder, with at least one urinary symptom such as urgency or frequency and with other diseases excluded by proper workup, including cystoscopy and bladder biopsy [6]. They define BPS as chronic bladder pain lasting for at least six months, with frequency and nocturia. Furthermore, pain must be related to bladder filling, increasing with volume and decreasing with emptying and be suprapubic with possible radiation to another pelvic organ, including the sacrum [5]. To help reduce variations in practice and outcome, this review explores the established and emerging controversies regarding the epidemiology, aetiology, pathogenesis, pathophysiology, clinical presentation, diagnostic criteria and work up, and management strategies of PBS.

Prevalence

In one study in a small region of Finland, the prevalence of PBS was estimated to be 10.1 cases per 100,000 people in 1975 [7], compared with 30 per 100,000 (0.03%) in 1987 and 510 per 100,000 (0.5%) in 1994 in the United States [8]. The criteria for a diagnosis of IC included a history of chronic lower urinary tract symptoms (mainly voiding) and a bladder biopsy showing fibrosis, edema and/or lymphocytic infiltration, in addition to sterile urine [7].

Clemens JQ et al., demonstrated that the prevalence of PBS differs between males and females, ranging from 16.5 cases per 100,000 males to 224 cases per 100,000 females [9], with an increasing prevalence in females with a first-degree relative with PBS [10]. Peters KM et al., reported in their study that 25% of adults with PBS have complained of PBS symptoms since childhood [11].

Aetiology

The strict inclusionary and exclusionary criteria recommended by the NIDDK, misses the diagnosis of at least 60% of patients with a high likelihood of having IC [12]. Moreover, the aetiology of the disease is not well-understood. Although some theories have been proposed, they have failed to find a statistically significant difference between patients

with PBS and control groups. Birder LA recently published an article on the pathophysiology of PBS, finding that the activation of the P2X3 purinoceptor can lead to an increase in the bladder afferent response after the release of ATP from the urothelium, which might lead to a new modality of treating PBS using a P2X3 purinoceptor blocker [13].

The Antiproliferative Factor (APF) is a unique protein that inhibits the proliferation of bladder cells which leads to bladder thinning and affects the bladder barrier [14,15]. In addition, the level of the heparin-binding epidermal growth factor, which is important in the epithelial repair process, is decreased by APF [16]. The autoimmunity theory is based on the difference in bladder urethral cells between patients with PBS and control groups. Patients with PBS have more CD41, CD81, B lymphocytes, immunoglobulins (IgA, IgG, and IgM), and plasma cells than control patients [17-19].

The central sensitisation of the spinal cord theory explains why PBS patients have pain even after cystectomies, as the sensitisation of the lower spinal cord is a chronic pain syndrome that leads to sensitisation in the pelvic organs such as the bladder [20]. Recently, Jhang JF et al., suggested a new theory related to the alteration of bladder Corticotropin-Releasing Hormone Receptors (CRHRs) in patients with PBS. CRHR staining has shown that CRHR1 is primarily expressed in the submucosa and CRHR2 is primarily expressed in urethral cells [21].

Histopathology

The histopathological diagnosis of PBS is based on exclusion of other possible diagnosis like eosinophilic cystitis, carcinoma in-situ and others [22,23]. There is no consistent histological features pathognomonic of PBS and variations are observed in histological findings of biopsies done on different patients with PBS and also biopsies repeated in same patients over a period of time [3]. Distinct histological findings are reported in ulcerative and non-ulcerative IC. A study involving 64 patients in ulcerative disease group and 44 patients with non-ulcerative disease group reported intense inflammatory infiltration with more number of mast cells, haemorrhage and granulation tissue in ulcerative group whereas the non-ulcerative disease group had multiple suburothelial haemorrhages with sparse infiltration [24].

Clinical Presentation

According to most recent studies, PBS can affect all ages, and the mean age at diagnosis ranges from the 40's to early 50's. In one survey study, the age at diagnoses of over 3397 women ranged from 18 to 92 years, with a mean age of 45.7 years [25]. Another study on the Danish population showed that the age of presentation ranges from 16 to 88 years, with a mean age of 53 years [26].

Symptoms in females of age 30-year-old or younger primarily include urgency, frequency, dysuria and dyspareunia, whereas some present with nocturia and vulvar pain. In patients over 30 years of age, the primary symptom is nocturia, which increases with age [4].

Nocturia and pelvic pain in young women should raise suspicions of PBS. Additionally, dyspareunia is reported in more than 60% of young women with PBS. The pain is not specific to intercourse and can happen in the genital area without or after intercourse [27]. Most patients with PBS report pain located in the bladder (88%), urethra (16%), genitals (3%), and non-genital areas (3%) [28].

Association of BPS with Other Diseases

Chronic fatigue

Nickel JC et al., observed chronic fatigue in 9.5% of patients with PBS, compared with 1.7% in the control group [19]. Another study on twins reported that a fatigued twin is 20 times more likely to have PBS than their non-fatigued twin [29]. Warren JW et al., reported that the odds ratio of IC occurring with chronic fatigue syndrome is 2.5, which is the same as all chronic pain syndromes. They noted that chronic fatigue might be a risk factor for PBS [30].

Fibromyalgia

Rodríguez MA et al., reported that 9% to 12% of patients with PBS have symptoms of fibromyalgia, and 2.25% to 27% of patients with fibromyalgia have symptoms of PBS [29]. In a study from Michigan, the odds ratio of diagnosing fibromyalgia in patients with PBS was 5.1 [31]. In a case-control study, Warren JW et al., compared 313 patients with PBS symptoms to a control group to evaluate their risks of fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and sicca syndrome. Seventy-eight percent of patients with PBS had more than two diseases, compared with 45% in the control group [32].

Irritable bowel

Rodríguez MA et al., reported that between 7%-48% of patients with PBS or symptoms of PBS have an irritable bowel, and the patients with IC are 11 times more likely than control group patients to be diagnosed with an irritable bowel [29].

Pelvic inflammatory disease

Chung SD et al., reported that there is a correlation between PBS and pelvic inflammatory disease, which is an inflammatory gynaecological disease associated with tubo-ovarian abscesses. In their case-control study, the prevalence of pelvic inflammatory disease in PBS cases and controls was 41.7% and 15.4%, respectively ($p<0.001$) [33].

Treatment for PBS

The treatment options range widely from dietary modification as a first-line therapy to surgical reconstruction and diversion as a sixth-line approach. The treatment options outlined by the Actual Ultrasound Date (AUA) are presented below [34].

Dietary modification

The fact that some foods irritate the bladders of patients with PBS is supported by many questionnaire-based studies [35,36]. Shorter B et al., found that 90% of patients with PBS report sensitivity to one or more types of food [37]. Citrus fruits, tomato products, alcohol, cola, and Mexican and Thai foods were the most common bladder irritants for patients with PBS. However, Fisher B et al., failed to find a statistical association between PBS and diet in a placebo-controlled study [38]. As dietary modification has a very low risk, it is recommended as an early management therapy option for patients with PBS [39].

Pelvic floor physical therapy

Fitzgerald MP et al., reported levator pain on examination in 87% of 70 women with PBS [4]. Schmidt RA and Vapnek JM noted that the pain appeared to be associated more with changes in sphincter tone than in detrusor muscle changes in the urodynamic testing of patients with PBS [40]. Physical therapy or trigger-point release is a valid treatment modality for patients with PBS. Weiss JM reported that 83% of patients with PBS improved markedly or completely with respect to bladder pain after 8–12 weeks of pelvic floor physical therapy, as documented by a 65% decrease in the resting pelvic floor pressure on an electromyography [41]. Owing to the low risk of pelvic floor therapy and evidence of improvement in patients with PBS, pelvic floor physical therapy is recommended as an early management modality for PBS [42].

Oral therapy

The oral therapeutic options for PBS include PPS, amitriptyline, cimetidine, hydroxyzine, immunotherapy, and cyclosporin A.

- **Oral Pentosan Polysulfate (PPS)**

PPS is a semi-synthetic chemical structure that produces a heparin-like macromolecular carbohydrate derivative similar to that found in the GAG layer of the bladder [43]. PPS replaces the deficit part of the GAG layer and decreases the permeability of solutes into the nerve endings, which, in theory, leads to an improvement in PBS symptoms, particularly pelvic pain [44,45].

- **Amitriptyline**

The therapeutic application of amitriptyline in urology is secondary to its central sedative activity, anticholinergic effect, antihistamine effect, and serotonin and noradrenaline re-uptake inhibition activity [46], and may be due to the effect of amitriptyline on the limbic pain center of the brain, which is usually up-regulated in patients with pelvic pain [46]. The recommended dose is 25-100 mg, but it must be titered according to improvements in symptoms. The side effects of amitriptyline increase with higher doses and include drowsiness, dry mouth, constipation, fatigue and malaise [47].

- **Cimetidine**

Cimetidine is a histamine H2-antagonist and is commonly used to treat peptic ulcers. Seshadri P et al., reported an improvement of symptoms after the oral administration of 300 mg of cimetidine twice daily in six of nine (66.67%) patients with PBS; four of these patients reported a complete and sustained improvement [48].

- **Hydroxyzine**

Hydroxyzine is an oral anti-allergic medication that blocks H1 receptors [49]. It is commonly used for urticaria and allergic rhinitis [50]. Patients with PBS are more prone to allergies than the general population [51]. Theoharides T and Sant GR reported a 40% improvement in PBS symptoms with hydroxyzine. The side effects of hydrazine include sedation and drowsiness, urine retention and an increased appetite [52]. The standard dose of hydrazine is 25 mg at bedtime, titered to 75 mg daily. Given the low severity of the adverse effects of hydrazine, it is recommended as a second-line therapy [42].

- **Immunotherapy**

There has been some evidence regarding improvement in PBS symptoms following the administration of immunotherapy medication, which may be explained by the fact that some patients with PBS might have autoimmune dysregulation [53-55]. Moran PA et al., studied the therapeutic effect of methotrexate in the management of refractory BPS, which produced a significant reduction in the pain score. However, there was neither an improvement in the voided volume nor a change in the frequency of symptoms [53].

- **Cyclosporin A**

Cyclosporin A is a calcineurin inhibitor and inhibits the activation of T cells [56]. Sairanen J et al., reported the results of a randomised study comparing the efficacy of PPS versus Cyclosporin A in patients with PBS, which showed a superior response with cyclosporin A [57]. Forrest JB et al., reported the outcome of cyclosporin A in refractory PBS: The GRA was 85% in Hunner's ulcer PBS compared with 30% in non-Hunner's PBS. The adverse effects of cyclosporin A (1.5 mg/kg twice daily) include renal impairment, an increased blood pressure and infection [58].

- **Intravesical Heparin, Sodium Bicarbonate, and Lidocaine**

Intravesical therapy is used in patients with PBS to restore the GAG layer, as with heparin [59], or for its anti-inflammatory properties and its ability to inhibit angiogenesis and fibroblast proliferation [60]. Considering the low severity of adverse effects, AUA guidelines recommend intravesical heparin, sodium bicarbonate, and lidocaine as a second-line therapy for PBS [42].

- **Dimethyl Sulfoxide (DMSO)**

DSMO is a wood-pulp industry material first synthesised in 1867 [61,62]. It has some bacteriostatic activity and analgesic and anti-inflammatory effects [63]. Perez-Marrero R et al., reported the results of a study on treating PBS with DSMO versus a placebo [63]. DSMO is administered intravesical once every week for 4 to eight weeks [64], and the response has been documented to last for one year [65]. The adverse effects of DSMO are mild and primarily related to bladder irritation, a garlic-like taste, and headaches [66]. Considering the low severity of adverse effects, AUA guidelines recommend intravesical DSMO as a second-line therapy [62].

Cystoscopy with short-duration hydrodistension

Cystoscopy of patients with PBS is essential for ruling out other causes of storage symptoms such as bladder tumours or carcinoma in-situ [67]. However, it is well-established that not all patients with PBS will have a positive finding under cystoscopy [68]. There is some evidence, based only on observational studies that hydrodistension is beneficial for PBS [69-71].

Hunner's ulcer fulguration

The presence of a Hunner's ulcer is one of the criteria used to diagnose PBS, based on the NIDDK guidelines. Hillelsohn JH et al., reported the results of a retrospective study of fulguration in 59 patients with PBS with Hunner's ulcers. Seventy-eight percent reported sustained improvement and almost half required repeated fulguration sessions with a 4-year follow-up [72]. A neodymium-yttrium-aluminum-garnet laser or injection with triamcinolone can be used instead of fulguration, and treatment sessions have been documented to last for up to one year [73,74]. AUA guidelines consider cystoscopy with Hunner's ulcer fulguration, a laser, or a triamcinolone injection to be a third-line therapy for patients with PBS [42].

Intravesical Onabotulinumtoxin A

Onabotulinumtoxin A is a strong toxin derived from Clostridium botulinum which inhibits neurotransmitter release (primarily acetylcholine) at the neuromuscular junction, ultimately causing muscle paralysis [75]. Lee HY et al., recently reported the results of a meta-analysis of 248 patients over six trials on the safety and efficacy of intravesical onabotulinumtoxin-A in treating an overactive bladder. Only the voided volume significantly improved, and all other parameters of overactive symptoms and bladder pain were insignificantly changed [76]. The most common adverse effects of intravesical onabotulinumtoxin-A injection are urine retention, urinary tract infections, haematuria, a high pulmonary vascular resistance, and complications of clean intermittent catheterisation [77]. Considering the side effects and the expected improvement with an intravesical injection of onabotulinumtoxin-A, AUA guidelines recommend intravesical onabotulinumtoxin-A as a fourth-line treatment for patients with PBS [42]. [Table/Fig-2] shows dosage of various therapeutic agents used in PBS.

Therapy	Dosage
Oral Pentosan Polysulfate (PPS) [45]	100 mg po* tid
Amitriptyline [47]	25-75 mg po qhs
Cimetidine [48]	400 mg po bid
Hydroxyzine [52]	10-50 mg po qhs
Cyclosporin A [58]	2-3 mg/kg bid
Intravesical Heparin, Sodium Bicarbonate, and Lidocaine [42]	20000-40000 IU heparin diluted in 10 mL NS for 30-60 minutes.
Dimethyl Sulfoxide (DMSO) [66]	50 mL solution of 50%
Intravesical Onabotulinumtoxin A [77]	100-200 IU suburothelial
Hydrodistension [69]	Bladder is filled with normal saline at a pressure of 80 cm of H20 and distended is maintained for not more than 10 minutes.

[Table/Fig-2]: Dosage of various therapeutic agents used in Painful Bladder Syndrome (PBS) [42,45,47,48,52,58,66,69,77].
*po: per orally; tid: three times/day;, qhs: four times a day; bid: two times/day

Neuromodulation

Abnormal pain signals and C-fiber activities constitute one of the proposed aetiologies of PBS [33]. Sacral neuromodulation might block C-afferent-fiber activity [78] and has been shown to alter the level of heparin-binding epidermal growth factor and APF in patients with PBS [79]. Wang J et al., published a meta-analysis of sacral neuromodulation used to treat PBS, in which a total of 583 patients were included in 17 studies, and the success rate was 84%, with minimal adverse effects. All PBS parameters significantly improved, including the frequency, nocturia, symptom index scores, voided

volume, and urgency [80]. Percutaneous Tibial Nerve Stimulation (PTNS) has been investigated in patients with PBS. O'Reilly B et al., found no difference in the pain scale between the treatment group and the control group [81], whereas Gokyildiz reported an improvement in the pain scale and quality of life scores of the PTNS group [82]. The AUA guidelines recommend neuromodulation as a fourth-line treatment for patients with PBS [42].

Surgical reconstruction/urinary diversion

The last solution to consider for patients with PBS is major surgical construction and urinary diversion. The consideration of this procedure depends on the patient and the surgeon's experience, and includes an ileal conduit, supratrigonal cystectomy, ileocystoplasty, continent urinary diversion (Kock pouch), continent orthotopic diversion, or cecocystoplasty. These surgeries are reserved for refractory PBS resistant to all other treatments or for patients with a small bladder capacity on hydrodistension (less than 300 mL) [83]. AUA guidelines recommend surgical reconstruction and urinary diversion as a sixth-line and final option in treating patients with PBS [53].

CONCLUSION(S)

PBS is a disease that causes conflict among investigators and has no standardised definition or diagnostic criteria. Moreover, there is no definitive aetiology for PBS. In addition, according to the AUA guidelines, there are six lines of treatment starting with behavioural modification and ending with major surgery for urinary diversion. This review recommends that further education for the general population, general urologists, and family physicians on PBS and its management is needed.

REFERENCES

[1] Hanno P, Lin A, Nordling J. Bladder pain syndrome committee of the international consultation on incontinence. Neurourol. Urodyn., 2010;29(1):191-98. DOI: 10.1002/nau.20847
[2] Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH, et al. The Interstitial Cystitis Guideline Committee. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Int J Urol. 2009;16(7):597-615.
[3] 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. J Urol. 1988;140:203-06.
[4] Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg LJ. The diagnosis of interstitial cystitis revisited: Lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol. 1999;161:553-57.
[5] Fall M, Baranowski AP, Elneil S, Engeler D, Hughes J, Messelink EJ, et al. EAU Guidelines on chronic pelvic pain. Eur Urol. 2010;57:35-48.
[6] Van De Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. Eur Urol. 2008;53:60-67.
[7] Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn. 1975;64:75-77.
[8] Jones CA, Nyberg L. Epidemiology of interstitial cystitis. Urology. 1997;49:02-09.
[9] Clemens JQ, Meenan RT, Rosetti MCO, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol. 2005;173:98-102.
[10] Warren JW, Jackson TL, Langenberg P, Meyers DJ, Xu J. Prevalence of interstitial cystitis in first-degree relatives of patients with interstitial cystitis. Urology. 2004;63:17-21.
[11] Peters KM, Killinger KA, Ibrahim IA. Childhood symptoms and events in women with interstitial cystitis/painful bladder syndrome. Urology. 2009;73:258-62.
[12] Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185:2162-70.
[13] Birder LA. Pathophysiology of interstitial cystitis. Int J Urol. 2019;26:12-15.
[14] Warren JW, Brown V, Jacobs S, Horne L, Langenberg P, Greenberg P. Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. Urology. 2008;71:1085-90.
[15] Keay SK. Cell signaling in interstitial cystitis/painful bladder syndrome. Cell Signal. 2008;20:2174-79.
[16] Chai TC, Zhang CO, Shoenfelt JL, Johnson HW, Jr, Warren JW, Keay S. Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis. J Urol. 2000;163:1440-44.
[17] MacDermott JP, Miller CH, Levy N, Stone AR. Cellular immunity in interstitial cystitis. J Urol. 1991;145:274-78.
[18] Liebert M, Wedemeyer G, Stein JA, Washington R, Faerber G, Flint A, et al. Evidence for urothelial cell activation in interstitial cystitis. J Urol. 1993;149:470-75.
[19] Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J Urol. 2010;184:1358-63.
[20] Warren JW, Van De Merwe JP, Nickel JC. Interstitial cystitis/bladder pain syndrome and nonbladder syndromes: Facts and hypotheses. Urology. 2011;78:727-32.
[21] Jhang JF, Birder LA, Jiang YH, Hsu YH, Ho HC, Kuo HC. Dysregulation of bladder corticotropin-releasing hormone receptor in the pathogenesis of human interstitial cystitis/bladder pain syndrome. Sci Rep. 2019;9:01-08.
[22] Hellstrom HR, Davis BK, Shonnard JW. Eosinophilic cystitis. A study of 16 cases. Am J Clin Pathol. 1979;72:777.
[23] Tsiriopoulos I, Lee GA, Smith R, Pancharatnam M. Primary splenic marginal zone lymphoma with bladder metastases mimicking interstitial cystitis. Int Urol Nephrol. 2006;38:475.
[24] Lepinard V, Saint-Andre JP, Rognon LM. Interstitial cystitis. Current aspects. J Urol. 1984;90:455.
[25] Konkle KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ, et al. Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND Interstitial Cystitis Epidemiology study. J Urol. 2011;187:508-12.
[26] Richter B, Hesse U, Hansen AB, Horn T, Mortensen SO, Nordling J. Bladder pain syndrome/interstitial cystitis in a Danish population: A study using the 2008 criteria of the European Society for the Study of Interstitial Cystitis. BJU Int. 2010;105:660-67.
[27] Laumann OE, Paik A, Rosen RC. Sexual dysfunction in the United States: Prevalence and predictors. JAMA. 1999;281:537-44.
[28] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, et al. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain. 2008;138:22-28.
[29] Rodríguez MA, Afari N, Buchwald DS. National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Urological Chronic Pelvic Pain. Evidence for overlap between urological and nonurological unexplained clinical conditions. J Urol. 2009;182:2123-31.
[30] Warren JW, Wesselmann U, Morozov V, Langenberg PW. Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. Urology. 2011;77:313-19.
[31] Reed BD, Harlow SD, Sen A, Edwards RM, Chen D, Haefner HK. Relationship between vulvodynia and chronic comorbid pain conditions. Obstet Gynecol. 2012;120:145-51.
[32] Warren JW, Howard FM, Cross RK, Good JL, Weissman M, Wesselmann U, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology. 2009;73:52-57.
[33] Chung SD, Chang CH, Hung PH, Chung CJ, Muo CH, Huang CY. Correlation between bladder pain syndrome/interstitial cystitis and pelvic inflammatory disease. Medicine. 2015;94:e1878.
[34] Dyer AJ, Twiss CO. Painful bladder syndrome: An update and review of current management strategies. Curr Urol Rep. 2014;15. doi:10.1007/s11934-013-0384-z.
[35] Friedlander JI, Shorter B, Moldwin RM. Diet and its role in interstitial cystitis/bladder pain syndrome (IC/IC/PBS) and comorbid conditions. BJU Int. 2012;109:1584-91.
[36] Bassaly R, Downes K, Hart S. Dietary consumption triggers in interstitial cystitis/bladder pain syndrome patients. Female Pelvic Med Reconstr Surg. 2011;17:36-39.
[37] Shorter B, Lesser M, Moldwin RM, Kushner L. Effect of comestibles on symptoms of interstitial cystitis. J Urol. 2007;178(1):145-52.
[38] Fisher B, Bavendam T, Roberts B, Karkeck J, Brannon C. Blinded placebo controlled evaluation on the ingestion of acidic foods and their effect on urinary ph and the symptomatology of interstitial cystitis. J Am Diet Assoc. 1993;93:A16. doi:10.1016/0002-8223(93)91040-w.
[39] Fitzgerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ, et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol. 2009;182:570-80.
[40] Schmidt RA, Vapnek JM. Pelvic floor behaviour and interstitial cystitis. Semin Urol. 1991;9:154-59.
[41] Weiss JM. Pelvic floor myofascial trigger points: Manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol. 2001;166:2226-31.
[42] American Urological Association. Diagnosis and Treatment Interstitial Cystitis/Bladder Pain Syndrome (2014). Available online: https://www.auanet.org/guidelines/interstitial-cystitis-(ic/bps)-guideline. Last access 15 May 2020.
[43] Janssen Pharmaceuticals, Inc. [Internet]. Elmiron® 100 mg (Pentosan Polysulfate Sodium) Capsules. Available online: http://www.orthoelmiron.com. Last access 15 May 2020.
[44] Holm-Bentzen M, Jacobsen F, Nerstrøm B. A prospective double-blind clinically controlled multicenter trial of sodium pentosan polysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol. 1987;138:503-07.
[45] Van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol. 2004;172:533-36.
[46] Fenton B. Limbic associated pelvic pain: A hypothesis to explain the diagnostic relationships and features of patients with chronic pelvic pain. Med Hypotheses. 2007;69:282-86.
[47] Foster HE Jr, Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA, et al. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. J Urol. 2010;183:1853-58.
[48] Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. Urology. 1994;44:614-16.

[49] Theoharides T. Hydroxyzine for interstitial cystitis. J Allergy Clin Immunol. 1993;91:686-87.
[50] Theoharides TC. Hydroxyzine in the treatment of interstitial cystitis. Urol Clin N Am. 1994;21:113-19.
[51] Koziol JA, Clark DC, Gittes RF, Tan EM. The natural history of interstitial cystitis: A survey of 374 patients. J Urol. 1993;149:465-69.
[52] Theoharides TC, Sant GR. Hydroxyzine therapy for interstitial cystitis. Urology. 1997;49:108-10.
[53] Moran PA, Dwyer PL, Carey M, Maher CF, Radford NJ. Oral methotrexate in the management of refractory interstitial cystitis. Aust NZJ Obstet Gynaecol. 1999;39:468-71.
[54] Oravisto K, Alfthan O. Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. Eur Urol. 1976;2:82-84.
[55] Alagiri M, Chottiner S, Ratner V, Slade D, Hanno PM. Interstitial cystitis: Unexplained associations with other chronic disease and pain syndromes. Urology. 1997;49:52-57.
[56] Ogawa H, Kameda H, Amano K, Takeuchi T. Efficacy and safety of cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. Lupus. 2009;19:162-69.
[57] Sairanen J, Tammela TL, Leppilahti M, Multanen M, Paananen I, Lehtoranta K, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: A randomized comparative study. J Urol. 2005;174:2235-38.
[58] Forrest JB, Payne CK, Erickson DR. Cyclosporine A for refractory interstitial cystitis/bladder pain syndrome: Experience of 3 tertiary centers. J Urol. 2012;188:1186-91.
[59] Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. BJU Int. 1994;73:504-07.
[60] Lose G, Frandsen B, Højensgård JC, Jespersen J, Astrup T. Chronic interstitial cystitis: increased levels of eosinophil cationic protein in serum and urine and an ameliorating effect of subcutaneous heparin. Scand J Urol Nephrol. 1983;17:159-61.
[61] Moldwin RM, Sant GR. Interstitial cystitis: A pathophysiology and treatment update. Clin Obstet Gynecol. 2002;45:259-72.
[62] Jacob SW, Bischel M, Herschler RJ. Dimethyl sulfoxide (DSMO): A new concept in pharmacotherapy. Curr Ther Res. 1964;6:134-35.
[63] Perez-Marrero R, Emerson L, Feltis J. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol. 1988;140:36-39.
[64] Biggers RD. Self-administration of dimethyl sulfoxide (DMSO) for interstitial cystitis. Urology. 1986;28:10-11.
[65] Stav K, Beberashvili I, Lindner A, Leibovici D. Predictors of response to intravesical dimethyl-sulfoxide cocktail in patients with interstitial cystitis. Urology. 2012;80:61-65.
[66] Hung MJ, Chen YT, Shen PS, Hsu ST, Chen GD, Ho ESC. Risk factors that affect the treatment of interstitial cystitis using intravesical therapy with a dimethyl sulfoxide cocktail. Int Urogyneco J. 2012;23:1533-39.
[67] Tissot WD, Diokno AC, Peters KM. A referral center's experience with transitional cell carcinoma misdiagnosed as interstitial cystitis. J Urol. 2004;172:478-80.
[68] Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn. 2005;24:638-42.
[69] Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM, et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol. 2007;177:556-60.
[70] Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology. 2005;66:494-99.
[71] McCahy P, Styles R. Prolonged bladder distension: Experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol. 1995;28:325-27.
[72] Hillelsohn JH, Rais Bahrami S, Friedlander JI, Okhunov Z, Kashan M, Rosen L, et al. Fulguration for Hunner ulcers: Long-term clinical outcomes. J Urol. 2012;188:2238-41.
[73] Rofeim O, Hom D, Freid RM, Moldwin RM. Use of the neodymium: YAG laser for interstitial cystitis: A prospective study. J Urol. 2001;166:134-36.
[74] Cox M, Klutke JJ, Kutlke CG. Assessment of patient outcomes following sub-musocal injection if triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. Can J Urol. 2009;16:4536-40.
[75] Tirumuru S, Al Kurdi D, Latthe P. Intravesical botulinum toxin A injections in the treatment of painful bladder syndrome/interstitial cystitis: A systematic review. Int Urogynecol J. 2010;21:1285-300.
[76] Lee HY, Doo SW, Yang WJ, Song YS, Sun HY, Nho EJ, et al. Efficacy and safety of noninvasive intravesical instillation of onabotulinum toxin-A for overactive bladder and interstitial cystitis/bladder pain syndrome: Systematic review and meta-analysis. Urology. 2019;125:50-57.
[77] Davis NF, Burke JP, Redmond EJ, Elamin S, Brady CM, Flood HD. Trigonal versus extra trigonal botulinum toxin-A: A systematic review and meta-analysis of efficacy and adverse events. Int Urogynecol J. 2015;26:313-19.
[78] Shaker H, Wang Y, Loung D, Balbaa L, Fehlings MG, Hassouna MM. Role of C-afferent fibres in the mechanism of action of sacral nerve root neuromodulation in chronic spinal cord injury. BJU Int. 2000;85:905-10.
[79] Elbadawi A. Interstitial cystitis: A critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology. 1997;49:14-40.
[80] Wang J, Chen Y, Chen J, Zhang G, Wu P. Sacral neuromodulation for refractory bladder pain syndrome/interstitial cystitis: A global systematic review and meta-analysis. Sci Rep. 2017;7:11031.
[81] O'Reilly B, Dwyer P, Hawthorne G, Cleaver S, Thomas E, Rosamilia A, et al. Transdermal posterior tibial nerve laser therapy is not effective in women with interstitial cystitis. J. Urol. 2004;172:1880-83.
[82] Gokyildiz S, Beji NK, Yalcin O, Istek A. Effects of percutaneous tibial nerve stimulation therapy on chronic pelvic pain. Gynecol Obstet Investig. 2012;73:99-105.
[83] Elliott CS, Payne CK. Interstitial cystitis and the overlap with overactive bladder. Curr Urol Rep. 2012;13:319-26.

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