CLINICAL REVIEW

The management of interstitial cystitis or painful bladder syndrome in women

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Interstitial cystitis or painful bladder syndrome is a chronic, often debilitating, condition largely defined by symptoms of urinary urgency and frequency associated with pelvic pain that varies with bladder filling.[1] Unlike bladder inflammation caused by bacterial infection, the condition occurs in the absence of urinary tract infection or other obvious pathology. Resulting discomfort may range from abdominal tenderness to intense pain. This difficult clinical entity has prompted debate with regard to definition, aetiology, and best methods of treatment. This review discusses the diagnosis and management of interstitial cystitis according to current best evidence. Few Oxford scale levels 1 and 2 evidence based research studies in interstitial cystitis are available because of the ethical difficulties in conducting randomised trials in this area. We have therefore referred to evidence that represents the majority opinion of researchers as being clinically relevant.

What is interstitial cystitis and who gets it?

The pathological features of bladder epithelial damage and related blood vessel transitions[2-4] in the absence of infection have been recognised for more than 100 years, yet this clinical entity remains baffling because many patients have symptoms but display no conclusive cystoscopic findings. Today, two types of interstitial cystitis are identified: the "classic" form initially described by Hunner, which is associated with gross inflammatory bladder wall changes, and the much more common "non-classic" form which exhibits characteristic symptoms but a lack of gross cystoscopic findings. Currently, patients without cystoscopic findings are diagnosed as having painful bladder syndrome and the diagnosis of interstitial cystitis is reserved for those with cystoscopic findings of glomerulations or Hunner's ulcers. Patients with interstitial cystitis or painful bladder syndrome experience suprapubic pain with bladder filling, as well as daytime and night-time frequency without a documented urinary tract infection (fig 1). Although some prevalence estimates indicate that nearly one million women and men in both the United States and Europe have this condition,[5] a recent managed care review asserts a female to male ratio of 5:1.[3]

Symptoms may mimic those of bladder cancer, sexually transmitted diseases, endometriosis, urinary or vaginal infections, prostatitis, and neurologically mediated bladder hyperactivity.[6] Patients are more likely to have other comorbidities—100 times more likely to have irritable bowel syndrome and 30 times more likely to have systemic lupus erythematosus.[3 5 6] Other associated chronic illnesses include migraine, asthma, fibromyalgia, incontinence, chronic fatigue syndrome, and vulvodynia.[2 4 6] In a survey of 464 symptom-free

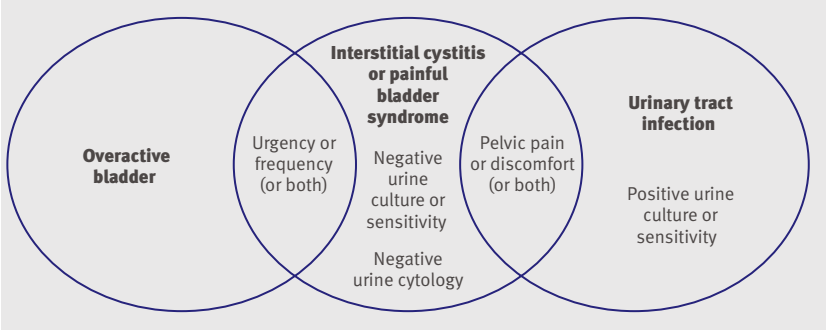

Fig 1 | Diagnosis of interstitial cystitis or painful bladder syndrome: negative urine cultures are important in differentiating overactive bladder and urinary tract infections from interstitial cystitis. Negative urine cytology for malignant cells is also important in the differential diagnosis

SUMMARY POINTS

- Interstitial cystitis or painful bladder syndrome is a chronic, often debilitating condition, typified by exacerbations, remissions, and varying degrees of symptom severity
- Symptoms include urinary urgency and frequency, with pelvic pain that varies from abdominal tenderness to intense pain
- Patients have a 100 times greater chance of having irritable bowel syndrome and 30 times increased likelihood of systemic lupus erythematosus
- Other associated illnesses include migraine, asthma, fibromyalgia, incontinence, chronic fatigue syndrome, and vulvodynia
- A history of abuse (domestic violence and emotional, physical, and sexual abuse) is higher than in controls (37% *v* 22%)
- Drugs (amitriptyline, pentosan polysulfate sodium, prednisone, and ciclosporin) and minimally invasive surgery are effective treatments
- In some patients symptoms are exacerbated by certain foods and drinks

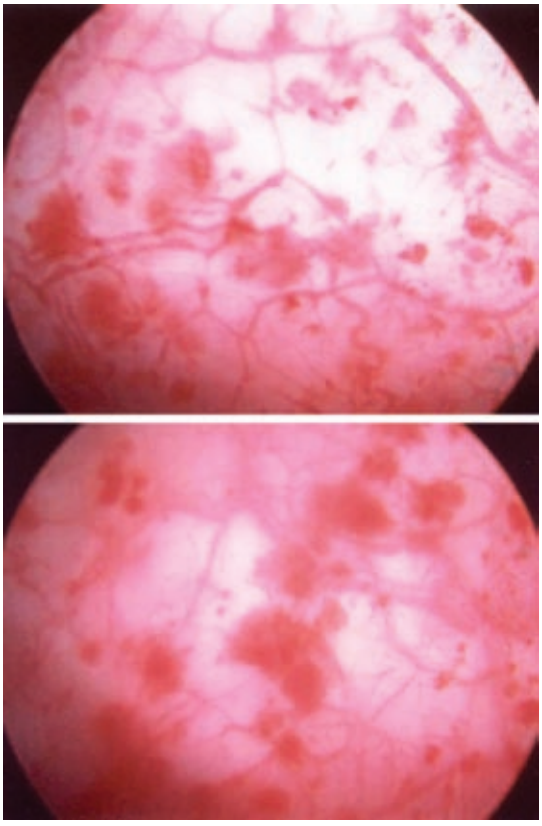

Fig 2 | Glomerulations (tiny haemorrhages), which appear after hydrodistension, help in the diagnosis of interstitial cystitis

controls, 215 patients with interstitial cystitis, and 121 people with a history suggestive of interstitial cystitis, 49% of the established patients reported a history of abuse (92% emotional, 78% physical, 68% sexual, and 49% domestic violence).[7] Establishing a connection with other pathogenic disorders would help in understanding and treating the condition.

What causes interstitial cystitis or painful bladder syndrome?

The disease process is probably multifactorial, with patients having one or more causative factors. Postulated yet unconfirmed causes include

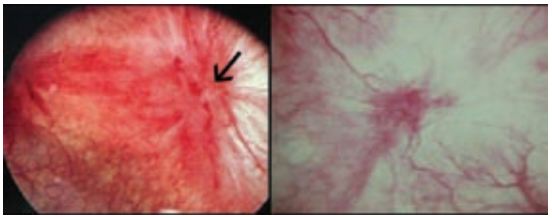

Fig 3 | Hunner's ulcers or "patches" are inflamed areas of the bladder wall, which may be seen on routine cystoscopic examination (arrow, left). Bladder scarring (white area, right) and radiating blood vessels are also visible

infection, autoimmune disease, inherited factors, allergic responses, and other genetic processes.[5-7] One theory is that increased permeability of the protective glycosaminoglycan lining of the bladder epithelium causes potassium, toxins, and other urine based substances to leak into the mucosal interstitium, activating mast cells and generating an autoimmune response.[8] Mast cells produce immune reactive chemicals, which in turn cause generalised bladder inflammation and bladder mucosal damage through the presence of tachykinins and cytokines. These further mediate the release of histamine, tumour necrosis factor, chymase, tryptase, and prostaglandins. Finally, inflammatory agents sensitise bladder neurones, producing pelvic and bladder pain.[5 9]

How is the condition diagnosed?

Historically, diagnosis depended on a complex of symptoms including pain related to the bladder, frequency, and urgency with no other definitive cause.[9 10] Although cystoscopy with hydrodistension may provide information on bladder abnormalities—such as glomerulations (fig 2), mucosal tears, low anaesthetic bladder capacity, and Hunner's ulcers or "patches" (fig 3)—a retrospective study of 84 consecutive patients with the condition found the procedure no better than taking a history and performing a physical examination.[11] Bladder biopsy is not a mandated procedure unless gross abnormalities of the bladder wall are found.

Table 1 | Pelvic pain, urgency, and frequency patient symptom scale[13]

	Score				
Question	0	1	2	3	4
1. How many times do you go to the toilet during the day?	3-6	7-10	11-14	15-19	20+
2a. How many times do you go to the toilet at night?	0	1	2	3	4+
2b. If you get up at night to go to the toilet, does it bother you?	Never	Occasionally	Usually	Always	
3. Are you currently sexually active? (yes or no)					
4a. If you are sexually active, do you now have or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always	
4b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always	
5. Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always	
6a. If you have pain, how strong is it usually?		Mild	Moderate	Severe	
6b. Does your pain bother you?	Never	Occasionally	Usually	Always	
7. Do you still have urgency after you go to the toilet?	Never	Occasionally	Usually	Always	
8a. If you have urgency, how severe is it usually?		Mild	Moderate	Severe	
8b. Does your urgency bother you?	Never	Occasionally	Usually	Always	

The symptom score is obtained by adding up the scores for questions 1, 2a, 4a, 5, 6a, 7, and 8a; the bother is obtained by adding up the scores for questions 2b, 4b, 6b, and 8b; the total score s obtained by adding up the symptom score and the bother score. Cumulative scores of 12 or more may be indicative of interstitial cystitis or painful bladder syndrome.

A survey has recently been developed to screen populations for interstitial cystitis or painful bladder syndrome.[12] The pelvic pain, urgency, and frequency patient symptom scale is a comprehensive symptom questionnaire that measures urinary urgency, frequency, pelvic pain, and sexually associated symptoms (table 1).[12] The score has recently been validated for screening in a urology clinic setting.[13] Screening indices, a detailed history, physical examination, and diagnostic tests (urinalysis, urine culture, cystoscopy, biopsy of the bladder wall, distension of the bladder under anaesthesia, and urine cytology) are most effective in excluding other diseases and directing the practitioner to a diagnosis of interstitial cystitis.

Referring to a specialist

Simple validated questionnaires such as the one described above may be used to identify patients who have interstitial cystitis or painful bladder syndrome. Those with a high score (cumulative score >12) may benefit from a specialist referral.

Is the condition related to diet?

Some patients have exacerbations of their symptoms after ingesting certain foods or drinks (table 2). In a study of 104 patients with interstitial cystitis, 90% of respondents to a validated questionnaire indicated that certain foodstuffs aggravated symptoms, as did larger meals (75%).[14] Patients were also asked whether each of 175 items worsened, improved, or had no effect on symptoms. Responses were numerically scored on a scale of −2 (worst) to 2 (best). Grapefruit, lemon, cranberry, orange, and pineapple juices (and their fruits) scored significantly lower than other fruits and juices, suggesting that citrate can worsen symptoms ($P<0.05$). Coffee, decaffeinated coffee, tea, cola, non-cola soda, caffeine-free soda, diet soda, beer, red and white wine, and champagne scored significantly lower than other drinks ($P<0.05$), suggesting that caffeine, alcohol, and carbonated drinks also worsen symptoms.[14-17]

Dietary manipulation

Food charts are available on several websites (www.ichelp.org) to help patients and clinicians regulate food intake more effectively. Advice to patients interested in this approach is to avoid foods on the chart for two weeks, then reintroduce them individually to discern whether particular items lead to an exacerbation of the original voiding or pelvic pain symptoms.[15-17] Patients must be careful not to eliminate more foods than necessary, however, because a severely restrictive diet may be inadequate to maintain health and long term symptom improvement.

What current treatment approaches have shown benefit?

Current treatments for interstitial cystitis are aimed at symptom relief. Table 3 provides details of the drugs currently used for the treatment of interstitial cystitis.

A patient's perspective

I was just 14 years of age when I first had sudden strong urges to urinate, without incontinence. By age 22, I also had pelvic pain. After being evaluated by several urologists and gynaecologists, and undergoing multiple cystoscopies and laparoscopies, I was given the tentative diagnosis of endometriosis, dysmennorhoea, and chronic pelvic pain.

All cultures were negative and transvaginal ultrasound was uninformative. I then underwent multichannel urodynamic studies to obtain objective physiological parameters of the bladder including first sensation, first urge, and bladder capacity. All three parameters were reduced, which is typical of interstitial cystitis. At that time I needed to urinate 18-25 times a day, four to eight times during the night, but I was not incontinent. I was treated with amitriptyline and pentosan polysulfate sodium. After one year of treatment, I needed to urinate less frequently (8-12 times a day, once at night) and pelvic pain was substantially reduced. My score on the visual analogue pain scale was 9 before treatment and 3 after treatment. For sudden severe exacerbations, I received intravesicular instillations of DMSO, heparin sulfate, and bicarbonate at weekly intervals for three or six weeks. My symptoms consistently improved within two weeks. At the age of 33, my life has finally normalised and I can now fulfil my role as a respiratory therapist. Three years after the start of multimodal therapy, I have lasting improvement in the need to urinate and relief from pelvic pain.

Table 2 | Recommended dietary restrictions[14]

Foodstuff	Avoid	May try
Meat and fish	Aged, cured, canned, and smoked meat; smoked fish; meat or fish that contains nitrates or nitrites	Poultry and unprocessed meats or fish
Fruits	Apples, apricots, avocados, bananas, cantaloupes, citrus fruit, cranberries, grapes, nectarines, peaches, pineapples, plums, pomegranates, rhubarb, and strawberries	Melons, blueberries, and pears
Vegetables	Lima beans, fava beans, soybeans, tofu, onions, and tomatoes	Home grown tomatoes and other vegetables
Beverages	Alcoholic and carbonated drinks, coffee, tea, fruit juices (citrus and cranberry)	Non-carbonated water, decaffeinated coffee and tea
Nuts	Most nuts	Almonds and cashews
Milk and dairy produce	Aged cheeses, sour cream, yogurt, and chocolate	Non-aged cheese, cottage cheese, milk, frozen yogurt
Carbohydrates	Sourdough and rye breads	Other breads, pasta, potatoes, and rice
Seasonings	Ketchup, mayonnaise, mustard, salsa, soy sauce, vinegar, all salad dressings; all Chinese, Indian, Mexican, and Thai foods	Garlic and basil
Preservatives	Monosodium glutamate, aspartame (Nutrasweet), saccharine, benzyl alcohol, citric acid, artificial colours	
Other	Tobacco, caffeine, diet pills, processed foods, drugs for colds and allergies containing ephedrine or pseudoephedrine, recreational drugs	

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Table 3 | Oral drugs recommended for interstitial cystitis[18-24]

Drug	Dose	Mechanism of action	Side effects
Pentosan polysulfate sodium	100 mg three times daily	Replaces inner lining of bladder; inhibits mast cell degranulation	May take up to 4-6 months for improvement in pain and frequency
Hydroxyzine	10, 25, 50, or 75 mg/day	Antagonist of H1 receptor; may inhibit serotonin secretion; decreases mast cell activation	Drowsiness, constipation, and dry mouth
Amitriptyline	10-100 mg/day	Blocks acetylcholine receptor; inhibits reuptake of serotonin and noradrenaline; blocks H1 receptor	Nausea, constipation, and drowsiness
Gabapentin	Start at 300 mg three times daily, then titrate to 400 mg in the morning, and 400 mg in the afternoon, with 800 mg at bedtime; may be titrated to 3600 mg total daily in 3 doses	Mimics γaminobutyric acid (GABA) receptor activation by an independent mechanism to modify pain response	Nausea, drowsiness, and constipation
Prednisone	25 mg daily for 1-2 months then titrate to lowest dose with symptom improvement	Anti-inflammatory effects mediated by transrepression of receptor ligands to decrease t cellular response to inflammation	Weight gain, raised blood sugar, hypertension, easy bruising, visual changes
Ciclosporin	Up to 1.5 mg/kg twice a day; blood concentrations of the drug will need to be checked because of renal and liver toxicity	Inhibits antigen triggered transduction; blunts lymphokines, including interleukin 2; decreases expression of antiapoptopic proteins and production of cytotoxic T cells	Hypertension, gingival hyperplasia, increased hair growth

See bmj.com for details of intravesicular therapy and surgical options.

Oral drugs

Pentosan polysulfate sodium

Antihistamines are used to prevent the activation and proliferation of mast cells, although the results are sometimes unsatisfactory. Currently, pentosan polysulfate sodium (Elmiron; Johnson and Johnson, NJ, USA) is the only oral treatment approved for interstitial cystitis in the US (it is also available in Canada, Europe, and South Africa).[5] The drug replaces the deficient inner lining of the bladder wall glycosaminoglycans and inhibits mast cell degranulation.[18] It may take up to six months for symptoms to improve, however, so patients must be prepared for this initial delay. A 32 week randomised double blind study was conducted in 380 adults whose diagnosis was determined by a positive cystoscopic examination, bladder pain, and urgency or symptoms of interstitial cystitis for at least six months. Participants completed the patient's overall rating of symptom index and the O'Leary-Sant interstitial cystitis symptom index (ICSI) at baseline and during follow-up visits. The mean ICSI scores improved significantly during the 32 weeks for all dosages of the drug, and the response to treatment was not dose dependent (baseline 11.2, 11.9, and 11.9 to end point 8.2, 8.1, 8.6 for 300, 600, and 900 mg, respectively; P<0.001; Oxford level 1b evidence). At the end of the study, most patients reported mild to moderate symptoms, and reports of severe symptoms decreased steadily over the 32 weeks.[18]

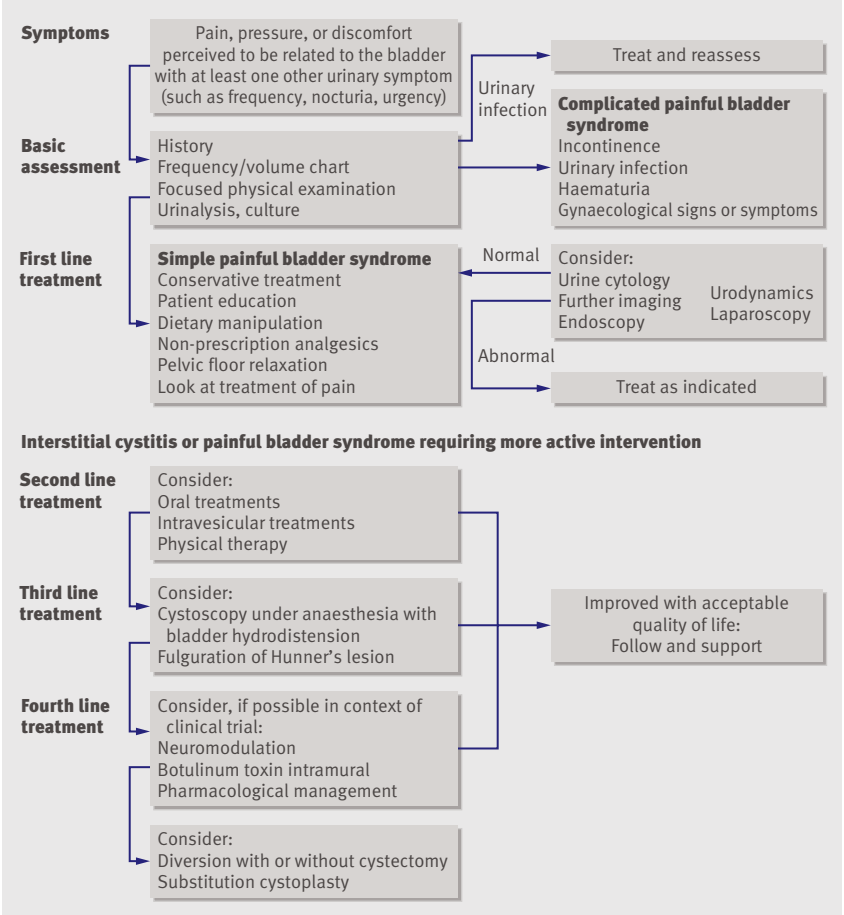

Fig 4 | Diagnostic algorithm for interstitial cystitis or painful bladder syndrome. Reproduced with permission from PM Hanno et al

Pentosan polysulfate sodium and heparin

A study of 41 patients taking oral pentosan polysulfate sodium for interstitial cystitis evaluated the effectiveness of adding subcutaneous low dose heparin.[19] Both drugs are thought to aid the recovery of dysfunctional bladder mucus by reducing epithelial permeability and protecting the bladder from toxic substances. The 41 patients were given heparin (3×5000 IU a day for two days, then 2×5000 IU a day for 12 days), and 17 patients taking pentosan polysulfate sodium only served as controls. Ten of the 41 patients improved at three months and nine improved at six months. A significant improvement of symptoms was reported at three months and six months compared with baseline (pain intensity reduction on the visual analogue pain scale –9.9; standard deviation 3.4; P<0.05). Researchers concluded that subcutaneous low dose heparin combined with oral pentosan polysulfate sodium is better than oral pentosan polysulfate sodium alone,

especially in patients who initially improve with pentosan polysulfate sodium.

Hydroxyzine

Hydroxyzine is an H1 receptor antagonist that blocks mast cell degranulation and may also have a neurogenic effect. An open label study of hydroxyzine showed a 40% improvement in symptom scores from baseline and an additional 55% improvement was seen in those patients who also had concomitant seasonal allergies.[20] A pilot study with hydroxyzine, however, found the drug no more effective than placebo for parameters such as improvement in quality of life or number of voids.[21] The response rate was 31% for those treated and 20% for those not treated (P=0.26).

Amitriptyline

The generic tricyclic antidepressant amitriptyline is useful in treating pain from interstitial cystitis because it stabilises mast cells and has anticholinergic, sedative, and serotonergic effects as a result of inhibiting reuptake of 5-hydroxytriptamine. A controlled escalating drug trial of 48 patients that began with 25 mg of amitriptyline a day (to a maximum of 100 mg a day) showed significant (P=<0.005) improvements over placebo in mean symptom score, pain, and urgency (Oxford level 1b evidence).[22] Improvements in frequency and bladder capacity were less impressive however (P=0.063). Mouth dryness was the most common side effect (79%), but more serious side effects led two patients to withdraw from the study. Taking the drug at bedtime may minimise sedative side effects and enhance sleep.

Prednisone and ciclosporin

These immunosuppressive drugs have been used as a second line treatment to reduce bladder inflammation. Advocates have used prednisone or ciclosporin in low dosages, but more studies are needed to ascertain the optimum dosages of each drug. In a prospective study of 14 patients with severe interstitial cystitis and Hunner's ulcers who were unresponsive to first line treatments, patients who received prednisone showed a 38% improvement in ICSI scores (P<0.005), and their pain scores were reduced by 88% (P<0.0001).[23] The minimal dose of prednisone for symptom relief varied from 5 mg to 10 mg daily. Another study evaluated ciclosporin in 23 patients fulfilling National Institute for Diabetes and Digestive and Kidney Diseases criteria for interstitial cystitis. Statistically significant improvements were seen after 60 months in maximal bladder capacity, mean voided volume, and number of voids, with few adverse side effects.[24]

What new developments does the future hold to treat this condition?

Intrinsic urothelial pathologies may yield new developments in the understanding and treatment of this condition. Urothelial cell cultures express abnormal gene variants; they show abnormal rates of proliferation when starved in cell culture; and during cell stretch they show increased intracellular release of ATP and increase expression of purinergic receptors P2X2 and P2X3.[25] When urothelial biopsies from patients with painful bladder syndrome were subjected to stretch (130% and 150% of the original length) and 10 Hz electrical stimulation, they released significantly higher concentrations of ATP than control biopsies (mean 3791.4 (standard error 667.9) *v* 77.6 (16.2) pmol/g tissue),[26] suggesting that ATP plays an important role in this syndrome. An investigation of cultured bladder urothelial cells from patients with interstitial cystitis showed that such cells had higher than normal concentrations of ATP, which decreases the ability of the bladder wall to conduct potassium ions.[25] Treatment with heparin binding epidermal growth factor reversed the impaired conduction of cellular potassium, which again indicates that impaired potassium conduction is involved in

SOURCES AND SELECTION CRITERIA

We conducted a Medline search for the years 1988-2009, using the key words "interstitial cystitis", "painful bladder syndrome", and "bladder inflammation." We initially selected 118 references, but only 26 were used.

ADDITIONAL EDUCATIONAL RESOURCES

Educational resources for healthcare professionals

Fall M, Oberpenning F, Peeker R. Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? *Eur Urol* 2008;54:65-75

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;53:60-7

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Nordling J. Interstitial cystitis: how should we diagnose it and treat it in 2004? *Curr Opin Urol* 2004;14:323-7

Websites for healthcare professionals and patients

Pelvic Pain Studies (www.pelvicpainstudy.net)—This website enables patients to investigate their potential participation in ongoing clinical studies. The studies are designed to help define interstitial cystitis clinically or to provide symptomatic improvement. Symptom definitions and study protocols enhance patients' understanding

Elmiron (www.orthoelmiron.com)—Website sponsored by the makers of Elmiron, Ortho-McNeil Pharmaceuticals. It explains the proposed usage and advantages of Elmiron in the long term treatment of interstitial cystitis and covers side effects and potential drug related problems

Interstitial Cystitis Network (www.ic-network.com)—Website that provides patients with a forum for discussions and access to email newsletters on new developments; drug assistance programmes; and the IC World Center, which discusses treatment options available in Europe, Asia, Africa, and South America. Questionnaires help patients gauge their symptoms

National Women's Health Resource Center (www.healthywomen.org)—Women's general health website. The site is organised but congested, with many options for every topic; nevertheless, it does provide useful essential information on interstitial cystitis

the pathophysiology of interstitial cystitis. A better understanding of these cellular changes may lead to the development of more effective treatments in the future. Figure 4 shows a suggested algorithm for the diagnosis and treatment of interstitial cystitis or painful bladder syndrome.

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From our archive

Arthur Conan Doyle takes it to the limit (1879)

Some years ago, a persistent neuralgia led me to use the tincture of gelseminum to a considerable extent. I several times overstepped the maximum doses of the text-books without suffering any ill effects. Having recently had an opportunity of experimenting with a quantity of the fresh tincture, I determined to ascertain how far one might go in taking the drug, and what the primary symptoms of an overdose might be. I took each dose about the same hour on successive days, and avoided tobacco or any other agent which might influence the physiological action of the drug. Here are the results as jotted down at the time of the experiment. On Monday and Tuesday, forty and sixty minims produced no effect whatever. On Wednesday, ninety minims were taken at 10.30. At 10.50, on rising from my chair, I became seized with an extreme giddiness and weakness of the limbs, which, however, quickly passed off. There was no nausea or other effect. The pulse was weak but normal. On Thursday, I took 120 minims. The giddiness of yesterday came on in a much milder form. On going out about one o'clock, however, I noticed for the first time that I had a difficulty in accommodating the eye for distant objects. It needed a distinct voluntary effort, and indeed a facial contortion to do it.

On Friday, 150 minims were taken. As I increased the dose, I found that the more marked physiological symptoms disappeared. To-day, the giddiness was almost gone, but I suffered from a severe frontal headache, with diarrhoea and general lassitude.

On Saturday and Sunday, I took three drachms and 200 minims. The diarrhoea was so persistent and prostrating, that I must stop at 200 minims. I felt great depression and a severe frontal headache. The pulse was still normal, but weak.

From these experiments I would draw the following conclusions.

1. In spite of a case described some time ago in which 75 minims proved fatal, a healthy adult may take as much as 90 minims with perfect immunity.
2. In doses of from 90 to 120 minims, the drug acts apparently as a motor paralyser to a certain extent, causing languor, giddiness, and a partial paralysis of the ciliary muscle.
3. After that point, it causes headache, with diarrhoea and extreme lassitude.
4. The system may learn to tolerate gelseminum, as it may opium, if it be gradually inured to it. I feel convinced that I could have taken as much as half an ounce of the tincture, had it not been for the extreme diarrhoea it brought on.

Gelseminum as a poison. *BMJ* 1879;2:481-4, doi: 10.1136/bmj.2.977.481
This wasn't the sole example of his self experimentation. See *BMJ* 2007;335:1315.
The entire archive of the *BMJ*, going back to 1840, is now available at www.bmj.com/archive.

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