

Early Identification of Interstitial Cystitis May Avoid Unnecessary Hysterectomy

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ABSTRACT

Background: Interstitial cystitis is a clinical syndrome characterized by symptoms of pelvic pain, urinary urgency and frequency, and nocturia. It can be difficult to accurately identify interstitial cystitis because the symptoms overlap many other common gynecologic and urologic conditions. Patients with undiagnosed interstitial cystitis may undergo unnecessary procedures, including hysterectomy.

Methods: A PubMed literature search for articles dating back to 1990 was conducted on the topics of interstitial cystitis and hysterectomy. Further references were identified by cross-referencing the bibliographies in articles of interest.

Results: The literature review found that hysterectomy is performed more often in patients with undiagnosed interstitial cystitis than in patients with a confirmed diagnosis. Interstitial cystitis often coexists with conditions like endometriosis, for which hysterectomy is indicated. Many patients subsequently diagnosed with interstitial cystitis continue to experience persistent pelvic pain despite having had a hysterectomy for chronic pelvic pain. Careful history and physical examination can identify the majority of interstitial cystitis cases.

Conclusion: Interstitial cystitis should be considered prior to hysterectomy in women who present with pelvic pain or who experience pelvic pain after a hysterectomy. If interstitial cystitis is diagnosed, appropriate therapy may eliminate the need for hysterectomy.

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INTRODUCTION

Hysterectomy is the second most frequently performed surgery, after cesarean delivery, among women of reproductive age in the United States. Over 600 000 hysterectomies are performed annually in the United States.¹ From 1994 through 1999, 1 in every 9 women aged 35 to 45 years was estimated to have had a hysterectomy.² The most frequent indications for hysterectomy during this time were uterine leiomyoma, endometriosis, and uterine prolapse.^{1,2} Chronic pelvic pain (CPP) was the primary indication for 10% to 12% of all hysterectomies performed.³⁻⁵ Although surgery provides some pain relief in a majority of patients, pain persists in a considerable proportion of patients.^{5,6} Hysterectomy for CPP should be considered after exclusion of other gynecologic and non-gynecologic diagnoses and after a trial of nonsurgical treatment.³

Interstitial cystitis (IC) is a clinical syndrome of the bladder characterized by pelvic pain and urinary urgency and frequency in the absence of an identifiable cause.⁷ The diagnosis of IC is based on history and physical examination; no definitive test for it exists.⁸ Diagnosis of IC can be elusive, because the symptoms of IC are variable and can mimic those of other urologic and gynecologic conditions.^{9,10} Patients may experience the symptoms of IC for years before receiving the correct diagnosis.¹⁰ The difficulty in accurately identifying IC may result in unnecessary hysterectomies to treat pelvic pain associated with IC.^{10,11} In the Interstitial Cystitis Database, 30.5% to 53.5% of women with IC had undergone a hysterectomy.¹² Interstitial cystitis should be considered in women who present with symptoms of CPP, along with dyspareunia and/or irritative voiding symptoms.¹³

Hysterectomy and Interstitial Cystitis

Several studies have found a high rate of hysterectomy in patients subsequently diagnosed with IC. In some cases, the hysterectomies may have been unnecessary, as the

pelvic pain was solely due to IC. In other cases, undiagnosed and untreated IC may have coexisted with the condition that was the indication for hysterectomy. It is also possible that the hysterectomy itself may have played a role in precipitating the neurogenic inflammation and visceral pain associated with IC.¹⁴

Driscoll et al¹⁰ conducted a retrospective review of 45 patients with IC to determine the presentation and history of their disease. Patients had been symptomatic for a median of 5 years before being diagnosed with IC. The diagnosis of IC was based on National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria or by clinical suspicion and a positive potassium sensitivity test (PST). The initial presentation of IC was highly variable: only 7% of patients presented with simultaneous symptoms of urinary urgency and frequency, nocturia, and pain. Most patients (89%) presented with only 1 symptom initially and then progressed to the full spectrum of symptoms over a mean time of 5 years. Among the 41 women in the study, 14 had received a previous gynecologic diagnosis. Hysterectomy had been performed in 11 patients with a gynecologic diagnosis, including 8 with a surgical indication of nonspecific pelvic pain.¹⁰

Another study looked specifically at the rates of pelvic surgeries in women with IC by comparing responses from a survey of 215 IC patients, with 823 women serving as a community-based control group (both groups, mean age 51 years).¹⁵ Women with an established diagnosis of IC were drawn from a database at a referral center. Diagnosis of IC was based on NIH criteria, which include positive cystoscopic findings in addition to symptoms. In this study, women with IC were twice as likely as controls to have had a hysterectomy (42.3% vs 21.4%; $P < 0.001$). Although the higher rates of hysterectomies in women with IC could have been due to a higher prevalence of concomitant conditions requiring this procedure, it is notable that 68.4% of the hysterectomies were done before the diagnosis of IC, 10.5% were performed in the same year as the diagnosis of IC, and 21.1% were performed after the diagnosis of IC.¹⁵ The authors concluded that some of the hysterectomies may have been performed for an indication of pelvic pain that was in fact due to undiagnosed IC.

A third study evaluated 111 women who had persistent or recurrent pelvic pain after a hysterectomy for CPP.¹¹ This study was conducted at a large regional CPP center. Patients were evaluated with a symptom questionnaire, a physical examination (to identify tenderness at the bladder base or anterior vaginal wall), a PST, and optional

cystoscopy with hydrodistention. Irritative voiding symptoms were present in 104 (94%) patients, and 88 (79%) had a positive PST. Of 66 patients who had cystoscopy with hydrodistention, 61 (92%) had cystoscopic evidence of IC.

In this study, patients were treated with dietary modification alone ($n=33$) or in combination with pentosan polysulfate and/or cystoscopy with hydrodistention ($n=78$). After 6 months of treatment, the diet-alone group showed a mean improvement of 15.4% in score on the Pelvic Pain and Urgency/Frequency (PUF) questionnaire, and the diet plus other treatment group showed a mean improvement of 34.2%.¹¹ This study showed that not only was IC diagnosed at a high rate among women whose CPP was not relieved by hysterectomy but also that these patients responded favorably to treatment for IC.

Another recent study characterized a clinical cohort of 87 women with IC or painful bladder syndrome (PBS) who were referred to a pelvic pain and sexual-health program.¹⁶ The diagnosis of IC had been made by board-certified urologists based on NIDDK criteria. A detailed history and physical examination were performed for each patient. The patients had an average of 4.4 previous pelvic surgeries, with 23% having had 3 surgeries or more. Almost half (48%) had had a hysterectomy, two-thirds of which were performed prior to the diagnosis of IC. Pelvic pain as a comorbidity was reported by 93% of patients.¹⁶

The high rate of hysterectomies among women later diagnosed with IC may suggest a potential cause of IC. Pelvic surgeries including hysterectomy may have a negative effect on the innervation, musculature, or vasculature of the bladder.¹⁵ Neural crosstalk between the afferents of irritated or damaged pelvic organs may adversely affect other organs, perhaps resulting in changes such as neurogenic inflammation in the secondary organ.¹⁴ In the last study discussed above, 59% of patients reported that their pain was initiated by a specific event, including surgery (25%) or a bladder infection (23%), suggesting that pelvic insults may have played a causative role.¹⁶

Even when the indication for hysterectomy (such as endometriosis) is clear, patients may also have IC. Endometriosis and IC often coexist in the same patient. In 2 different studies of select groups of patients with CPP (who exhibited both bladder base and uterine tenderness [$N=178$] or in whom all other nongynecologic or nonurologic causes had been ruled out [$N=162$]), 75% to 76% of patients were found to have endometriosis, 82% to 89% had IC, and 65% to 66% had both conditions concomitantly.^{17,18} Interstitial cystitis should be considered in any patient who

presents with CPP, even if another condition is diagnosed that could be partly responsible for the symptoms.¹¹

INTERSTITIAL CYSTITIS

Pathophysiology

The cause of IC is unknown although several potential mechanisms have been proposed, including abnormal permeability of the bladder epithelium, neurogenic inflammation, an autoimmune or allergic response, and occult infection. It is likely that several of these factors interact to produce the clinical picture of IC (**Figure 1**).^{19,20} Furthermore, the cause of this condition may not be the same for all patients.²⁰

A large body of evidence indicates that the symptoms of IC may be caused by abnormal permeability of the urothelium due to a defect in the glycosaminoglycan (GAG) layer lining the bladder surface. Abnormalities in the GAG layer may be causative or the result of poor healing of the epithelium in patients following an injury to the bladder, eg, from an infection or pelvic surgery.²⁰ The increased permeability is thought to allow irritating solutes and toxins, such as potassium from the urine, to contact the underlying epithelium, triggering the symptoms of pain and urinary urgency and frequency.²¹ In response to toxic stimuli and the resulting pain, mast cells degranulate, releasing histamine.²² Bladder biopsies from patients with IC show increased numbers of degranulated mast cells, as well as increased numbers of substance P-positive nerve fibers near the mast cells.^{22,23} The continued inflammation and nerve-fiber activation can lead to neural upregulation

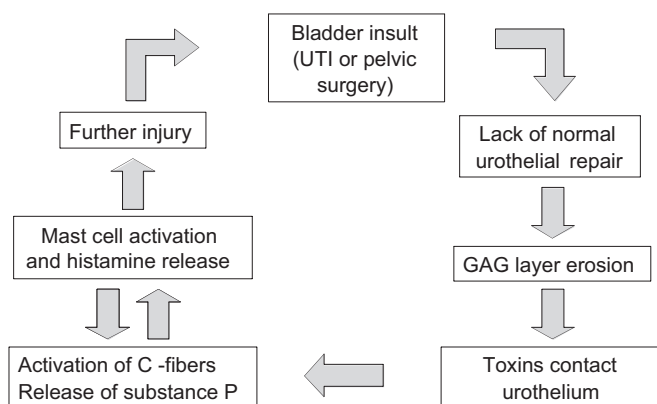


Figure 1. A proposed model of the etiology of interstitial cystitis.²⁰ Adapted with permission from Evans RJ. Treatment approaches for interstitial cystitis: multimodality therapy. *Rev Urol.* 2002;4(suppl 1):S16-S20. GAG = glycosaminoglycan.

and hyperalgesia.²⁰ Injury and irritation in one organ can contribute to hyperalgesia in other organs through viscerovisceral crosstalk.²²

Diagnosis

The diagnosis of IC is one of exclusion based on history, physical examination, laboratory studies, symptom questionnaires, and other optional tests.⁸ The NIDDK created criteria to ensure inclusion of comparable groups of patients in studies of IC.^{24,25} These criteria to some extent became the standard for diagnosis in the clinic.²⁵ Although the NIDDK criteria clearly identify a subgroup of patients with IC, they also exclude a substantial proportion of patients (up to two-thirds) who were clinically diagnosed with IC.²⁵

In a diagnostic workup for IC, the history should address the initial presentation and progression of symptoms as well as any factors that trigger or worsen the symptoms, such as allergies, certain foods, the menstrual cycle, and sexual activity.^{8,26,27} Patients often present initially with only 1 or 2 mild symptoms then progress over time to the full symptom complex of urinary urgency and frequency, nocturia, and pelvic pain.²⁶ Symptoms may occur in a pattern of flares and remissions.⁸ The pain caused by IC is most commonly felt in the suprapubic region but can be referred to other areas, including other areas of the pelvis and the thighs.^{8,26}

Symptom questionnaires can help identify the symptoms of IC for screening and diagnosis. Patients may not report symptoms such as dyspareunia, because they do not connect it with their urinary symptoms.²⁷ Two commonly used questionnaires are the PUF questionnaire and the O'Leary-Sant (OLS) interstitial cystitis symptom and problem indices (ICSI and ICPI).^{28,29} Both questionnaires address the characteristic symptoms of IC as well as the degree of bother that patients associate with each symptom. The PUF questionnaire was designed primarily as a clinical screening tool, whereas the OLS indices were designed for disease follow-up.^{8,27}

The physical examination in a diagnostic workup for IC should include a bimanual assessment for pain or tenderness at the bladder base or along the urethra. The examination should assess levator ani tenderness and pelvic floor dysfunction. Tenderness along the anterior vaginal wall or at the bladder base can help establish a diagnosis of IC.^{8,26,30}

Laboratory tests to rule out UTI include urinalysis and urine culture. Bladder cancer must be ruled out if the

patient has hematuria or is at risk for bladder cancer (history of smoking, age >40 years, occupational or other risk factors).^{8,31} Cytology of bladder-washing specimens in combination with cystoscopy is the gold standard for detection of urothelial neoplasia.³² Cytology of voided urine samples is less sensitive and should be used as an adjunct to cystoscopy.³³ Noninvasive urine-based immunoassays such as the nuclear matrix protein 22 test and the Bard tumor antigen test may also be used to screen for bladder cancer; in combination, results from these 2 tests approach the accuracy of cystoscopy.³⁴ Both tests are approved by the FDA as an adjunct to but not as a replacement for cystoscopy.^{32,33}

Several optional tests may aid in the diagnosis of IC. Urodynamics may be helpful in determining whether detrusor instability exists, although this does not rule out the diagnosis of IC.^{8,26} Voiding diaries can also be helpful in identifying frequency, as not all patients recognize their symptoms of frequency.⁸

Cystoscopy with hydrodistention is not required for the diagnosis of IC, except to rule out bladder cancer.³¹ Among patients with IC, those with positive findings of cystoscopy (glomerulations or Hunner's ulcers) are more likely to have symptoms of IC (although glomerulations may also be present in women with normal bladders); however, not all patients with IC will have positive cystoscopy.^{25,35,36}

The potassium sensitivity test (PST) identifies patients with abnormal urothelial permeability by their provoked response of pain and urgency to intravesical instillation of potassium.^{37,38} The PST will be positive in any patient with increased epithelial permeability of the bladder, including UTI or radiation cystitis. The PST may be useful to help identify the bladder as the source of pain.³⁸

A test using intravesical instillation of anesthetics plays a similar role to that of the PST, but without provoking symptoms of pain and urgency. Relief of pain following instillation of a solution of bupivacaine and/or lidocaine can identify the bladder as the source of pelvic pain in patients with IC. This test cannot be used in patients without significant pain, and the lack of a positive result does not rule out IC as the cause.³⁹

Treatment

Once IC is diagnosed, it is important for the clinician to counsel the patient and help set treatment expectations. Patients may feel frustration after years of experiencing symptoms and not receiving an accurate diagnosis or

effective therapy. A clinician should acknowledge the patient's frustration, and reassure her that, once identified, the condition can be effectively managed. It is important to let the patient know that it may take several months for treatment to reach full efficacy and that adherence to the treatment regimen is crucial to reducing symptoms. Patients should be educated about the condition as well as diet and lifestyle changes that can help avoid symptom flares.^{40,41}

There are several pharmacologic options for the treatment of IC (**Table 1**). Pentosan polysulfate sodium (PPS; Elmiron, Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, NJ) is the only FDA-approved oral agent for the treatment of IC symptoms and is first-line therapy for most patients with this condition.^{41,42} PPS is a heparin-like compound that is thought to act by replenishing the GAG layer on the bladder surface, thus restoring urothelial impermeability.⁴³ PPS is dosed at 100mg tid. In clinical trials, PPS was shown to be effective for symptom relief in patients with IC.^{44,45} Symptom improvement with PPS is gradual. Patients should be counseled to stay on PPS therapy for 3 to 6 months to see a clinical response.⁴⁰ Some patients on PPS continue to experience improvement in symptom relief for up to 36 months.⁴⁶

Other pharmacologic agents (although not FDA-approved for IC treatment) may be added to PPS as needed for symptom relief. Antihistamines, such as hydroxyzine, may be used to reduce mast cell activity,⁴⁷ and have been shown to have some efficacy for IC symptom relief, particularly in patients who are prone to allergies.⁴⁸ Hydroxyzine should be taken at bedtime to minimize sedation side effects at doses up to 75mg/day.⁴⁰

Tricyclic antidepressants (TCAs), such as amitriptyline, also benefit many patients with IC.^{49,50} These drugs have mild antihistamine, analgesic, and anticholinergic effects, and are widely used in the treatment of neuropathic pain because of their effects on CNS pain transmission.⁵¹ In addition, TCAs may help improve sleep because of their sedative effect.²⁰ Anticholinergic side effects like dry mouth occur in the majority of patients and may lead to treatment discontinuation for some patients.^{49,50} Careful dosing (25mg/day to 50mg/day at bedtime) can minimize these side effects.^{27,50}

Anticonvulsants, such as gabapentin and pregabalin, have been used to treat neuropathic pain⁵¹ and may be of benefit for IC patients with severe pain.^{20,52} Gabapentin should be dosed from 300mg/day to 2400mg/day and requires careful dose titration.²⁰

Table 1.
Pharmacologic Therapies for Interstitial Cystitis^{20,27,42,54,56,67}

Agent	MOA	Dose	Side Effects
Oral			
PPS*	May repair GAG layer on urothelial surface, restoring impermeability	100 mg tid	Hair loss, GI upset, headache, rash
Hydroxyzine	Controls allergic response and mast cell activation	10 to 25 mg/day qd at bedtime Increase up to 100 mg/day during allergy season	Drowsiness, dry mouth
Amitriptyline	Inhibits neural activation, also analgesic, anticholinergic	10 to 50 mg/day qd at bedtime	Dizziness, dry mouth, drowsiness, weight gain, nausea
Gabapentin	Unknown	Up to 2400 mg/day qd at bedtime	Dizziness, somnolence, nausea, edema
Oxycodone	Control of severe pain	5 to 10 mg every 4 h prn	GI upset, somnolence
Intravesical			
DMSO	Anti-inflammatory, analgesic, muscle relaxant	50 cc 50% qw for 6 weeks	Worsening of IC symptoms, garlic-like taste and breath odor
Anesthetics†	Control of pain	0.5% bupivacaine; 2% alkalized lidocaine prn	Postinstillation pain; urinary retention
Heparin†	May help restore mucous layer	10 to 40,000 IU/day in 10 mL water qd to qw	Postinstillation pain

*PPS = pentosan polysulfate sodium; DMSO = dimethyl sulfoxide.
†May be used in combination with each other.

Several intravesical therapies are also used for IC, often in combination with oral agents.²⁰ Cocktails consisting of a local anesthetic (bupivacaine or alkalized lidocaine) and heparin (as a bladder surface coating agent) may be administered as initial therapy while oral agents take effect or can be used for treatment of symptom flares.^{53,54} Dimethyl sulfoxide (DMSO) is approved by the FDA as an intravesical agent for the relief of IC symptoms.⁵⁵ DMSO has both anti-inflammatory and analgesic properties.⁵⁶

In addition to pharmacologic agents, nonpharmacologic approaches to therapy can provide symptom relief for patients with IC. Every patient with IC should be counseled about dietary and lifestyle changes that can minimize symptom flares. A range of foods have been associated with symptom flares, particularly foods or drinks that contain caffeine or alcohol, are spicy, or have a low pH. Patients may already be aware of some of their “triggers”; use of a diary can help track others.⁵⁷ Symptom flares are also associated with stress, which patients can reduce by using stress-reduction techniques.⁵⁷ For patients who experience dyspareunia, use of lubricants, lidocaine jelly, or premedicating with antispasmodics or muscle relaxants can reduce pain during sex.⁵⁸

Bladder training is an option to reduce urination frequency in patients who experience only mild pain on bladder filling. The patient slowly lengthens the intervals between voids, increasing the interval by up to 15 minutes every week.^{57,59}

High-tone pelvic floor dysfunction (PFD) involving pelvic floor muscle tenderness and spasm is commonly found in patients with IC.⁶⁰ Patients with high-tone PFD respond favorably to physical therapy, including realignment of the sacrum and ilium, myofascial release, and overall strengthening and stretching.⁶¹ Internal (Thiele) massage can be effective for the relief of IC symptoms in patients with high-tone PFD or in patients who have not responded to medical therapy.^{60,62}

For patients who do not respond to pharmacologic and behavioral therapies, sacral neuromodulation has been shown to be beneficial in several studies, with improvements in pain and urinary-symptom scores, as well as decreased need for narcotics.^{63–66}

Patients should be reevaluated 1 month to 3 months after therapy is initiated and therapy adjusted as needed.^{40,41} Further follow-up visits should occur at 3-month to

6-month intervals. Patients should be told to contact their physician as soon as possible when symptom flares occur and can be treated immediately with intravesical instillation of an anesthetic cocktail.⁴¹

CONCLUSION

Hysterectomies may be performed unnecessarily in women with IC. Clinicians should consider all sources of pelvic pain before performing a hysterectomy for the primary indication of CPP. Patients with documented endometriosis may still have concomitant IC and should be evaluated and treated for IC prior to hysterectomy. With the appropriate diagnostic tools, IC can be identified early in the progression of the disease. An individualized, multimodal approach to treatment—including both pharmacologic and nonpharmacologic therapies—can provide symptom relief in the majority of patients with IC.

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