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Chronic Pelvic Pain of Bladder Origin: A Focus on Interstitial Cystitis

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ABSTRACT: Chronic pelvic pain afflicts some 9,000,000 women in the United States. Of these, perhaps 10%—although the true number of those affected is actually much greater—are found to have interstitial cystitis (IC), that is, pain of bladder origin. The etiology is multifactorial, but a fairly good marker is dysfunction of the glycosaminoglycan/mucus/mucin layer of the bladder as detected by a potassium (KCl) sensitivity test. A cascade starting with Substance P seems to be involved in generating inflammation, and even ulceration, which is the focus of pain. This article describes means of diagnosis, including the KCl test and cystoscopy, and both U.S. FDA-approved and extended-use medical treatment options which are always to be attempted before the final step of surgery. *Int J Fertil* 48(4):154–162, 2003

KEY WORDS: epidemiology, diagnosis (differential), patient history, Pelvic Pain Urgency Frequency (PUF), O'Leary-Sant Interstitial Cystitis Symptom Inventory, intravesical Potassium Sensitivity Test, cystoscopy, DMSO, pentosan polysulfate

INTRODUCTION

CHRONIC PELVIC PAIN SYNDROMES are common, affecting more than 9,000,000 women in the United States [1]. Although the underlying cause of chronic pelvic pain can be identified and treated in the majority of cases, no definitive etiology underlying the chronic pain is present for a large number of women who continue to suffer, despite numerous clinical interventions. A significant number of these women—approximately 700,000—are found to have chronic pelvic pain of bladder origin, and eventually are diagnosed with the syndrome known as interstitial cystitis. Characterized by urinary frequency, urgency and pelvic discomfort or pain in the absence of other obvious bladder pathology, interstitial cystitis (IC) is commonly misdiagnosed as recurrent urinary tract infection (UTI) or endometriosis; women often suffer for 5–7 years from onset of symptoms until an accurate diagnosis is provided [4]. As yet, no definitive diagnostic test or cure exists for IC; however, early, accurate diagnosis and treatment can significantly reduce the pain and suffering of women afflicted by this syndrome. Two pharmacologic agents are currently approved by the U.S. Food and Drug Administration (FDA) for the management of IC: the oral agent pentosan polysulfate sodium (PPS) and intravesical dimethyl sulfoxide (DMSO).

Chronic pelvic pain syndromes (CPPS) account for 10% to 12% of outpatient gynecologic referrals [2] and are responsible for 5% to 10% of laparoscopies [3], although no obvious pelvic pathology is ascertained in up to 60% of these surgeries [3]. For many of these women, the source of the pelvic pain is of bladder origin—interstitial cystitis—a condition which often is influenced by bladder filling and emptying. The actual prevalence of interstitial cystitis is unknown; estimates range from 67/100,000 [4] to 510/100,000 women [5]. It is believed that

another one to two million people are currently undiagnosed. The overwhelming majority of patients are Caucasian, with a median age at diagnosis of 42–46 years [4,6,7].

Many women first experience symptoms during their thirties and see an average of eight physicians over 5 to 7 years before a correct diagnosis of IC is made, during their forties [4]. Oftentimes, these patients have been diagnosed as having a urinary tract infection, overactive bladder, or endometriosis. They are then treated with what seems to be appropriate medication, but fail their courses of therapy. Consequently, these women live with pain that is chronic and often severe, a pain that has a significant effect on their quality of life (QOL). In fact, QOL inventories suggest that patients with IC score lower than patients on dialysis; 60% of patients with IC report dyspareunia, and nearly 50% are unable to work full-time [8]. It is thus not surprising that patients with IC are three to four times as likely to have suicidal ideation than the general population and are five times as likely to have been treated for emotional problems [9]. Obviously, it is imperative that these women receive prompt and accurate diagnosis in order to minimize their suffering.

PATHOPHYSIOLOGY

Numerous theories have been proposed to explain the pathophysiology of IC, but none appears to cover all cases. Indeed, at present IC is thought to have a multifactorial pathogenesis, and abnormalities of the "IC bladder" have been identified. One hypothesis suggests that IC results from an alteration of the glycosaminoglycan (GAG)–mucus–mucin layer, allowing continued transvesical absorption of urea and potassium, which induces tissue damage and pain in response to urine solutes [10]. IC patients have increased levels of the neuropeptide Substance P (secreted from sensory nerve endings that transmit pain information and stimulate inflammation); an increased number of C-fibers (pain-carrying nerves) that carry and release Substance P; and an increased number of mast cells (or specialized inflammatory cells) in the bladder wall [11], which contain numerous inflammation-provoking substances, including histamine, leukotrienes and prostaglandins. Thus, the release of Substance P initiates a cascade of events that results in nerve activation and inflammation.

Patients with IC also have significantly lower levels of the urinary glycoprotein GP51 than patients without IC [12], which may make this a useful clinical marker. Similarly, Antiproliferative Factor (APF) is found in 94% of IC patients—in contrast to only 10% of control patients—a finding which ultimately may provide another explanation for the development of IC, as well as become another possible clinical marker [13–15]. Additional theories note the apparent relative lack of blood flow in the bladder among patients with classical/ulcerative IC, and there has been proposed the possibility of unusual microbes in bladder cells that are not yet detectable through current routine urine tests [16].

DIAGNOSIS

Clinical Presentation

IC initially manifests as sudden onset of urologic symptoms: frequency and urgency in combination with pelvic pain that worsens with bladder filling and lessens with bladder emptying. This often results in a diagnosis of acute urinary tract infection (UTI) and consequent treatment with antibiotics. However, IC does not respond to antibiotics. It is also commonly misdiagnosed as endometriosis, and patients frequently undergo laparoscopic evaluation (unnecessarily). In fact, a recent study demonstrated that 38% of women presenting with chronic pain and a presumptive diagnosis of endometriosis who underwent concurrent laparoscopy and cystoscopy with hydrodistension were subsequently diagnosed with IC based upon the cystoscopic examination [17]. While there is, as yet, no single definitive test for IC, a variety of diagnostic measures can be utilized to rule out other possible causes, and ultimately diagnose IC.

The initial diagnostic process involves a patient history, clinical presentation of urgency/frequency and pelvic pain, urinalysis and urine culture. Patients can experience a wide spectrum of symptom severity, ranging from infrequent nocturia (twice per night) to significant (≥12/night) nighttime voiding. In fact, 10% to 15% of patients with IC have overlapping symptoms of overactive bladder. Often, patients are asked to keep a voiding log. Healthy patients have an average of 6.5 voids per day compared with 16.5 voids per day among patients diagnosed with IC [18] (Figure 1). Some women report that the pain increases 1 week before menses, and others report dyspareunia. Additional symptoms include a slow urinary stream, vulvar pain, increased pelvic pain 12–24 hours after intercourse, low back pain, and depression.

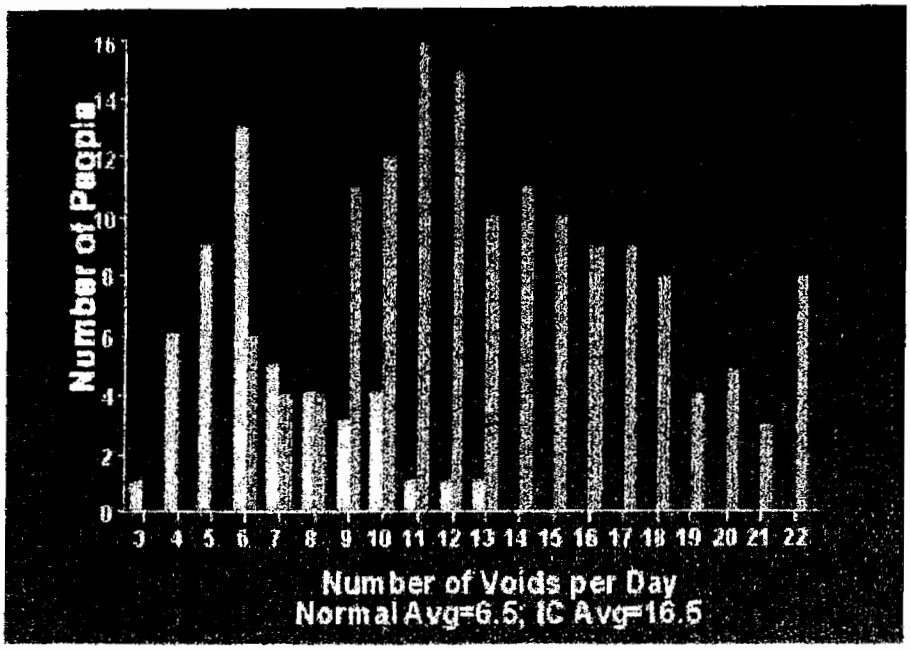

FIG. 1. Voids per day: normal subjects versus interstitial cystitis (IC) patients. Bars to the left of each number of the horizontal axis represent normal subjects (N = 48), those to the right, IC patients (N = 145).

Diagnostic Tests

Diagnostic measures include: (1) two written questionnaires, the Pelvic Pain Urgency Frequency (PUF) Patient Symptom Scale and the O'Leary–Sant Interstitial Cystitis Symptom Index (ICSI); (2) the intravesical Potassium Sensitivity Test (PST) to assess epithelial permeability; and (3) cystoscopy with hydrodistension under anesthesia. Pelvic or transvaginal ultrasound may be useful in identifying subtle abnormalities not easily detected by physical examination. An intravenous pyelogram can rule out the presence of stones in the lower ureter; a uroflow examination can assess urine flow rate to rule out blockages in the passage of urine or abnormal behavior of the bladder and urethra. This last test is often done in conjunction with a cystometrogram to assess incontinence. Specialized ultrasound units to measure post-void residual (PVR) urine volume can help rule out urinary retention and overflow incontinence.

Pelvic Pain Urgency and Frequency Patient Symptom Scale. The Pelvic Pain Urgency Frequency (PUF) Patient Symptom Scale is an 8-question symptom scale that measures both the presence and severity of symptoms as well as how much a patient is bothered by the symptoms (Table I). Questions address the frequency and urgency of voiding during waking and sleeping hours, the presence of urgency after urination, the presence of pain in the pelvic region, the influence of pain or urinary urgency on sexual intercourse, and how bothersome the pain and urgency have become. Higher symptom, bother and total scores (15+ points) are highly suggestive of IC (Table II) and of a positive PST [19], whereas PUF scores of control patients are low (<3 points) with 0% positive PST. The PUF appears to be an accurate questionnaire for facilitating early detection of IC [19] and should be strongly considered in all patients suspected of having IC.

O'Leary–Sant Interstitial Cystitis Symptom Index. The O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) is a four-item questionnaire that measures urinary urgency and frequency, nighttime urination, and pain or burning [19]. The ICSI can assess a patient's experience of IC symptoms and can be used to measure treatment outcome. It appears to be a highly sensitive tool in identifying women with IC [20].

Potassium Sensitivity Test. A recent addition to the diagnostic armamentarium is the intravesical Potassium Sensitivity Test (PST) [21–23]. The PST is based upon the finding that many IC patients have an abnormality of the bladder surface that allows potassium and urea to leak and be absorbed into the bladder interstitium. The PST involves the very slow introduction of sterile water into the bladder through a thin catheter to establish the baseline of pain and urgency upon bladder filling (using a 0–5 point scale with 5 denoting most severe pain); this is then emptied through the catheter. Potassium chloride (KCl) solution is then instilled, and any increase in pain or urgency of 2 points indicates abnormal epithelial dysfunction and is considered suggestive of IC [21,24]. In patients with no response, the catheter is removed and the patient is asked to urinate and reevaluate the level of pain.

Patients with a normal bladder typically do not absorb or react to potassium chloride with urgency or pain. In contrast, potassium in an IC bladder

TABLE I
Pelvic Pain Urgency Frequency (PUF) patient symptom scale [18].

Circle the answer that best describes how you feel for each question.

	0	1	2	3	4	*Symptom Score*	*Bother Score*
1. How many times do you void during waking hours?	3–6	7–10	11–14	15–19	20+		
2. a. How many times do you void at night?	0	1	2	3	4+		
b. If you get up at night to void, to what extent does it usually bother you?	None	Mild	Moderate	Severe			
3. Are you currently sexually active? Yes ___ No —							
4. a. If you are sexually active, do you now have or have you ever had pain or urgency to urinate during or after sexual intercourse?	Never	Occasionally	Usually	Always			
b. Has pain or urgency ever made you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5. Do you have pain associated with your bladder or in your pelvis, vagina, lower abdomen, urethra, perineum, testes, or scrotum?	Never	Occasionally	Usually	Always			
6. Do you still have urgency shortly after urinating?	Never	Occasionally	Usually	Always			
7. a. When you have pain, is it usually—?		Mild	Moderate	Severe			
b. How often does your pain bother you?	Never	Occasionally	Usually	Always			
8. a. When you have urgency, is it usually—?		Mild	Moderate	Severe			
b. How often does your pain bother you?	Never	Occasionally	Usually	Always			
						Symptom Score (1, 2a, 4a, 5, 6, 7a, 8a)	
						Bother Score (2b, 4b, 7b, 8b)	
						Total Score (Symptom Score + Bother Score) =	

stimulates the nerves and results in significant discomfort and inflammation in the bladder wall in the majority (>70%) of patients [11,21–23] (Table III). A positive PST therefore suggests a bladder component such as IC in the etiology of chronic pelvic pain. In fact, despite alternative initial diagnoses (including endometriosis and vulvodynia), one recent study demonstrated that a majority of gynecologic patients complain of pelvic pain have a positive PST [23]. In this study, approximately 80% of patients with chronic pelvic pain had a positive PST (Table IV). These results support the concept that pain of bladder origin can masquerade as a variety of other complaints, and that women with pelvic pain may

TABLE II
PUF demonstrates correlation with interstitial cystitis diagnosis [19].

PUF Score	*Likelihood of IC*
10–14	74%
15–19	76%
20+	91%

IC = Interstitial cystitis; PUF = pelvic pain urgency frequency.

represent significant numbers of unrecognized cases of IC [19]. However, a negative PST does not conclusively rule out IC. Owing to the variable nature of the symptoms, a patient with IC may have a negative PST result on any given day [24].

False negatives on the PST can occur in patients who have had recent intravesical DMSO (dimethyl sulfoxide) or heparin therapy, recent hydrodistension, or are on pain medications or already maximally stimulated [10]. Unlike cystoscopy with hydrodistension, the PST can be performed on an outpatient basis by non-urologists, and has a rapid recovery time. It cannot be used to inspect the bladder wall or perform a biopsy, and the test may cause immediate discomfort and flare-ups of the disorder.

TABLE III
Potassium sensitivity test (PST).

- Measures epithelial permeability
- Procedure
  - Introduce H_2O into bladder—establish baseline of pain/urgency (0–5)
  - Empty bladder
  - Introduce KCl into bladder—reevaluate pain
  - Any increase in pain or urgency ≥2 suggests IC
  - If no response: remove catheter; urinate
  - Reevaluate pain
- Role of PST in diagnosis
  - Healthy bladders do not respond with pain/urgency to H_2O or KCl
  - Majority of patients with IC have positive PST (>70%)
  - Majority of patients with pelvic pain have positive PST (80%)
- Positive PST: Not sufficient to diagnose IC conclusively
- Negative PST: Does not rule out IC

TABLE IV
Initial clinical diagnoses and potassium test results for patients with pelvic pain.

Initial Clinical Diagnosis	*No.*	*Median Age (yr)*	*Patients with + PST* (%)*
Pelvic pain	93	35	71 (76%)
Vulvar vestibulitis/ vulvodynia	45	36	37 (82%)
Dyspareunia	28	40	25 (89%)
Urgency-frequency syndrome	24	41	18 (75%)
Endometriosis	22	33	19 (86%)
Recurrent urinary tract infection	15	31	12 (80%)
Yeast vaginitis	7	38	6 (86%)
Other†	6	39	5 (83%)
IC	4	35	4 (100%)
Total	244	36	197 (81%)

*There were no statistically significant differences between any groups ($P > .5$ for all comparisons, Fisher exact test). The only groups with sufficient subjects available for meaningful statistical power were pelvic pain, vulvar vestibulitis/vulvodynia, endometriosis, and dyspareunia.

†Urethral syndrome (3 patients), detrusor instability (1 patient), pelvic floor dysfunction (1 patient), and urinary incontinence (1 patient)

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Cystoscopy With or Without Hydrodistension. Cystoscopy can be performed in the office or operating room using either a rigid or flexible cystoscope. It provides a magnified inspection of the bladder and urethral surface to rule out any abnormalities. Cystoscopy is routinely performed on any patient with micro- or gross hematuria, regardless of the presence or absence of IC. Cystoscopy with hydrodistension under anesthesia is of great use in helping to make a final diagnosis of IC in late-stage/severe disease, but is not sufficient in and of itself. Hydrodistension allows for inspection of the bladder to rule out tumors or inflammation, and when performed under anesthesia can assess the patient's maximum bladder capacity. A small bladder capacity under anesthesia supports a diagnosis of IC [6]. In addition to the diagnostic use of hydrodis-

tension, the procedure has been found to improve IC symptoms in 30% to 60% of patients within 2 to 4 weeks (after an initial temporary period during which symptoms worsen) and is therefore considered to be a short-term therapeutic option.

THERAPY

Until recently, few effective therapeutic options were available for the management of acute and/or chronic interstitial cystitis, although there was significant diversity in the types of therapies used [25]. In addition to specific diet and behavioral interventions, the U.S. FDA has approved two pharmacologic treatments for the management of IC: oral pentosan polysulfate sodium (PPS) and intravesical dimethyl sulfoxide. Numerous other intravesical and oral agents are also utilized to help manage the pain and inflammation associated with IC. Surgery (see below) is used only as a last resort.

Nonpharmacologic Interventions

Nonpharmacologic interventions, including specific diet modifications and behavioral interventions, can augment the relief provided by traditional therapies. Anecdotal evidence suggests that cigarette smoking and highly acidic foods, such as alcohol, tomatoes, chocolate, and caffeinated or citrus beverages, and even artificial sweeteners can exacerbate symptoms of IC. In contrast, specific bladder training techniques, in which patients are instructed to initiate a new voiding pattern based upon scheduled voiding, may afford symptomatic relief to that subset of patients with (at most) minimal-to-moderate pain [18]. Relaxation and distraction techniques also can be used to maintain the schedule, and gentle stretching and pelvic floor relaxation exercises may be used to relieve the symptoms. Finally, psychological counseling often helps patients with pain management; it may also be of benefit to those patients suffering concomitant anxiety/depression.

Pharmacologic Interventions

Oral Pentosan Polysulfate Sodium. Pentosan Polysulfate Sodium therapy (PPS; Elmiron®, Ortho-McNeil Pharmaceutical, Raritan, NJ) is the first and only oral drug approved by the U.S. FDA (1996) for the relief of bladder pain or discomfort associated with IC. PPS is chemically and structurally similar to naturally occurring glycosaminoglycans (GAG) produced in the urinary epithelium [26]. It is thought to act by replenishing a defective GAG layer and inhibiting inflammatory processes. As such, it provides a buffer to control cell permeability and prevent irritating solutes from reaching epithelial cells—in much the same manner that Pepto-Bismol® (Procter & Gamble, Cincinnati, OH) is used for gastrointestinal distress. In other words, PPS coats the bladder epithelium and soothes the inflammation.

The FDA-recommended dosage of oral PPS is 100 mg three times daily. Pain relief may require treatment for 2 to 4 months (6 months for patients with increased urinary frequency) [27]. Patients are encouraged to remain on oral PPS therapy for at least 6 months. A double-blind, randomized, placebo-controlled trial of PPS demonstrated that PPS reduced pain by at least 50% (versus placebo) after 3 months [27]. Symptomatic improvement has also been shown to increase with duration of usage [28].

Clinical trials demonstrate that oral PPS is significantly more effective than placebo in reducing the pain, urgency, frequency and nocturia associated with IC. PPS also appears to increase bladder capacity and volume per void [29,30]. The benefits of PPS continue for at least 3 years after treatment, and PPS treatment can lead to longer-duration remissions [29,30]. PPS is well-tolerated, with infrequent, mild and transient side effects including headache, alopecia, and minor gastrointestinal discomfort; approximately 1% of patients have slight liver function changes, which have not been associated with jaundice or other clinical signs and symptoms.

Intravesical Dimethyl Sulfoxide. Bladder instillation with dimethyl sulfoxide (DMSO) is the only other therapy approved by the FDA for the management of interstitial cystitis. DMSO is an anti-inflammatory analgesic agent with muscle relaxing properties; weekly or biweekly DMSO treatments provide at least moderate symptomatic relief for patients with IC [31,32]. Treatments are offered either in-office or, for highly motivated patients, at home with self-catheterization. DMSO is instilled through a catheter and retained in the bladder for 15 minutes before being expelled. Although DMSO has a good safety profile, it leaves a garlic-like taste/odor on the breath and skin for up to 72 hours post-treatment [33], and patients are advised to undergo blood testing (including kidney and liver function tests) every 6 months. A majority of patients report sustained remissions [34], but repeated treatments are often

necessary [35], and with continued instillations there may be reduction in the length of remissions.

Other Pharmacologic Agents. While not specifically sanctioned by the FDA, a variety of other intravesical and oral agents have been used for the management of IC. Intravesical heparin sulfate has been used as both monotherapy and as combination therapy (with intravesical DMSO) for the acute management and continued prophylaxis of IC, with generally good results. Similarly, intravesical administration of PPS has been found to afford patients with extremely severe disease a significant increase in urodynamic capacity (after only 3 months of therapy) with a reduced side effect profile [36]. Ongoing intravesical PPS therapy provides a continued slow, but steady, increase in urinary retention time, increasing asymptomatic relief, and prolonged symptomatic remissions [37].

In addition, a wide range of oral treatments has been used to augment the symptom and pain relief of traditional agents. Antibiotics may be indicated if there is concurrent urinary tract infection, but are not effective in the symptomatic relief of IC. Analgesics, including aspirin and acetaminophen (possibly with codeine), may help alleviate pain; however, nonsteroidal anti-inflammatory (NSAID) agents (including ibuprofen) may release histamine, which exacerbates IC symptoms. Antidepressants, particularly amitriptyline and other tricyclic antidepressants, provide mild to moderate central pain modulation and reduce nocturia and frequency [38]. Patients must be told that these agents are being prescribed for their analgesic properties and not for psychiatric reasons. Antihistamines can facilitate sleep and alleviate nocturia. Additional agents include antispasmodics and the antiepileptic agent gabapentin [39] (Table V).

TABLE V
Other pharmacologic agents.

- Intravesical heparin sulfate
  - As both monotherapy, or in combination with DMSO
- Antibiotics
  - Not effective in the symptomatic relief of IC
- Analgesics (for pain relief)
- Antidepressants
  - Amitriptyline/other tricyclic agents can provide mild/moderate pain modulation and reduce nocturia/frequency
- Antihistamines
  - Facilitate sleep/reduce nocturia
- Antispasmodics (e.g., hyoscyamine)

Surgery

Surgery is reserved for those patients with IC who have severe disease and have not responded to any other therapies; however, success is not assured. Fulguration under general anesthesia can be used to cauterize IC lesions; resection (also through the urethra under general anesthesia) cuts around and removes any ulcerations. While patients initially report dramatic improvements, recurrence of the ulcer or pain often occurs within 1 to 2 years. Augmentation enlarges the bladder and may minimize frequency of voiding, but it does not eliminate pain and can lead to incontinence. Cystectomy (removal of the bladder) is performed only when all other forms of therapy have failed—that, fortunately, is very rare.

MANAGEMENT GUIDELINES

It is of great importance that patients be accurately diagnosed and receive prompt treatment if they have IC. To facilitate this, a diagnostic and treatment algorithm is presented in Figure 2.

Patients with IC initially present with urinary urgency and frequency, with or without pain. Diagnostic assessment includes a medical history, physical examination, a urinalysis, and a urine culture. In the event that patients have no pain, and both the examination and the culture yield normal or negative results, the likely diagnosis is overactive bladder (OAB). A positive urine culture finding, with or without pain, is indicative of a UTI; treatment involves appropriate antibiotic therapy. Patients who present with urinary urgency and frequency, chronic pain, and negative findings from the urinalysis and urine culture should be assessed for chronic pelvic pain syndromes, particularly IC. Additional diagnostic tests, including the PUF scale, intravesical PST, and cystoscopy with hydrodistension, are often warranted. Initial therapy for IC includes oral PPS, intravesical DMSO or heparin, and adjuvant medical agents (along with nonpharmacologic interventions).

If treatment fails after an initial diagnosis of OAB, IC should be suspected, and appropriate therapy begun. Similarly, women diagnosed with a UTI who fail standard antibiotic therapy may require antibi-

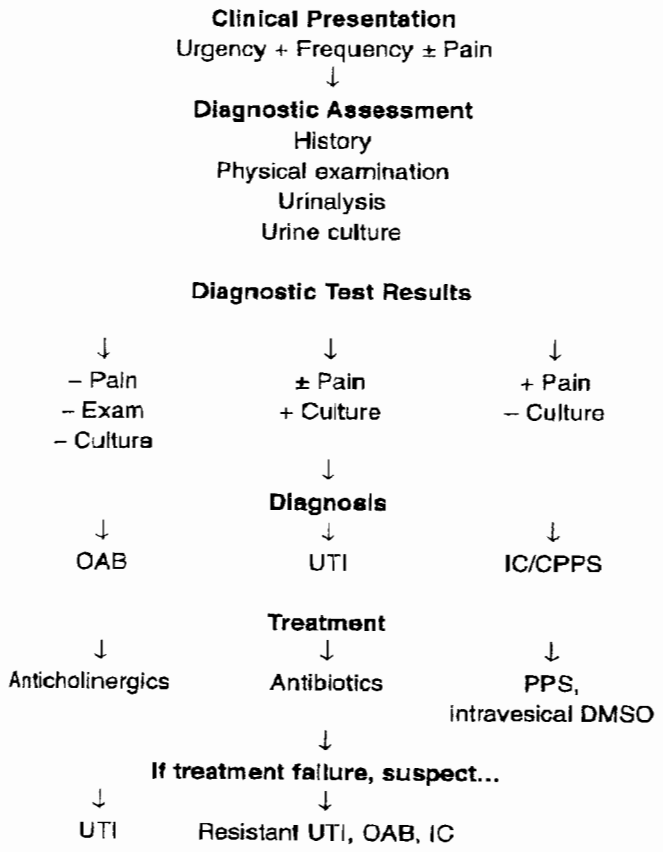

FIG. 2. Diagnosis and treatment algorithm for interstitial cystitis.

otics that cover resistant uropathogens. In addition, such patients may benefit from additional diagnostic assessment to rule out OAB and IC.

CONCLUSIONS

Interstitial cystitis is far more common than previously believed, with a potential patient population numbering in the millions. The sometimes severe and chronic pain associated with the syndrome can have significant ramifications to quality of life; the common 5–7-year delay in diagnosis and treatment initiation only further exacerbates and prolongs the suffering. In considering the diagnosis of IC, there may be the need for a reevaluation in the traditional gynecologic paradigm surrounding the assessment of chronic pelvic pain. The fact that the symptoms of IC are often gynecologic in nature reinforces the need for clinicians to include IC in the differential diagnosis when evaluating chronic pelvic pain.

Advances in the diagnostic process, including the PUF questionnaire and potassium sensitivity test, may facilitate more rapid diagnosis for women presenting with urinary frequency, urgency, and pelvic pain of unknown etiology. Finally, pentosan polysulfate sodium capsules afford women a safe and effective oral alternative to weekly or biweekly bladder instillations with DMSO or heparin for the management of IC. It is hoped that as more clinicians become knowledgeable about the signs and symptoms of IC, prompt diagnosis and effective treatment can be initiated, thereby minimizing the pain and suffering of the afflicted women.

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