REVIEW

MATT ROSENBERG, MD*
Mid-Michigan Health Centers, Jackson, MI

C. LOWELL PARSONS, MD†
Division of Urology, University of California San Diego Medical Center, San Diego, CA

SHARI PAGE, FNP‡
Mid-Michigan Health Centers, Jackson, MI

Interstitial cystitis: A primary care perspective

ABSTRACT

Interstitial cystitis is more common than previously thought and is often diagnosed only when pain, frequency, and urgency become continuous and severe. Its diagnosis is straightforward, and effective therapies are available. Physicians should keep the diagnosis of interstitial cystitis in mind for all patients presenting with pelvic pain or urinary symptoms.

KEY POINTS

Overly restrictive diagnostic criteria identify only patients with severe and advanced disease and have led to missed diagnosis and underreporting of this debilitating condition.

Symptoms of interstitial cystitis include urinary urgency and frequency, pelvic pain at various locations, nocturia, and dyspareunia.

The clinical presentation of interstitial cystitis has been well characterized and its symptoms can be quantified with validated, brief questionnaires. Although the diagnosis can often be made empirically on the basis of symptoms alone, office-based diagnostic tools now enable the physician to diagnose the disease with confidence.

Conservative therapies relieve symptoms and address the underlying cause of the disease in most patients. Referral to a specialist is necessary only for patients with refractory disease.

*Dr. Rosenberg has indicated that he has received grant or research support from the Ortho-McNeil corporation and has served as a consultant for and on the speaker's bureaus of the GlaxoSmithKline, Lilly, Novartis, Ortho-McNeil Pharmaceutical, Pfizer, and Reliant corporations.
†Dr. Parsons has indicated that he has served as a lecturer and consultant for the Ortho-McNeil corporation.
‡Ms. Page has indicated that she has served as a lecturer and consultant for the Ortho-McNeil corporation.

INTERSTITIAL CYSTITIS is a chronic condition of the lower urinary tract that causes urinary urgency and frequency, pelvic pain, or both.[1,2] Untreated, it may progress to severe, continuous symptoms resulting in a substantially compromised quality of life and permanent tissue damage.[3,4] The primary care patient population may include many women and men who have interstitial cystitis and are not yet diagnosed.

Historically, interstitial cystitis was considered rare, difficult to diagnose, and difficult to treat. Recent data, however, show that it is more common than previously thought,[5] and physicians now have validated diagnostic tools to detect it in patients whose symptoms were previously unrecognized or misdiagnosed. In addition, effective treatments exist that can relieve symptoms in a number of cases. The primary care physician can initiate conservative measures that are appropriate and effective for many patients, leaving only refractory cases to the specialist.

MORE COMMON THAN THOUGHT

To determine the true prevalence of a disease, one must screen a population for symptoms rather than only count the patients who have already received a diagnosis. The latter method gives a very low prevalence rate for interstitial cystitis: 0.052% to 0.067%.[6] In contrast, investigators who screened for its symptoms in various populations have reported prevalence rates as high as 25%.[5,7–10]

Earlier prevalence studies used diagnostic criteria[11] that recognized only advanced cases.[4] It is easier to recognize advanced disease, with

TABLE 1

Evaluation of urinary urgency, frequency, or pelvic pain

History and physical examination with focus on the lower abdomen

If any of the following are present, the Pelvic Pain and Urgency/Frequency Scale (PUF) questionnaire may be helpful (see FIGURE 1)

- Eight or more voids per 24 hours
- Recurrent urinary tract infections
- Pain with sexual activity
- Nighttime urination
- In women: Frequent vaginitis
  Anterior vaginal wall tenderness on vaginal examination
- In men: Chronic prostatitis
  Pain in perineum or prostate on digital rectal examination

Urinalysis, urine culture and sensitivity

- If bacteriuria, treat for bacterial cystitis
- If gross or microscopic hematuria, refer to urologist for appropriate workup
- If negative, consider the PUF questionnaire (FIGURE 1)

PUF SCORE	ACTION
0–4	Interstitial cystitis is doubtful
5+	If clinical impression is that interstitial cystitis is present, begin conservative treatment at your discretion. Potassium sensitivity test is optional to confirm diagnosis (FIGURE 2), but do not withhold treatment from symptomatic patient if test is negative and suspicion is high.

its attendant excruciating pain, urgency, and frequency, but the key is to recognize the disease in the same patient years earlier, when symptoms are insidiously progressing and intermittent. Depending on their sex and their symptom pattern, patients in the earlier phases of interstitial cystitis may receive diagnoses such as chronic pelvic pain, endometriosis, or recurrent urinary tract infections before their interstitial cystitis is discovered.

POTASSIUM PROVOKES SYMPTOMS

The pathophysiology of interstitial cystitis may involve a number of factors.[1,12] Possible causes include an autoimmune disorder or neurogenic abnormalities.

Growing evidence indicates that interstitial cystitis is associated with abnormal epithelial permeability in the lower urinary tract.[1] Normally, the bladder epithelium is coated with a glycosaminoglycan-containing mucous layer, which protects it from irritants in the urine.[13] The dysfunctional epithelium loses this barrier, increasing its permeability to damaging urinary solutes.[14]

In particular, potassium appears to be a major factor in provoking symptoms and producing tissue injury. When Parsons et al[15] instilled potassium chloride into the bladders of 231 patients with interstitial cystitis and 41 normal subjects, the potassium induced symptoms of urgency and pain in 75% of the patients with interstitial cystitis, but not in the normal subjects unless the bladder mucosa had been injured with protamine. Potassium absorption correlated with symptoms; instilling heparin reversed the symptoms and potassium absorption. These findings led to development of the potassium sensitivity test, a specific and sensitive office-based procedure that will be described in the following sections.

Flares of interstitial cystitis may be misdiagnosed as urinary tract infections

SYMPTOMS PROGRESS SLOWLY

Interstitial cystitis tends to exist as a continuum that spans decades of life, with symptoms gradually progressing from mild and intermittent to severe and constant.[2,4]

The clinical presentation is variable.[2]

Pelvic Pain and Urgency/Frequency (PUF) symptom scale

Please circle the answer that best describes how you feel for each question below.

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3–6	7–10	11–14	15–19	20+	____	
2 a.	How many times do you go to the bathroom at night?	0	1	2	3	4+	____	
b.	If you get up at night to go to the bathroom, does it bother you?	Never	Occasionally	Usually	Always			____
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 symptoms during or after sexual activity?	Never	Occasionally	Usually	Always		____	
b.	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		____	
6 a.	If you have pain, is it usually		Mild	Moderate	Severe		____	
b.	Does your pain bother you?	Never	Occasionally	Usually	Never			____
7	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always		____	
8 a.	If you have urgency, is it usually		Mild	Moderate	Severe		____	
b.	Does your urgency bother you?	Never	Occasionally	Usually	Always			____
	SYMPTOM SCORE (1, 2a, 4a, 5, 6a, 7, 8a)—SUBTOTAL						____	
	BOTHER SCORE (2b, 4b, 6b, 8b)—SUBTOTAL							____
	TOTAL SCORE (symptom score + bother score)							_____

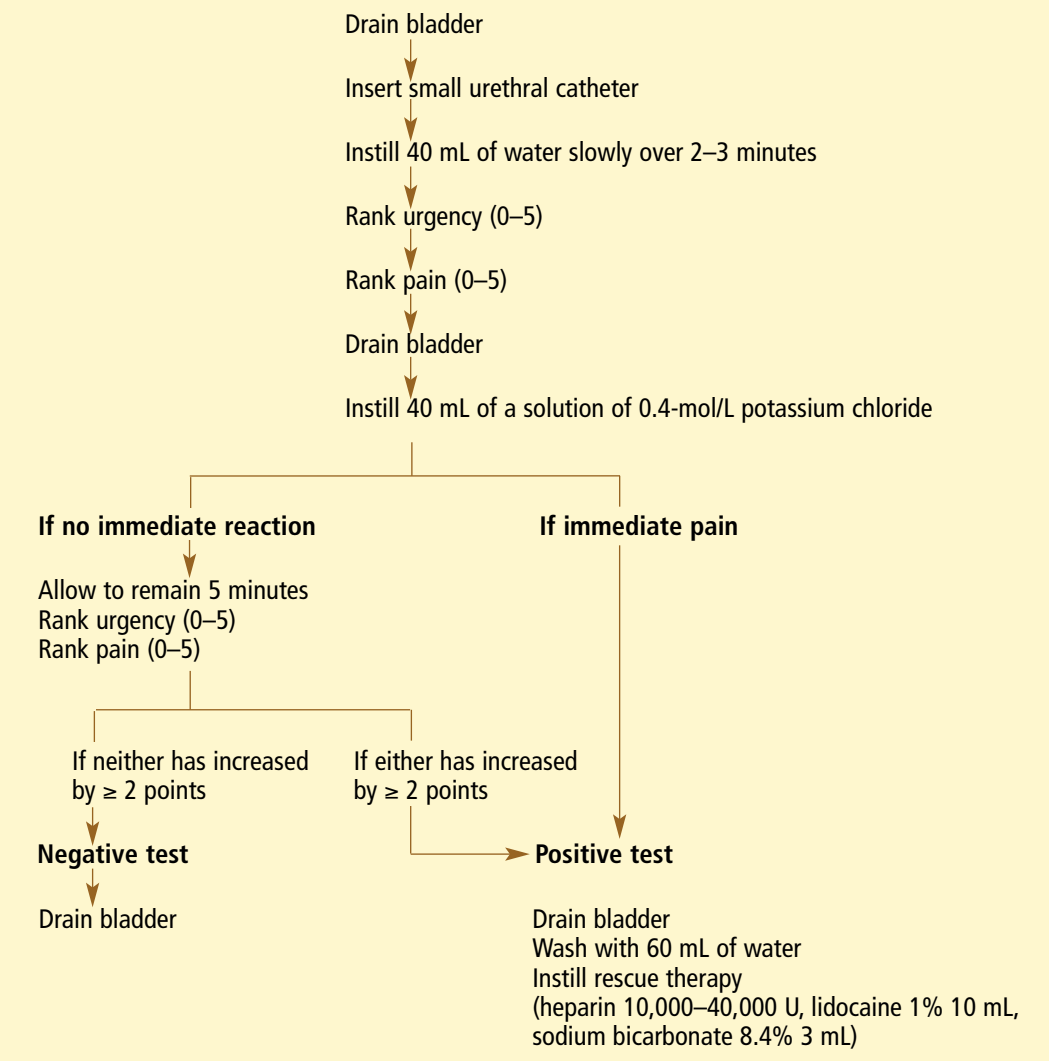
FIGURE 1

Most cases have an insidious onset, although the disease can present suddenly. Most patients have urgency, frequency, and pain, but some have only pain and others only urgency. A patient may not report or even perceive urinary frequency.[1] It is not always obvious that the bladder is the source of a patient's symptoms, because pain of bladder origin refers throughout the pelvis.[4,16] Pain with sexual activity is common in men and women with interstitial cystitis.[3,16,17]

Flares of symptoms may last several days and involve significant urgency and pain that may be misdiagnosed as a urinary tract infection. For both women and men, flares can be triggered by sexual activity or activation of allergies.[16] Women may have flares during the premenstrual week.[1,16]

Red flags. Interstitial cystitis should be considered if a patient presents with any of the following:

- Pelvic pain (although pain is not always present in interstitial cystitis, most patients with interstitial cystitis do present with pain)
- Dyspareunia (pain with sexual intimacy)
- Frequent urinary tract infections
- Frequent vaginitis
- Nighttime urination
- Urinary frequency.



ADAPTED FROM THE PROCEDURE DESCRIBED IN PARSONS CL, GREENBERGER M, GABAL L, BIDAIR M, BARME G. THE ROLE OF URINARY POTASSIUM IN THE PATHOGENESIS AND DIAGNOSIS OF INTERSTITIAL CYSTITIS. J UROL 1998; 159:1862–1867.

Urinalysis is essential for any patient with urgency, frequency, or pelvic pain

FIGURE 2

EVALUATION IS OFFICE-BASED

The evaluation of a patient with urinary urgency and frequency and pelvic pain includes a thorough history and physical examination (TABLE 1), as with any primary care patient.

The physical examination concentrates on the lower abdomen and pelvis. In women, a vaginal examination is important, particularly to test for tenderness at the anterior vaginal wall (bladder base). In men, any pain in the perineum or the prostate upon digital rectal examination may indicate interstitial cystitis.

Urinalysis is essential for any patient who presents with urgency and frequency or pelvic pain regardless of the physician's impression based on the presenting symptoms. Urine microscopy can rule out hematuria, kidney stones, and bacteriuria. Although the symptoms of interstitial cystitis can be confused with those of urinary tract infections, to date no evidence exists for an infectious agent in interstitial cystitis. Blood in the urine mandates an evaluation for genitourinary cancer. In patients

at high risk, urine cytologic study may be used to exclude carcinoma in situ of the bladder.

Other testing, such as evaluation for sexually transmitted diseases, pelvic ultrasonography, or computed tomography, may be necessary, depending on clinical circumstances.

The Pelvic Pain and Urgency/Frequency (PUF) scale, a validated questionnaire that quantifies the patient's symptoms (FIGURE 1), is useful for identifying interstitial cystitis.[5] Patients with higher scores on the PUF—reflecting multiple and more pronounced symptoms—have a greater likelihood of a positive result if they undergo a potassium sensitivity test (see below).

The potassium sensitivity test is an optional method that can be used to help confirm the suspicion of interstitial cystitis (FIGURE 2).[15] It is designed to detect dysfunction of the bladder epithelium using potassium as an irritant: a solution of potassium chloride is instilled to determine if it provokes pain or urgency.

Parsons[18] reviewed results of this test from centers around the world and found that 1,746 (78%) of 2,234 patients with suspected interstitial cystitis had a positive test. A positive test indicates epithelial dysfunction, which is seen in patients with radiation cystitis or an acute urinary tract infection as well as in interstitial cystitis. However, patients with chronic urinary tract infections, bladder outlet obstruction, or overactive bladder have a low rate of response to intravesical potassium.[15,18]

The potassium sensitivity test helps confirm interstitial cystitis, with discomfort similar to that of a Pap smear

The potassium sensitivity test is as well tolerated as other common office-based procedures. In a survey, 111 patients who underwent the test judged the discomfort to be equal to or less than that of standard procedures such as a Papanicolaou (Pap) smear or digital rectal examination.[19] Among patients who had undergone both procedures, the percentages who reported greater discomfort with the potassium sensitivity test were 8% vs a Pap smear, 10% vs a digital rectal examination, 5% vs a mammogram, and 21% vs a blood draw. The potassium sensitivity test is as easy to perform as urethral catheterization.

To avoid inflicting pain needlessly, the decision to perform the test should be thoughtfully considered for each patient. When the test is properly administered, an anesthetic solution is given quickly to minimize any discomfort.

Urodynamic testing and cystoscopy are not necessary to diagnose interstitial cystitis.[1,20] Traditionally, cystoscopy and hydrodistention have been considered essential for diagnosis, but no reports in the peer-reviewed literature have demonstrated their sensitivity and specificity for diagnosing interstitial cystitis.

VARIOUS TREATMENTS AVAILABLE

Various behavioral, pharmacologic, and interventional treatments are available for interstitial cystitis.

Behavioral treatment

Behavioral treatment is centered around changing a stressful lifestyle and excluding possible dietary irritants.

Foods that cause irritation include caffeine-containing substances (eg, coffee, chocolate), citrus fruits (including juices), alcohol, tomatoes, and carbonated beverages. However, each patient is different. Keeping a diary of foods consumed and symptoms that occur may help patients identify the culprit. As a general rule, foods rich in potassium are problematic.

Pharmacologic treatment

Pharmacologic treatment for interstitial cystitis has several components (TABLE 2).

Amitriptyline is used to increase the pain threshold.[21] (Interstitial cystitis is a symptom complex, and pain is generally the worst symptom.)

Hydroxyzine can be used as a mast cell stabilizer,[12] as the inflammatory response associated with interstitial cystitis is thought to be driven by histamine release from the mast cells.

Pentosan polysulfate sodium (PPS) has become a cornerstone of treatment of interstitial cystitis, owing to its ability to restore the integrity of the mucous layer. Currently, it is the only oral medication approved for treating interstitial cystitis in the United States. The molecular structure of PPS is similar to that of the glycosaminoglycans in the bladder surface mucus, and the drug is

TABLE 2

Conservative treatment of interstitial cystitis

Pentosan polysulfate sodium (PPS) 100 mg three times day

Hydroxyzine (if needed) 25 mg at bedtime, increase to 50–100 mg/day during allergy season

Amitriptyline (if needed) 25 mg at bedtime, increase to 50 mg/day after 1–2 months

Intravesical therapeutic solution 3–7 times a week for at least 2 weeks (for immediate, temporary symptom relief at start of treatment or for symptom flares)
Patients can be taught to administer at home
Mix together the following, instill into an empty bladder, and retain for approximately 30 minutes

- **Pentosan polysulfate sodium** 100–200 mg (one or two 100-mg oral capsules, each dissolved in 10 mL buffered normal saline) or **heparin** 10,000–40,000 U (to aid in repair and restoration of bladder mucus)
- **Lidocaine** 1% 10 mL or 2% 16 mL (as an anesthetic)
- **Sodium bicarbonate** 8.4% 3 mL (to increase absorption of lidocaine)

Evaluate at 3–6 months after start of treatment

- **If responding,** continue treatment
- **If not responding,** refer for further urologic workup, including cystoscopy

believed to help restore the mucous layer to reestablish impermeability to urine solutes.[22]

Several long-term clinical studies showed PPS to be effective in treating interstitial cystitis.[23–27] Adverse effects tended to be mild, infrequent, and transient, the most common being alopecia, diarrhea, nausea, headache, rash, dyspepsia, and abdominal pain.[28]

PPS is more beneficial the longer it is used,[26] and patients who understand this are more likely to comply with the treatment regimen.

The standard dosage is 100 mg three times a day, given 1 hour before or 2 hours after a meal.[28] PPS can be coupled with hydroxyzine or amitriptyline for symptom relief in severe or advanced cases.

Interventional treatment

Patients with interstitial cystitis may benefit from intravesical instillation of therapeutic solutions.[29]

Dimethyl sulfoxide was approved by the US Food and Drug Administration for use in interstitial cystitis and is reported to provide good to excellent symptom relief in at least 50% of patients.[30] Newer solutions include the combination of PPS or heparin with lidocaine and sodium bicarbonate (TABLE 2).[31] In a preliminary study, the intravesical solution relieved symptoms significantly and immediately in 41 (75%) of 55 patients with interstitial cystitis.[29] Patients can easily be taught to perform instillations at home.[31]

Cystoscopy with hydrodistention may offer some symptomatic relief, but it is not proven in the treatment of interstitial cystitis.

Bladder resection should be considered only if the disease is completely refractory to treatment.

Once treatment is started, symptoms may take up to 2 years to resolve

CLOSE FOLLOW-UP IS ESSENTIAL

In caring for patients with interstitial cystitis, the most important tasks are to discover the correct diagnosis and prescribe appropriate treatment. By the time interstitial cystitis is diagnosed, many patients have had progressive disease and associated symptoms for a considerable time.[1,2] Symptoms may take months or even up to 2 years to improve maximally with treatment.[26,29] Appropriate therapy can result in substantial medical cost

savings, for example, by preventing unnecessary surgery.

Close follow-up is essential. To ensure that treatment is as effective as possible, we follow up with our patients monthly for the first 3 months and then every 3 months thereafter. Frequent follow-up enables us to improve compliance, titrate medications, and reinforce behavioral modifications such as dietary changes.

REFERENCES

1. **Metts JF.** Interstitial cystitis: urgency and frequency syndrome. Am Fam Physician 2001; 64:1199–1214.
2. **Driscoll A, Teichman JMH.** How do patients with interstitial cystitis present? J Urol 2001; 166:2118–2120.
3. **Koziol JA, Clark DC, Gittes RF, Tan EM.** The natural history of interstitial cystitis: a survey of 374 patients. J Urol 1993;149:465–469.
4. **Parsons CL.** Interstitial cystitis. In: Teichman JMH, editor; Weiss BD, series editor. 20 Common Problems in Urology. New York, NY: McGraw-Hill Medical Publishing Division; 2001:119–132.
5. **Parsons CL, Dell J, Stanford EJ, et al.** Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. Urology 2002; 60:573–578.
6. **Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ.** Epidemiology of interstitial cystitis: a population based study. J Urol 1999; 161:549–552.
7. **Parsons CL, Tatsis V.** Prevalence of interstitial cystitis in young females. Presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30–November 1, 2003; Alexandria, Va.
8. **Dell JR.** Use of the PUF questionnaire to determine the prevalence of IC in obstetrics and gynecology practices. Presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium. October 30–November 1, 2003; Alexandria, Va.
9. **Rosenberg MT, Page S, Roth L, Areaux D, Thallman C, Kval TE.** Identification of interstitial cystitis in women in a primary care setting using a symptom questionnaire and potassium sensitivity testing. Presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30–November 1, 2003; Alexandria, Va.
10. **Rosenberg MT, Hazzard MA.** Prevalence of interstitial cystitis symptoms in women: a population-based study in the primary care office. J Urol. In press.
11. **Gillenwater JY, Wein AJ.** Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 1988; 140:203–206.
12. **Sant GR, Theoharides TC.** The role of the mast cell in interstitial cystitis. Urol Clin North Am 1994; 21:41–53.
13. **Hurst RE.** Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. World J Urol 1994; 12:3–10.
14. **Parsons CL, Lilly JD, Stein P.** Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol 1991; 145:732–735.
15. **Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G.** The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998; 159:1862–1867.
16. **Parsons CL, Zupkas P, Parsons JK.** Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology 2001; 57:428–433.
17. **Parsons CL, Albo M.** Intravesical potassium sensitivity in patients with prostatitis. J Urol 2002; 168:1054–1057.
18. **Parsons CL.** Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. Urology 2003; 62:976–982.
19. **Rosenberg MT, Page SA, Roth L, Areaux D, Thallman C, Kval TE.** Tolerability of the potassium sensitivity test for interstitial cystitis. Presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30–November 1, 2003; Alexandria, Va.
20. **Pontari MA.** Use of cystoscopy, bladder biopsy and hydrodistension in the diagnosis and treatment of interstitial cystitis. Presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30-November 1, 2003; Alexandria, Va.
21. **Hanno PM, Buehler J, Wein AJ.** Use of amitriptyline in the treatment of interstitial cystitis. J Urol 1989; 141:846–848.
22. **Parsons CL.** Epithelial coating techniques in the treatment of interstitial cystitis. Urology 1997; 49(suppl 5A):100–104.
23. **Parsons CL, Mulholland SG.** Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987; 138:513–516.
24. **Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR.** Pentosan polysulfate sodium for therapy of interstitial cystitis: a double-blind placebo-controlled clinical study. Urology 1990; 35:552–558.
25. **Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G.** A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol 1993; 150:845–848.
26. **Hanno PM.** Analysis of long-term Elmiron therapy for interstitial cystitis. Urology 1997; 49(suppl 5A):93–99.
27. **Parsons CL, Forrest J, Nickel JC, et al.** Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. Urology 2002; 59:329–333.
28. Elmiron (pentosan polysulfate sodium capsules) prescribing information. Mountain View, CA: Alza Pharmaceuticals; 2002.
29. **Parsons CL.** Current strategies for managing interstitial cystitis. Exp Opin Pharmacother 2004; 5:287–293.
30. **Sant GR.** Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of interstitial cystitis. Urology 1987; 29(suppl):17–21.
31. **Moldwin RM, Sant GR.** Interstitial cystitis: a pathophysiology and treatment update. Clin Obstet Gynecol 2002; 45:259–272.

ADDRESS: *Matt Rosenberg, MD, Mid-Michigan Health Centers, 214 North West Avenue, Jackson, MI 49201; e-mail matttoren@yahoo.com.*