Looking Out For
Interstitial Cystitis

Joel M.H. Teichman, MD, FRCSC

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Louise's case

- Louise, 43, has a two-year history of recurrent episodes of urgency, frequency and dysuria.

Then:

- During her first episode, she had a positive urine culture.
- She was originally diagnosed with bacterial cystitis and treated with nitrofurantoin.
- Her symptoms resolved.
- Each subsequent episode has been treated empirically with antibiotics, without relief.

Now:

- Her symptoms have been unremitting and progressive over the last two months.
- She complains of frequency every hour, nocturia twice, dyspareunia and pelvic pain.
- Her abdomen is soft with mild suprapubic tenderness.
- Her anterior vaginal wall is tender at the level of the bladder neck.
- Urinalysis and urine culture are negative.

For more on Louise, go to page 79.

History

Presentation

- Symptoms include: urinary urgency, frequency, nocturia, pelvic pain and dyspareunia (or ejaculatory pain in men).
- Pain may be constant or intermittent. It is felt in the suprapubic or retropubic areas, pelvis, perineum, lower back, vagina, genitals, penis or medial thighs.
- In early phases, patients note dysuria and relief post-micturition; as the disease progresses, pain may become unremitting and no longer relieved by voiding.
- In at least one-third of patients, pain is a late phenomenon and, in fact, many present only with frequency and/or urgency at first. As many as 40% of patients report pressure or discomfort rather than pain, *per se*. Thus, it is important to elicit pain, pressure and discomfort as manifestations of bladder "pain."

What to look for

- Gross or microscopic hematuria (its presence warrants urine cytology and/or cystoscopy to exclude bladder cancer).
- Antibiotic history and response to antibiotics (the typical patient has had at least four courses of antibiotics with little response).
- Urinary incontinence (usually not present).
- Fluid intake (to exclude polydipsia).
- Vaginal discharge.
- Medication history.

Jennifer's case

- Jennifer, 28, presents with a one-month history of pelvic pain.

Then:

- Her family physician prescribed ciprofloxacin for a presumed bacterial cystitis, but Jennifer got no relief.
- The physician then did a urine culture, which was negative.
- Levofloxacin was prescribed, again without relief.

Now:

- Upon questioning, Jennifer reports a progressive seven-year history of daytime urinary frequency of three times per hour, and nocturia seven times.
- She had considered this voiding pattern normal and did not associate it with her pelvic pain.

Fact Box: Did you know?

- In the U.S., at least **800,000** women suffer from IC.
- Although women are diagnosed 10 times more frequently than men, there is emerging evidence that perhaps **60%** of men diagnosed with CPPS may instead have IC.
- IC is most commonly diagnosed in the **5th decade**, but does occur in children and the elderly.
- The average time from symptom onset to diagnosis is **2 to 5 years**.
- The typical patient sees **8** physicians before the correct diagnosis is made.

Physical exam may show:

- A dysphoric mood (up to 90% of IC patients are depressed).
- A lower quadrant or suprapubic tenderness and anterior vaginal wall tenderness over the bladder neck.
- Pelvic floor spasm is common.
- Levator tenderness and spasm, tenderness of anterior and posterior vaginal wall and rectal sphincter tenderness may also be present.

Lab tests

- Urinalyses and urine cultures are almost always negative. (Urine should be obtained as a sterile catheterized specimen if any concern that patient voids small volumes.)
- Urinalysis showing pyuria or bacteriuria, and/or a positive urine culture should be treated as a bacterial cystitis; patient should be re-evaluated after therapy.
- Hematuria warrants urine cytology, upper tract imaging and cystoscopy.
- Any patient with irritative voiding symptoms and risk factors for bladder cancer warrants cystoscopy.
- A voiding diary will often show frequent, small voided volumes (median voided volumes in most studies are approximately 90 cc to 125 cc), with little or no incontinence; it will also exclude rare cases of polydipsia.
- There are no currently accepted tests to definitively diagnose IC; the National Institute of Diabetes and Digestive and Kidney Diseases consensus criteria are too restrictive and would falsely exclude diagnosis in 60% of patients.
- Presence of a Hunner's ulcer is pathognomonic, but occurs in < 7% of cases.
- Reduced anesthetic capacity and submucosal petechial hemorrhages are not specific and may not be sensitive.
- Biopsy is not helpful, as there are no histopathologic diagnostic criteria.
- Recent data show a promising new urine test, antiproliferative factor, may be an important diagnostic or disease marker.

More on Louise's case

- Louise completes a 48-hour voiding diary, which shows:
  - approximately 1.5 L fluid intake daily,
  - voided volumes ranging from 50 cc to 175 cc
  - voiding frequency confirming her daytime frequency of every hour and nocturia twice and
  - no incontinence.
- She completes a Pain Urgency Frequency (PUF) questionnaire and scores 17—a high score.
- Urine cytology is negative.
- She is started on:
  - pentosan polysulfate, 100 mg orally three times daily,
  - hydroxyzine, 25 mg orally one hour before bedtime and
  - amitriptyline, 25 mg orally, one hour before bedtime, for six months.
- She is also initiated on dietary management.
- Louise undergoes a cystoscopy and hydrodistension; they show mild submucosal petechial hemorrhages and a mildly reduced anesthetic capacity, at 875 cc.
- The procedure provides mild pain relief for three weeks.
- When Louise returns six months later:
  - her voiding frequency is improved,
  - her pain is less intense and less frequent and
  - her PUF score is 12.
- Louise continues on medical management and is seen once a year.

Dr. Teichman is an associate professor, division of urology, University of British Columbia, and head, section of urology, Providence Healthcare, St. Paul's Hospital, Vancouver, British Columbia.

Office-based tests

- The potassium sensitivity test takes 10 minutes and is an excellent way to diagnose epithelial dysfunction; its greatest utility may be to identify early-phase patients whose symptoms are relatively mild. The test is not without controversy and is not specific for IC, but rather for epithelial permeability.
- The Pelvic Pain Urgency and Frequency (PUF) questionnaire is easy to administer and has been correlated to a positive potassium test.
- The PUF has been used successfully to screen for IC in primary care, however, most experts recommend urine cytology be done to exclude bladder carcinoma in situ.

Misdiagnoses

- Endometriosis, vulvodynia and overactive bladder are common misdiagnoses.
- In men, the most common misdiagnoses are chronic bacterial or nonbacterial prostatitis (CPPS II or III).
- Thus, patients so diagnosed who fail to respond to appropriate therapies for these conditions, or patients so diagnosed whose test results do not support these diagnoses, should prompt the clinician to consider IC in the differential diagnosis.

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Overall, IC diagnosis is largely based on clinical suspicion, with the elimination of competing alternative diagnoses.

Table 1

Therapies for interstitial cystitis

Category	Examples
Patient education, self-help, coping stratgeies	IC Association (www.ichelp.org)
Dietary management	Remove food triggers, calcium glycerophosphate
Oral agents	*Pain:* • Amitriptyline, 25-100 mg po qhs • Paroxetine hydrochloride, 20 mg po qam • Gabapentin, 600-900 mg po tid *Epithelial coating:* • Pentosan polysulfate, 100 mg po tid *Antihistamine:* • Hydroxyzine, 25-50 mg po qhs
Intravesical agents	• DMSO, RIMSO-50, 500 cc x 20 minutes, q week x 6 • Intravesical heparin, 20,000 IU in 10 cc of water x 30 minutes daily • "Rescue" solution (heparin, bicarbonate, lidocaine)
Surgery	• Cytoscopy and hydrodistension under general anesthesia • Neurostimulation • Cystectomy and urinary diversion

IC: Interstitial cystitis
po: Orally
qhs: Every bedtime
DMSO: Dimethyl sulfoxide
qam: Every morning
tid: Three times daily
q: Every

Treatments

- Some treatment options are listed in Table 1.
- Randomized trials show therapy should be continued for at least six months to assess efficacy.
- Open-label trials show response rate may take up to two years in some severely affected patients.
- The use of multimodal therapy is common, but the only randomized trial to assess efficacy of multimodal therapy was underpowered and failed to reach statistical significance.

The GP's role

- The family doctor should be quick to refer the patients previously diagnosed:
  - with recurrent bacterial cystitis whose urine cultures are sterile or who fail antibiotics;
  - who fail empiric hormonal therapy;
  - who have laparoscopies that fail to show endometriosis;
  - who return post-hysterectomy with pelvic pain;
  - with overactive bladder who fail anticholinergics;
  - with chronic prostatitis who fail a one-month trial of a fluoroquinolone.
- It is reasonable for GPs to initiate medical therapy (pentosan, amitriptyline and hydroxyzine), but they should nonetheless refer suspected IC patients to urologists with an interest in IC. Dx