

# Interstitial Cystitis

Deborah L. Myers, MD

**Interstitial cystitis (IC) is a chronic** condition of urinary urgency, frequency, and suprapubic pain in the absence of bacteruria. It is part of the painful bladder syndrome whose known causes are tuberculosis, stones, malignancy, previous chemotherapy of the bladder, and pelvic radiation. Interstitial cystitis is a diagnosis of exclusion when no known cause of painful bladder can be identified. It has classically been diagnosed by the presence of “Hunner’s ulcers”, a lesion noted on cystoscopy in 1915.<sup>1</sup> The word “ulcer” has proven to be a misnomer; the lesion is actually a coalescence of vessels. IC is a chronic illness for which we do not have a full understanding in terms of etiology or management.

IC occurs predominantly in women between 40-60 years, and in a ratio of 9:1 of women to men. With newer diagnostic techniques and less stringent cri-

teria, the estimated prevalence of IC in the United States is approximately 1.5 million to 25 to 30 million women. Practitioners involved in women’s health should know about this condition.<sup>2</sup>

The pathophysiology of IC remains unknown, but two integrated theories, the (1) “leaky epithelium” and (2) “neurogenic up-regulation” are proposed. The bladder uroepithelium has a protective mucous coat layer, the **glycosaminoglycan (GAG)** layer, which, when injured, becomes deficient, or “leaky”, thus allowing potassium and toxins in the urine to penetrate into the underlying bladder and causing inflammation and pain.<sup>3</sup> In response to this bladder insult, detrusor mast cells release substance P, histamines and prostaglandins which cause vasodilatation and pain. The sensory C afferent nerve fibers of the bladder can become “up-regulated.” (Figure 1) Studies have shown increased nerve fi-

ber density including sympathetic nerves in bladders of patients with IC. IC could be a type of reflex sympathetic dystrophy with abnormal spinal sympathetic activity.<sup>4</sup>

The cause of the “leaky epithelium” still remains unknown. Work by Keay et al has identified proteins in the urine which affect the ability of the uroepithelium to regenerate and repair. Patients with IC have increased levels of **Anti-proliferative factor (APF)**. APF inhibits the growth of the bladder lining. IC patients have lower levels of other proteins HB-EGF (heparin binding epidermal growth factor-like), required for epithelial growth.<sup>5</sup> In summary, the damaged epithelium leads to a complex cascade of interactions involving urinary cations, activated mast cells, sensory nerves, detrusor muscle overactivity, and spinal cord sensitization.

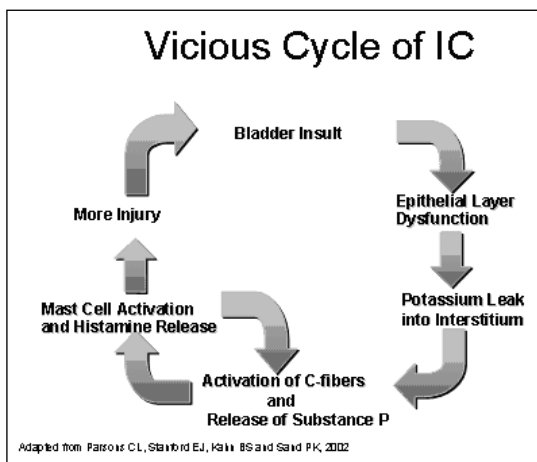


Figure 1. The Integrated Theories of Interstitial Cystitis.

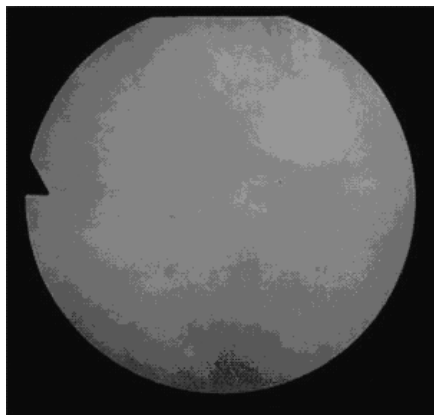


Figure 2. Hunner’s Ulcer

Figure 3. The O’Leary- Sant Interstitial Cystitis Symptom and Problem Index (9)

Interstitial Cystitis Symptom Index

Interstitial Cystitis Problem Index

During the past month, how much has each of the following been a problem for you?

<p>Q1. During the past month, how often have you felt the strong need to urinate with little or no warning?</p> <p>0. ___ not at all</p> <p>1. ___ less than 1 time in 5</p> <p>2. ___ less than half the time</p> <p>3. ___ about half the time</p> <p>4. ___ more than half the time</p> <p>5. ___ almost always</p>	<p>Q1. Frequent urination during the day?</p> <p>0. ___ no problem</p> <p>1. ___ very small problem</p> <p>2. ___ small problem</p> <p>3. ___ medium problem</p> <p>4. ___ big problem</p>
<p>Q2. During the past month, have you had to urinate less than 2 hours after you finished urinating?</p> <p>0. ___ not at all</p> <p>1. ___ less than 1 time in 5</p> <p>2. ___ less than half the time</p> <p>3. ___ about half the time</p> <p>4. ___ more than half the time</p> <p>5. ___ almost always</p>	<p>Q2. Getting up at night?</p> <p>0. ___ no problem</p> <p>1. ___ very small problem</p> <p>2. ___ small problem</p> <p>3. ___ medium problem</p> <p>4. ___ big problem</p>
<p>Q3. During the past month, how often did you most typically get up at night to urinate?</p> <p>0. ___ none</p> <p>1. ___ once</p> <p>2. ___ 2 times</p> <p>3. ___ 3 times</p> <p>4. ___ 4 times</p> <p>5. ___ 5 or more times</p>	<p>Q3. Need to urinate with little warning?</p> <p>0. ___ no problem</p> <p>1. ___ very small problem</p> <p>2. ___ small problem</p> <p>3. ___ medium problem</p> <p>4. ___ big problem</p>
<p>Q4. During the past month, have you experienced pain or burning in your bladder?</p> <p>0. ___ not at all</p> <p>2. ___ a few times</p> <p>3. ___ almost always</p> <p>4. ___ fairly often</p> <p>5. ___ usually</p>	<p>Q4. Burning pain, discomfort, or pressure in your bladder?</p> <p>0. ___ no problem</p> <p>1. ___ very small problem</p> <p>2. ___ small problem</p> <p>3. ___ medium problem</p> <p>4. ___ big problem</p>
<p>Add the numerical values of the checked entries; total score:</p>	<p>Add the numerical values of the checked entries; total score:</p>

(9) O’Leary MP, Sant GR, et al. The interstitial cystitis symptom and problem index. *Urol* 1997;49(suppl 5A).

Figure 4<sup>11</sup>

**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		___	___
<b>SYMPTOM SCORE (1, 2a, 4a, 5, 6a, 7, 8a)—SUBTOTAL</b>						___	___
<b>BOTHER SCORE (2b, 4b, 6b, 8b)—SUBTOTAL</b>						___	___
<b>TOTAL SCORE (symptom score + bother score)</b>						___	___

**Table 1. NIH-NIDDK Diagnostic Criteria of Interstitial Cystitis<sup>7</sup>**

**Category A:** At least one of the following findings on cystoscopy:

- Diffuse glomerulations (at least 10 per quadrant) in at least three quadrants
- A classic Hunner's ulcer

**Category B:** At least one of the following symptoms:

- pain associated with the bladder
- urinary urgency

**Exclusion criteria:**

- age < 18 years
- urinary frequency while awake <8/ per day
- nocturia <2/night
- maximal bladder capacity >350ml while patient awake
- absence of an intense urge to void with bladder filled to 150ml during cystometry
- involuntary bladder contractions on cystometry
- duration of symptoms < 9 months
- symptoms relieved by antimicrobial agents, anticholinergics, or antispasmodics
- urinary tract or prostatic infection in the past 3 months
- active genital herpes
- vaginitis
- uterine, cervical, vaginal, or urethral cancer within the past 5 years
- bladder or ureteral calculi
- urethral diverticulum
- hx of cyclophosphamide or chemical cystitis or tuberculous or radiation cystitis
- benign or malignant bladder tumors

IC can be associated with irritable bowel syndrome, migraines, endometriosis, vestibulitis, vulvodynia, and collagen vascular diseases such as systemic lupus erythematosus. Depression and anxiety are often seen in these women; however, this is likely secondary to the chronic pain of IC. Women with IC score poorly on quality of life questionnaires, but IC should not be considered a psychosomatic disorder.<sup>6</sup>

**SYMPTOMS**

Patients with IC will complain of urgency, frequency (> 8 voids per day), and bladder pain. Nocturia (>2xs/night) is almost always present. Episodes of incontinence are rare. These women often complain of difficulty voiding or post-void fullness. These patients do not tolerate large volumes of urine in their bladder, thus often sensing fullness. Many patients have been on chronic antibiotic therapy for supposed chronic urinary tract infections. Symptoms of IC overlap with overactive bladder, i.e., urgency and frequency, and thus some patients may have received anti-cholinergic therapy without relief.

Patients with IC can complain of either cyclic or constant pelvic pain. They may also complain of vaginal burning and/ or painful intercourse. Bladder symptoms are often increased with intercourse and near the menses. Symptoms of IC can mimic some gynecologic disorders, particularly endometriosis.

**DIAGNOSIS**

Traditionally the diagnosis has been made by cystoscopy with other criteria as described by the **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)** in 1988. Table 1<sup>7</sup> Inclusion criteria require that the patient complain of urgency/ frequency or pain in the bladder, and have the presence of either glomerulations or Hunner's ulcers (Figure 2) in the bladder at cystoscopy. The exclusion criteria have been shown to be too strict for general clinical use, because approximately 60% of patients judged to have IC by experienced clinicians fail to meet the NIDDK criteria. Clinically, the diagnosis of IC can often be made by history, physical, screening questionnaires, laboratory studies, and office testing.<sup>8</sup>

Figure 5. SAMPLE BLADDER RECORD

Time Interval	Amount voided	Activity	Urge present	Leak / symptoms	Amount/type fluid intake

**Instructions:**

This is a record of your voiding (urinating) of urine or symptoms. Please complete this according to the following instructions. Choose a 1-2 day period to keep this record when you can conveniently measure every void, and begin with your first voiding upon arising as in the sample below.

Time Interval	Amount voided	Activity	Urge present	Symptoms	Amount/type fluid intake
645 am	550 cc	awakening			
7 00 am		Turned on water	yes		2 cups of coffee, 6 oz juice

1. Record time of all voids, leakage or symptoms, intake of liquids.
2. Measure all intake and output in cc's or oz's. You can measure the amount of urine that you pass by placing a large plastic bowl on the toilet seat for collection. Measure the amount and type of all liquid intake using either cc's or oz's (1 cup = 8 oz = 240 cc).
3. If the urge to urinate accompanied (or preceded) the urine leakage write YES. If you felt no urge when the leakage occurred, write NO
4. Use additional sheets as needed.

History taking should query for urinary tract infections, pelvic surgery, known causes of painful bladder syndrome, IC symptoms and the associated conditions described above. O'Leary et al, in 1997, developed two validated self-administered questionnaires to monitor symptoms.<sup>9</sup> (Figure 3) Clemons et al in 2002 found that a score of = 5 on the symptom index was 94% sensitive in diagnosing interstitial cystitis.<sup>10</sup> Parsons CL et al developed the PUF (pelvic pain and urgency/ frequency) questionnaire as another tool to detect IC.<sup>11</sup> (Figure 4)

Physical and pelvic exam will most likely have few findings, but is necessary to rule out other causes of pelvic pain and urgency/ frequency symptoms. Gastrointestinal conditions such as irritable bowel syndrome, neurological conditions of the sacral nerves, musculoskeletal disorders, gynecologic conditions and other

urinary causes (bladder stones or malignancy, urethral diverticulum) and urinary tract infection should be considered. In lieu of findings, pelvic exam may only show tenderness of the anterior vaginal wall, bladder and urethra. Spasticity, tenderness, and localized 'trigger points' of the levator ani muscles of the pelvic floor may be elicited. Women with chronic pelvic pain can develop levator spasm which in turn can continue to cause symptoms of pain, urinary urgency, and frequency.<sup>12</sup>

**LABORATORY**

Urinalysis and urine culture are required laboratory studies. Urine cytology would be obtained in patients who have risk factors for bladder cancer. An abnormal urine cytology or microscopic hematuria, will require radiologic studies such as CT nephrogram and referral for cystoscopic evaluation.

**UROLOG**

A 24-48 hour voiding diary (urolog) records the amount and type of fluid intake, the time of each void and the volume voided at each micturition. Patients with IC will usually have frequent voids (>12/ day) and small voided volumes (average of 75-100cc). Nocturia will usually be present. The urolog also allows the clinician to determine if the fluids consumed are potential bladder irritants. (Figure 5)

**ASSESS POST VOID RESIDUAL**

Patients with IC often complain of incomplete emptying and/ or post void fullness, therefore an assessment of post-void residual urine volume is needed, either by bladder ultrasound or by catheterization.

**TREATMENT IN THE PRIMARY CARE SETTING**

Treatment can be initiated based after careful assessment and exclusion of other causes. Treatment ultimately is multi- modality, but may need to be introduced one at a time, to determine which options will be long term.

**SELF HELP AND PATIENT EDUCATION**

The chronic nature of the disease, including the possibility of relapses, should be explained to the patient. Several self-help books are available and agencies from which to get additional information on the condition.<sup>13</sup> Both the NKUDIC (3 Information Way Bethesda, MD 20892-3580 Phone: 1-800-891-5390) and the Interstitial Cystitis Association (110 North Washington Street, Suite 340, Rockville, MD, 20850 301-610-5300, 1-800-helpica) have accurate information. The **Interstitial Cystitis Association (ICA)** provides support group information, conferences and medical information. Patients can be referred to the various websites; e.g., [www.ichelp.org](http://www.ichelp.org) and [www.ic-network.com](http://www.ic-network.com). Stress reduction techniques (self-visualization, yoga, baths, deep breathing, meditation) can create a sense of well being. Development of coping mechanisms, problem solving, and also sex therapy with the help of a psychologist may also be needed.

**Table 2. Dietary irritants to avoid<sup>14</sup>**

All alcoholic beverages  
Apples  
Apple juice  
Cantaloupes  
Carbonated drinks  
Chili,  
Spicy foods  
Citrus fruits (lemons, limes,  
oranges, etc.)  
Coffee  
Cranberries  
Grapes  
Guava  
Lemon juice  
Peaches  
Pineapple  
Plums  
Strawberries  
Tea  
Tomatoes  
Vinegar

### **Dietary recommendations**

Avoidance of (1) carbonated, citrus and caffeinated beverages, (2) foods high in potassium content such as citrus fruits and tomatoes or (3) foods with a high acid content, and (4) spicy foods and foods rich in tyrosine and tryptophan can help relieve symptoms in some patients.<sup>14</sup> (Table 2) Increasing water intake is another important dietary recommendation. Patients with IC tend to decrease their fluid intake to limit the frequency of voids; however this concentrates the urine, leading to increased irritation.

### **Over the counter (OTC)**

#### **Supplements and alternatives**

Glucosamine/ chondroitin sulfate taken 1000mg daily and the amino acid supplement L-arginine taken 500 mg PO TID for 6 months can provide relief of symptoms. Other alternatives Algonot Plus® and CystoProtek®, (Alaven Pharmaceutical, Marietta GA) and Cysta-Q™ (Farr Laboratories, Westwood, CA) are found at various websites on the Internet. Calcium glycerophosphate (Preliel®) from AKPharma Inc., Pleasantville, NJ, a tasteless deacidifier, taken before meals can reduce food acidity.

### **ANALGESICS AND ANTI-SPASMODICS**

Phenazopyridine (Pyridium® Warner Chilcott, Rockaway, NJ) is a bladder analgesic that can relieve symptoms and on an

as-needed basis for symptom flares. The anti-cholinergic medications used to treat overactive bladder may improve urinary frequency and urge incontinence if present. However, if used alone, the anti-cholinergics are unlikely to be effective based upon our current understanding of the pathophysiology of IC, since they do not affect the cascade pathway.

### **SPECIALIZED DIAGNOSIS AND MANAGEMENT**

If initial diagnostic maneuvers are not conclusive and/ or initial treatments have not proven to be effective, then further testing or referral to indicated specialists: urogynecology, urology, physical therapy, psychology, psychiatry or pain clinics for further diagnostic steps and/ or treatment is indicated. The primary care physician should have a working knowledge of the methods used to manage more advanced cases of IC.

### **POTASSIUM TESTING**

In 1996, Parsons introduced the potassium sensitivity test as an office test that can detect IC.<sup>15</sup> The KCL test involves instilling two different solutions in to the bladder (sterile H<sub>2</sub>O vs. a KCl solution) and comparing symptoms. Instilling a solution of potassium chloride into the bladder of a patient with IC with a “leaky epithelium” should cause symptoms of urinary urgency, frequency and pain, but not into the bladder of a normal patient. Although the potassium test may only detect 66% of women with IC, it is still a useful simple office diagnostic test.<sup>16</sup>

### **CYTOSCOPY**

Cystoscopy with hydrodistension, the traditional method in the diagnosis of IC, is done under either general or regional anesthesia. During cystoscopy the bladder is filled to 70- 80 cm H<sub>2</sub>O pressure and held at this capacity for 2-5 minutes. Cystoscopic findings of IC are glomerulations and Hunner’s “ulcers” are sought. (Figure 2). Suspicious areas for carcinoma are biopsied. Traditionally, biopsies were routinely taken to look for a high number of mast cells in the bladder muscularis. However, as more research has been done, no characteristic pathologic change has been described for the tissue diagnosis of IC.

### **URODYNAMIC TESTING**

In general full urodynamic studies (cystometrogram, assessment of sphincter function, pressure flow studies, uroflowmetry) are not necessary. However, if after initial screening post void residual volumes are found to be >100cc or if the patient complains primarily of urgency and frequency, then urodynamic testing would be indicated.

### **MANAGEMENT**

#### **Pharmacologic therapy**

##### **Pentosan polysulfate**

Pentosan polysulfate (Elmiron®, Ortho-McNeil, Raritan, NJ) is the only FDA-approved oral medication for the treatment of IC. Its chemical structure is similar to the GAG layer and it works to rebuild “leaky epithelium”. Elmiron has 1/15<sup>th</sup> of heparin’s anticoagulant effects and should be used with caution in women with a bleeding diathesis. Possible side effects include gastrointestinal distress, headache and reversible hair loss. Only 60 % of patients will experience relief of symptoms and relief may not be seen until 4- 6 months of use.<sup>17</sup> Therefore, continued use, despite no change of symptoms at 3 months, is recommended. Other treatment options may be needed during this waiting period as described.

##### **Tricyclic Anti-depressants**

Tricyclic anti-depressants such as amitriptyline and nortriptyline are frequently prescribed “off-label” for IC. Tricyclic anti-depressants (1) reduce bladder urgency by their anticholinergic properties, (2) raise the pain threshold, (3) improve sleep by sedation, and (4) elevate mood. Tricyclics can give prompt relief of symptoms in most patients. They should be used with caution in the elderly because they can cause confusion and electrocardiogram changes. Van Ophoven et al, recently demonstrated in a prospective randomized placebo controlled double blind study that amitriptyline can improve symptoms in IC patients.<sup>18</sup>

##### **Central Nervous System Drugs**

Medications for neuropathic pain are used off label to manage the pain component of IC. Gabapentin, pregabalin, carbamazepine and duloxetine are used. Prescribing neuroleptics is done as for other pain conditions with escalating

doses until desired effect or until side effects become intolerable. Black box warnings should remain mindful.

### Anti-histamines

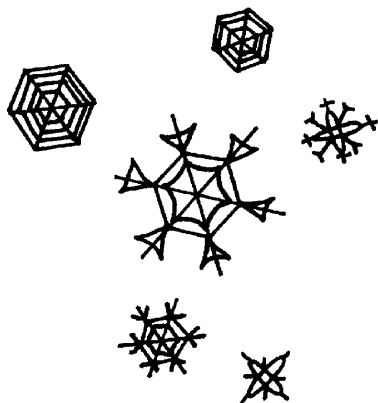
Hydroxyzine is used off-label in the management of IC. Possible mechanisms of action include stabilization of mast cells, anti-cholinergic properties, and a sedative effect. Theoharides and Sant in a 1997 clinical trial demonstrated that hydroxyzine provided an overall 40% reduction of symptoms; in patients with a history of allergies, they found a 55% reduction of symptoms.<sup>19</sup> Hydroxyzine has a sedating effect, thus it can also improve sleep. The allergy/ asthma medication montelukast a leukotriene inhibitor, may prove to be effective as leukotrienes are released from mast cells and thought to play a role in inflammation

### Physical therapy and bladder retraining

Referral to a physical therapist who specializes in treatment of pelvic floor dysfunction can help patients re-educate the levator ani muscles. Women with IC often have levator ani muscle spasm. Bladder retraining can be introduced if symptoms are mild or after symptoms are controlled. Monthly provider visits assist with maintaining compliance, providing motivation, and monitoring progress.

### Intravesical therapy

Intravesical therapy may be needed if initial oral medications cannot control symptoms or if patients on oral therapy have a flare in symptoms. Intravesical treatments are done by instilling medications into the bladder through a catheter. Dimethylsulfoxidole (Rimso-50® Bioniche Pharma USA, Lake Forest, IL)



was FDA-approved for treatment of IC in 1978. Heparin, hyaluronic acid (available only in Canada), BCG (Bacillus Calmette Guerin), Elmiron, anesthetic agents, and “cocktails” of combinations of xylocaine, corticosteroid, heparin, antibiotics, and sodium bicarbonate have all been used. Frequency of installations will vary.

### Surgical treatments

Cystoscopy with hydrodistention causes epithelial damage by mechanical trauma with regeneration of new epithelium and improvement of symptoms. Sympathetic fiber density has been found to be decreased after bladder distension, thus explaining the relief of symptoms after the procedure.<sup>4</sup> Remission generally lasts for 6 months, with a gradual recurrence of symptoms in most patients. More radical surgical procedures such as enterocystoplasty, cystolysis, urinary diversion alone, and urinary diversion into a continent pouch combined with cystectomy, have been used to treat intractable cases of IC. However, these radical end stage procedures have not shown to be beneficial: patients continue to suffer from sensory urgency/ pain.<sup>20</sup>

### Sacral neuromodulation

Sacral neuromodulation (Interstim® Medtronic Corp., Minneapolis, MN) is FDA-approved for patients with urge incontinence, urinary retention and urinary urgency/ frequency, but not yet for IC. It offers a less radical and reversible option than an extirpative procedure and should be considered before an end stage procedure. There are preliminary reports of its use in patients with IC, but the long term success of the sacral stimulation and its management of pain in these patients is still preliminary.<sup>21</sup>

### Primary Care Provider's Role

The primary care provider can diagnose IC and initiate several treatment protocols. Simple treatments can be instituted based on symptoms, physical examination, and screening labs. If sufficient relief is not obtained, the provider can initiate further testing or refer to the appropriate specialist for more special-

ized diagnostics and therapies. The primary care provider should stay involved in the management of these patients as part of a multi-disciplinary team to provide the best overall care for the patient.

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### Disclosure of Financial Interests

The author has no financial interests to disclose.

### Off-Label Usage of Medications

All medications for IC except DMSO and Elniunrion are off-label.

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