

## INTERSTITIAL CYSTITIS

This condition is defined as a syndrome of urgency, frequency and supra-pubic pain in the absence of a positive urine culture or obvious bladder pathology. No specific etiology has been identified yet and no specific methodology exists for diagnosis of this condition.

Studies have demonstrated about 30% of women with chronic pelvic pain in a primary care population have pain of urologic origin. [1] Further, approximately 85% of women who see a gynecologist for pelvic pain have Interstitial Cystitis in addition to or instead of a gynecologic diagnosis. [2] Quality of life, ability to carry on activities of normal daily living and depressive symptoms are far more common in women with Interstitial Cystitis than in the general population. [3] One study showed 80% of chronic pelvic patients not improving after hysterectomy had Interstitial Cystitis. [4]

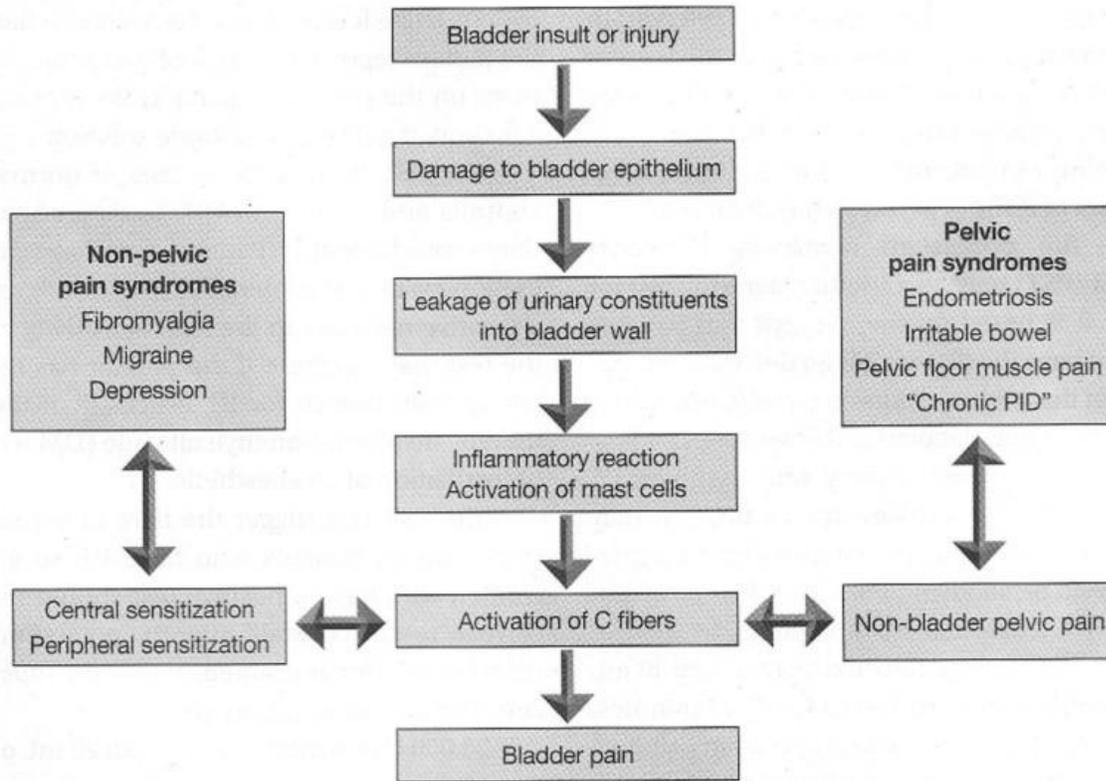
One of the most frequent Urologic disorders responsible for pelvic pain is Interstitial Cystitis / BPS. Other common Urologic causes for pain include urethral syndrome, trigonitis, peritoneal endometriosis overlying the urinary tract, bladder endometriosis, chronic cystitis, bladder carcinoma, radiation cystitis, urethral diverticulum, and stones.

Because of the extensive differential diagnoses for pelvic pain, it is important to implement a multidisciplinary approach to this symptom complex to assure that patients have the most complete evaluation available. It is also important to coordinate and administer the widest range of therapies possible for reduction or alleviation of pain.

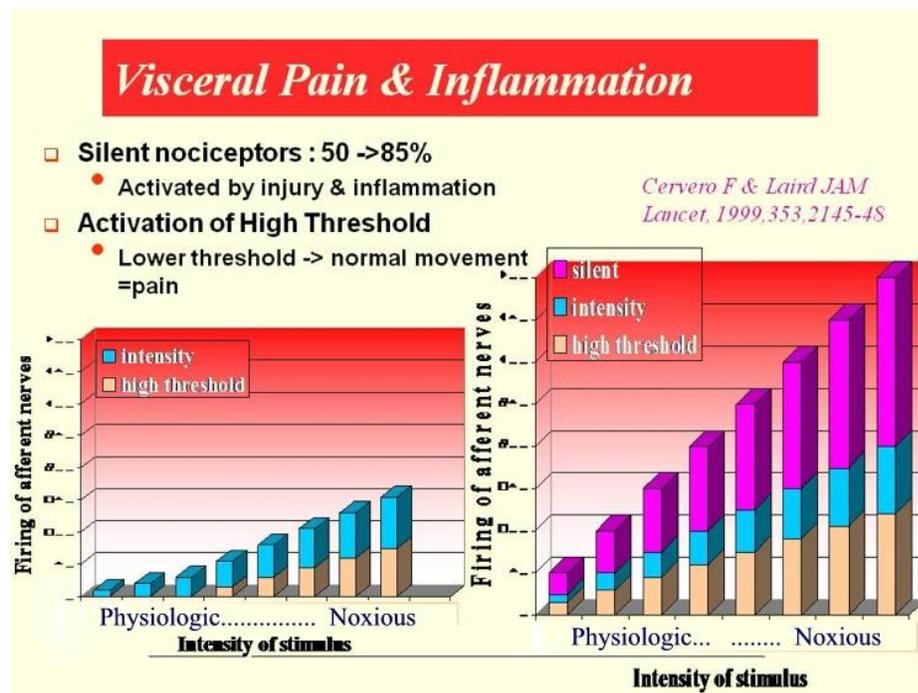
The goal of our Multi-Disciplinary Program is to assure simultaneous evaluation of the various organ systems by our contributing specialists to minimize the length of time from initial presentation to diagnosis and institution of a treatment plan, and in so doing, to minimize the potential for habituation to narcotic analgesics. Our pain program is guided by advice of normative bodies including American College of Obstetricians & Gynecologists (Practice Bulletin 51), International Pelvic Pain Society and others.

Authorities believe an injury to the bladder or significant infection is the inciting factor in development of Interstitial Cystitis / BPS. The bladder lining is damaged allowing fluids to leak into the bladder wall. Inflammatory reaction ensues activating pain receptors in the bladder including receptors that commonly do not respond to bladder distention. Other mechanisms can also activate bladder pain receptors—non-pelvic pain syndromes (fibromyalgia, migraines and depression) and pelvic pain syndromes (endometriosis, irritable bowel syndrome, chronic pelvic infection and pelvic floor muscle pain).

Diagnosis of Interstitial Cystitis / BPS is complicated and more difficult in the early stages of the disease. Time from onset of first symptoms to manifestation of all symptoms ranges from two to five years. [5] Symptoms of Interstitial Cystitis / BPS include: pelvic pain, urinary frequency, discomfort or increased pain leading to urinary urge, nocturia and anterior pain with vaginal intercourse. Early on symptoms may be sporadic leading to suspicion of urinary tract infection.



Patients with IC /BPS, endometriosis, fibromyalgia and other chronic pain syndromes tend to have more pain over time and develop lower threshold to experience pain than their disease-free peers. In the late 1990's studies began to show a relationship between injury, inflammatory response and pain sensitization.



Silent pain receptors (nociceptors) proliferate in these patients and are often activated at stimulus-levels far below those required in disease-free individuals. Over time pain, even at rest, can become significant.

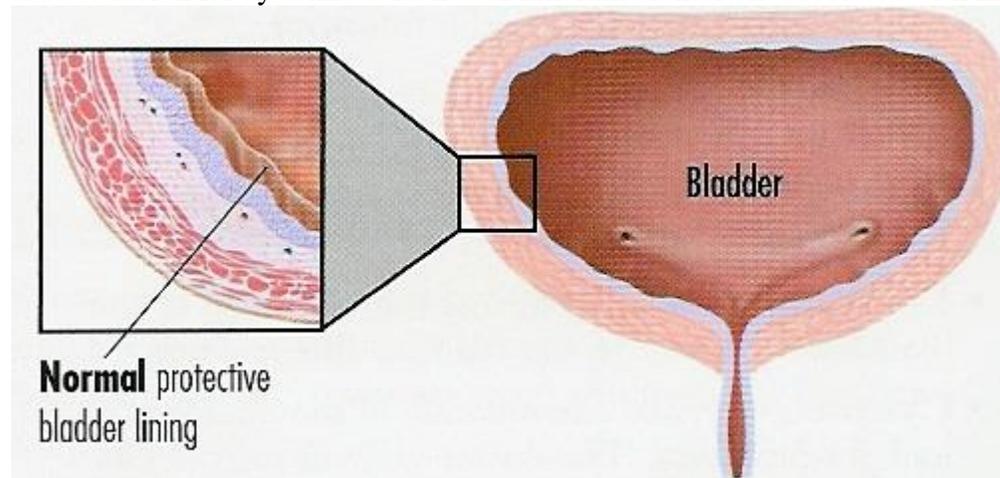
#### Diagnostic Evaluation--

At Desert Women's Care, our initial work-up often includes:

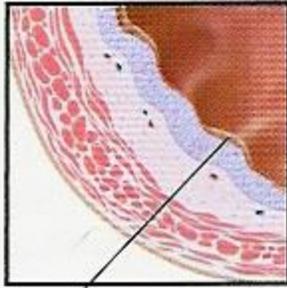
1. Consultation
2. PUF Questionnaire / O'Leary - Sant Questionnaire
3. Urine Tests
4. Blood Tests
5. Cystoscopy with hydrodistention

The PUF Questionnaire (Pelvic Pain and Urgency / Frequency) and the O'Leary-Sant Questionnaire are the two commonly used screening tools used to identify pelvic pain patients in whom Interstitial Cystitis / BPS should be considered. It is also used serially to objectify results of treatment once it has begun.

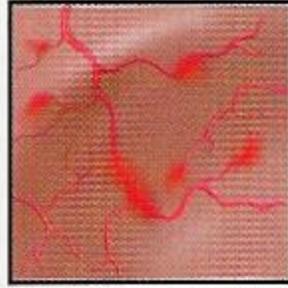
Urinalysis and Urine Culture & Sensitivity are essential to exclude infection as the cause of pain. These studies may also suggest the possibility of stones in the urinary tract (nephrolithiasis). DNA probes for Gonorrhea and Chlamydia are performed to exclude causes of infective urethritis. CBC with differential, Erythrocyte Sedimentation Rate and C - Reactive Protein are used to search for systemic evidence of inflammation often associated with infection.



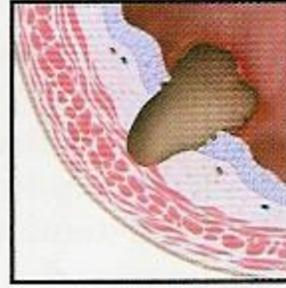
Patients with normal anatomy have a layer of material protecting the uro-epithelium. This is called the GAG layer (composed of glycos-amino-glycans). This layer protects the uro-epithelium and nerve endings from irritants in the urine.



**Thinning** of the protective bladder lining



**Pinpoint bleeding** (glomerulations) on the bladder wall



**Hunner's ulcer** in the bladder wall

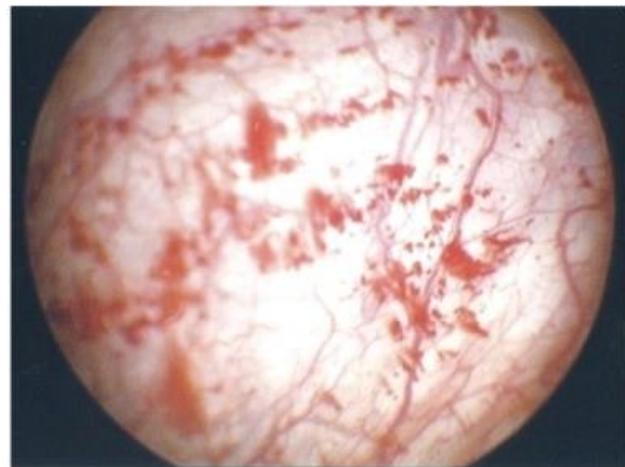
When the GAG layer is thin or absent, it is easier for toxins and other chemicals in the urine to irritate the bladder wall. This is the basis of Interstitial Cystitis / BPS patients having intense bladder pain with the Potassium Sensitivity Test (PST). The first image (below) shows Potassium having no effect on the bladder wall with an intact GAG layer. Because patients with Interstitial Cystitis / BPS have thinned bladder mucosa and areas without an intact GAG layer Potassium directly irritates the nerve endings in the uroepithelium causing a sensation of pain. A local anesthetic is given to patients with a positive test to relieve the pain.

#### CYSTOSCOPY--

Cystoscopy is the key to affirmative diagnosis of Interstitial Cystitis / BPS. Identification of Hunner Ulcers is pathognomonic (below, right). During cystoscopy hydrodistension is also performed. Three to four hundred ml of sterile saline is infused into the bladder until a pressure of 60 - 80 cm of H<sub>2</sub>O is achieved. This is left for up to eight minutes. The bladder is then drained. Glomerulations can be observed as the pressure is relieved after the hydrodistention (below, right).



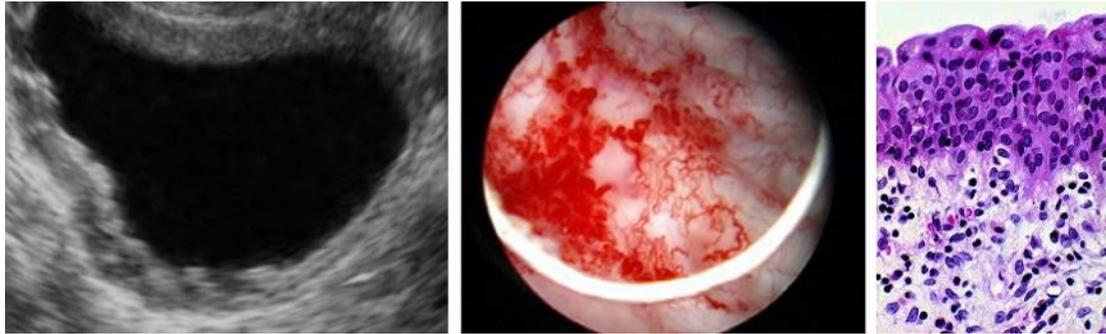
**Hunner Ulcer**



**Glomerulations**

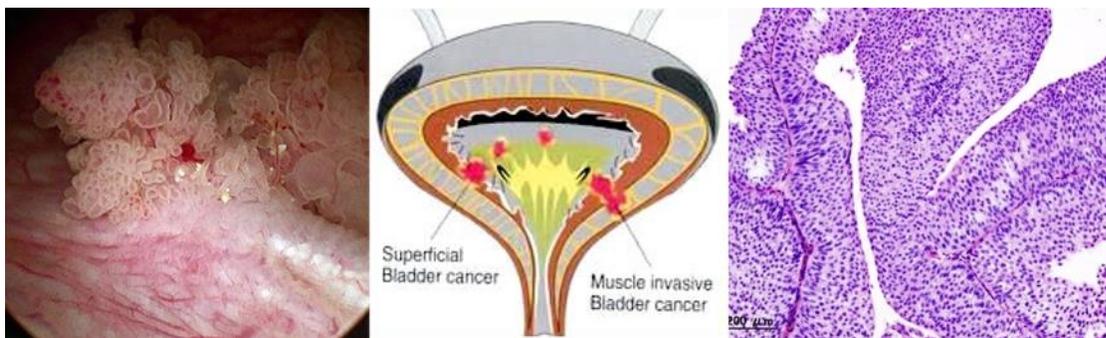
Glomerulations are progressive areas of petichial hemorrhage that evolve over time. Findings of both Hunner's Ulcers and Glomerulations following hydrodistention makes Interstitial Cystitis a highly probable diagnosis.

Cystoscopy will also permit the diagnosis of other common bladder conditions that may cause pain. The most common bladder condition in females is cystitis or urinary tract infection.



The ultrasound image (above, left) shows a thickened posterior bladder wall. Cystoscopy shows injection and hemorrhage (above, middle). The biopsy specimen shows chronic inflammation with lymphocytes, plasma cells and macrophages in the submucosa.

Cystoscopy is also important in the context of chronic pelvic pain to exclude life threatening conditions that can also cause pain, including bladder cancer. Bladder cancer is detectable at the time of cystoscopy. Immediate treatment with a Urologist is required.



**Interstitial Cystitis / Painful Bladder Syndrome Treatment—**

In 2011 the American Urologic Association has developed a six-tiered guideline for treatment of patients with Interstitial Cystitis / Bladder Pain Syndrome. Because not every patient responds to a single intervention, and because various treatments have varying, general risks of use, the goal is to start with the simplest and least risky treatments and progress until a solution for the patient's discomfort is found. [6]

## First-Line Therapy:

1. Application of hot or cold packs over the bladder or perineum
2. Dietary modification to eliminate known irritants from the diet
3. Fluid management: For patients whose pain is worse when the urine is concentrated, vigorous hydration may be of benefit. Conversely, patients with more urgency symptoms may benefit from fluid restriction. Fluid restriction, especially in the evening, will benefit patients with nocturia (needing to awaken and void at night).
4. Pelvic Physical Therapy.

Dietary modification may assist in reduction of pain from Interstitial Cystitis / BPS. The following items are known irritants:

Alcoholic beverages	Guava
Apple juice	Peaches
Cantaloupe	Pineapple
Carbonated sodas	Plums
Chili peppers and sauces	Strawberries
Chocolate	Sugar
Citrus fruits	Tea
Coffee	Tomatoes
Cranberry juice	Vinegar
Grape juice	Vitamin B Complex

The listed items are known to irritate the bladder and cause discomfort in interstitial cystitis patients. Elimination or reduction of these items from the diet is the first line therapy. Paradoxically, Cranberry juice, the well known home remedy for urinary tract infection, actually exacerbates pain from Interstitial Cystitis. Over the counter Preliel (calcium glycerophosphate) prevents dietary-related flairs in about 70% of Interstitial Cystitis / BPS patients.

Pelvic therapy in expert hands is another prong in the initial treatment of women with IC / BPS. Done once to twice weekly over a minimum of six weeks, improvement will be noted in many patients.

## Second-Line Therapy:

1. Pelvic physical therapy is of particular benefit to patient in whom pelvic exam produces the bladder pain or who have pelvic floor muscle tenderness on exam.
2. Oral medications including oral analgesics, antihistamines, amitriptyline or pentosan sulfate.

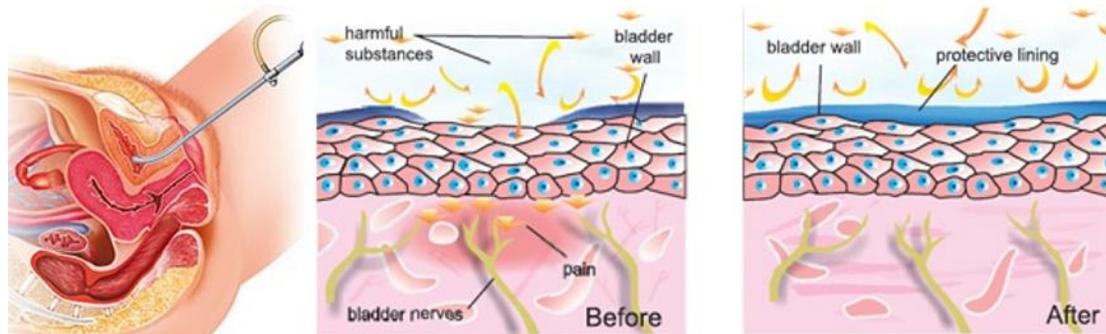
Treatment for patients with Interstitial Cystitis / BPS is variable—numerous agents and treatment algorithms are effective but not all work for every patient. Treatment with oral analgesics is often offered when there is significant pain and compromise to the patient's ability to carry on her

normal daily activities. Initially, non-narcotic analgesics can be used with addition of narcotics if relief is not noted.

Antihistamines are of benefit in improving pain scores by reducing mast cell activation—this benefit has been shown to be most significant in patients suffering from allergies. In one study hydroxyzine reduced symptoms of interstitial cystitis by 40% overall, but by 55% in patients bothered by chronic allergies. [7] Hydroxyzine is started at 25 mg at bedtime but may be increased to 50 mg if needed.

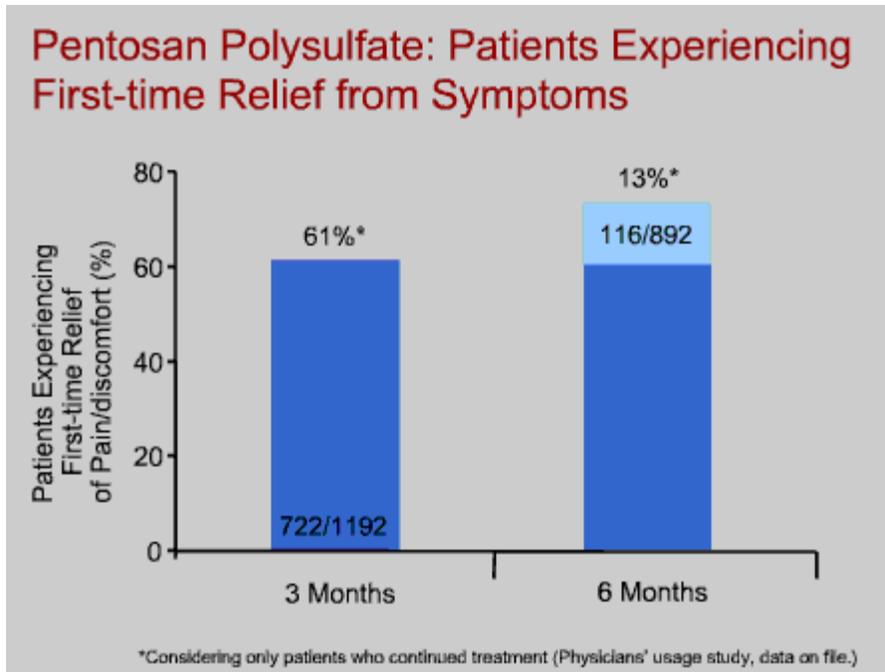
Antidepressants are used both because many chronic pain sufferers are clinically depressed and because various properties are beneficial. Its anticholinergic effects reduce urinary frequency and its sedating properties decrease nocturia. This class of drug (tricyclic antidepressants) also treats neuropathic pain. The most commonly used drugs in this class is amitriptyline used 25 to 100 mg per day. A randomized, double blinded study showed decrease in symptom scores by 31% in amitriptyline treated patients compared with 13% reduction in placebo treated patients. [8] Amitriptyline is started at 10 mg at bedtime and increased weekly in a stepwise manner to 50, 75 and 100 mg.

Pentosan sulfate is one of two FDA recognized treatments for IC / BPS. Pentosan sulfate thickens the GAG layer (glycos-amino-glycan layer) or most superficial lining of the bladder to protect it from irritants in the urine.



At Desert Women's Care we often begin with Elmiron therapy. Available since 1996, Elmiron was the first drug patients could use at home. A dose of 100 mg, three times per day is given. Patients considering this drug need to commit to a minimum therapy interval of three to six months to determine whether the drug will be effective for them. This is because the drug works by building up the bladder lining (uroepithelium) which takes time. At three months a 25 – 50% response rate is observed. [9-10]

Initial experience suggests 61% of users will see a positive response within three months. By six months another 14% of users will have improvement in symptoms. In some cases up to twelve months may be required to note a benefit in women who will ultimately have a long-term favorable response to Elmiron. [11]



#### Third-Line Therapy:

1. Bladder hydrodistention
2. Treatment of Hunner lesions
3. Instillations of Dimethyl sulfoxide (DMSO)

Third-line interventions are more invasive and some require anesthesia or sedation.

Bladder hydrodistention is done in the Operating Room under anesthesia. It is often part of the initial cystoscopy used to make the diagnosis of IC / PBS. The bladder is filled with sterile saline to a pressure of 60 - 80 cm H<sub>2</sub>O for a period of 6 - 9 minutes. Hydrodistention in some patients gives relief lasting up to six months. Serial treatments can be undertaken for the most severe patients to bring meaningful relief.

Treatment of Hunner ulcers requires cystoscopy. These lesions can be excised or electrocoagulated. Alternatively, they can be injected with hydrocortisone.

Another common therapy is intravesical administration of DMSO. This was the first drug approved by the FDA for interstitial cystitis / BPS. DMSO is administered in the physician's office through bladder catheterizations. A 50 ml volume is infused through a small bladder catheter and expelled after 15 - 30 minutes. Premedication with Motrin or Narcotic analgesics may help some patients tolerate the catheterization procedure. A "garlic taste" in the mouth can

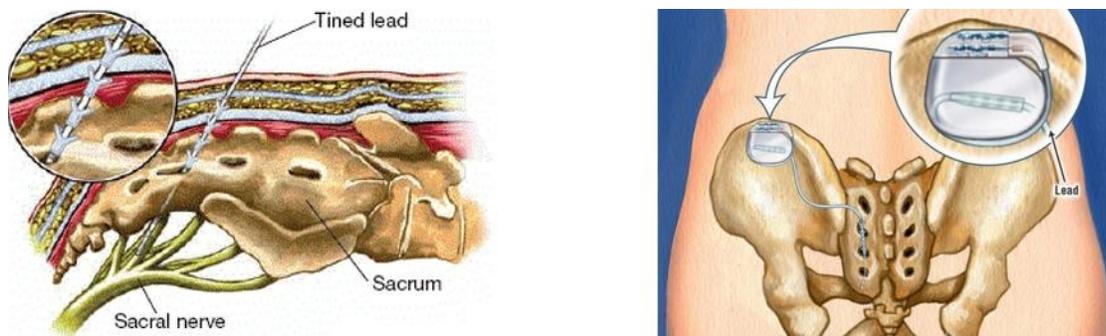
be observed for a day or two after each treatment. The first DMSO study reported significant improvement in patients treated every two weeks for eight treatments. [12] At Desert Women's Care we now treat weekly for six to eight weeks then every two weeks for a total of 3 to 12 months depending on the level of relief achieved.

Catheterization with instillation of local anesthetics combined with heparin has also been shown to be beneficial in reduction of pain. The usual mixture includes 40,000 Units of heparin, 8 ml of 2% lidocaine and 3 ml of 8.4% sodium bicarbonate given every other day for two weeks. Based on the currently postulated pathophysiology of interstitial cystitis, it is felt local anesthetic down regulates bladder afferent nerves and improves pain scores. Local anesthetics can also be combined with DMSO instillations to give more immediate relief.

#### Fourth-Line Therapy:

##### 1. Nerve modulation

The rationale for attempting neuromodulation relies on the relationship between "Over Active Bladder" (OAB) symptoms and Bladder Pain syndrome. The US Food and Drug Administration has approved the use of neuromodulation for treatment of Over Active Bladder. Studies on these individuals have shown a decrease in bladder pain as well as decreased urinary frequency, nocturia and episodes of "urge incontinence." [13-14]



Neuromodulation is a two-step process. In the first step a lead is placed under Fluoroscopic guidance into the sacrum adjacent to nerve roots S2 - S4 (distribution of the pudendal nerve). It is taped in place and a two week trial is conducted with a portable generator transmitting low-energy, electrical current through the lead. If the trial is successful in relieving pain, a smaller generator is implanted for permanent use.

#### Fifth-Line Therapy:

##### 1. Intravesical injection of Botulinum Toxin

##### 2. Cyclosporin A

Fifth-line therapies have been tried with occasional success yet there is no good evidence in the medical literature to suggest how effective these interventions are in large numbers of patients.

Injection of botulinum toxin into the bladder likely diminishes transmission of afferent sensory pain from the bladder to the brain. A single randomized trial compared botulinum toxin and hydrodistention to patients receiving just hydrodistention. [15] In the study significantly more patients had pain improvement in the botulinum / hydrodistention group compared to hydrodistention alone at three months (71% vs 38%). This difference was also maintained at twenty-four months.

Additional investigation is underway to see if these results can be repeated in larger patient populations. Because botulinum toxin injection has little scientific foundation many insurance companies do not cover this type of therapy as yet.

Oral use of Cyclosporine A has even fewer reported patient trials. In a single randomized trial oral Cyclosporin A (oral Cy A) was tested against oral pentosine sulfate (Elmiron). [16] Cyclosporin A was statistically more effective in relieving pain and urinary frequency than pentosan sulfate (75% vs. 19% ). Other observational studies have confirmed the success of Cyclosporin A but suggest its side effect profile is more troubling than that of pentosan sulfate.

#### Sixth-Line Therapy:

##### 1. Urinary diversion and cystectomy

Urinary diversion is the most radical therapy for Interstitial Cystitis / Bladder Pain Syndrome and the one that is irreversible. In short, the bladder is removed and the ureters are connected to a bowel pouch. Patients then void through an artificial stoma in the abdominal wall. It is impossible to guarantee alleviation of pain from this procedure and centers offering it only do so to patients with marked impairment in their quality of life.

#### Summary--

It is well known that interstitial cystitis occurs commonly in patients with other pain syndromes. At Desert Women's Care we believe in a Multi-Disciplinary evaluation and treatment of chronic pelvic pain. Thorough evaluation will assure all causes of a patient's pain are identified and treated expediently.

**REFERENCES**

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## DESERT WOMEN'S CARE I.C. ORDER SHEET

ORDER                      ACTION

**Office Based:**

\_\_\_\_ GC and CT probes  
\_\_\_\_ CBC with differential  
\_\_\_\_ ESR and CRP  
\_\_\_\_ UA with C&S

\_\_\_\_ PUF Questionnaire

**Imaging Studies:**

\_\_\_\_ CAT Scan of Urinary Tract with contrast to r / o nephrolithiasis or  
other abnormalities  
\_\_\_\_ Ultrasound of kidneys

**Surgery:**

\_\_\_\_ Schedule cystoscopy, possible bladder biopsy, possible  
hydrodistension, possible retrograde

**Consultations:**

\_\_\_\_ Referral to Urology  
\_\_\_\_ Referral to Psychiatry  
\_\_\_\_ Referral to Pain Management  
\_\_\_\_ Referral to Psychology / Psychiatry