Clinical Communiqué

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Interstitial Cystitis

A Clinical Spectrum

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Editorial Choosing the right treatment

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In this issue, Dr. Jack Barkin's article outlines very well the generally accepted concepts and strategies in managing patients with interstitial cystitis (IC). But IC is not a definable disease associated with proven curative treatments. It is a clinical syndrome, a constellation of symptoms in which the diagnosis is fundamentally based on excluding all other causes. More importantly, it is a spectrum of symptoms that ranges from mild to very severe. A rigid treatment plan is not only inappropriate, but may cause more harm than good. Most physicians do tailor their treatment plan to the severity of presenting symptoms — below is my personal approach to this very variable symptom-based syndrome.

Dr. Barkin discusses the various diagnostic steps in evaluating a patient suspected of having IC and describes many helpful tests for ruling out other causes of the genito-urinary symptoms or characterizing the patient's condition. But generally, treatment decisions are not solely based on tests. Once we have excluded other possible etiologies, we need to evaluate the variability of symptoms, using visual analogue scales (0-10) — to assess the degree of pain and urgency — and a voiding log to document the degree of frequency and nocturia. The severity of the symptom complex is determined by assessing the impact of IC on the patient's quality of life. Ask 3 simple questions:

- **How unhappy or distressed would you be if you had to live the rest of your life with the symptoms you have now?**
- **How much do you think about your symptoms during waking hours?**
- **How much have your symptoms kept you from doing what you would like to do during a normal day?**

In our urology practice we tend to use the O'Leary-Sant Symptom Score and Problem Index in clinical research trials. The KCl test and urodynamic assessment are also used in all these trials, but only for selected cases in our clinical practice. Cystoscopy — when necessary — is done with local anesthesia, biopsy is rarely performed and, except for some patients who have had a KCl test, we usually do not use these procedures to make treatment decisions.

Essentially, the decision on a therapy regimen is based not on the degree of symptoms, but according to their impact on the patient's quality of life. Regardless of severity, all patients are first given a conservative patient-oriented treatment plan. This involves educating them on IC (the more patients know, the better they feel about themselves and the more willing they are to be treated conservatively), and they are coached on bladder retraining, developing coping skills, modifying their diets (extremely important), avoiding stress and anxiety-provoking situations, and using analgesics, phenazopyridine (Pyridium®) and anticholinergics (Detrol®, Ditropan XL®) during flare-ups.

Mild IC. **Some patients, after receiving the "empowering" diagnosis of IC, feel they can cope with their symptoms — they do not think a great**

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deal about their symptoms and can function reasonably well. For these mild cases, the conservative treatment plan mentioned above is often adequate.

Moderate IC. If symptoms cause moderate distress — they preoccupy patients much of the time and prevent them from performing many of their normal day-to-day activities, then we suggest some form of medical therapy, usually oral. We start with pentosan polysulfate (Elmiron®), adding amitriptyline (Elavil®) for those with moderate pain as the major symptom and hydroxyzine (Atarax®) if there are multiple allergies (seasonal, food or other). One medication is initiated at a time; if the therapy is not providing enough relief so that the patient experiences minimal interference in daily living, we progressively add a second or a third (multimodal therapy).

Severe IC. Patients who are severely distressed by their symptoms, cannot stop thinking about their condition, who experience significant interference with their ability to do almost any type of leisure and employment activity need a much more aggressive treatment approach. They are immediately advised to begin all the conservative measures described above, along with instituting intravesical therapy with a combination DMSO (RIMSO-50®) and a heparinoid (such as heparin sulfate or hyaluronic acid). In addition, a long-term therapeutic strategy is tailored for the each patient according to the individual circumstances. This may involve any or all of the treatments described for the moderate patient (pentosan polysulfate, amitriptyline and/or hydroxyzine) or may involve long-term patient-administered intravesical heparinoid therapy. Very severe cases that do not respond to this therapeutic approach are offered hydrostatic bladder dilation under general anesthesia or one of the experimental therapies that we are evaluating at our Queen's University Interstitial Cystitis Research Clinic (Bacillus Calmette-Guerin, alkalized lidocaine or neuromodulation therapies).

Managing IC can be challenging, but treating patients as individuals and addressing the affect of symptoms can improve their quality of life and ease discomfort.

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A mucosal layer of glycosaminoglycans (GAGs) lines the bladder wall and acts as a buffer — it is very hydrophilic, and prevents the binding of certain bacteria, ions, crystals and chemicals to the bladder wall. The hypothesis is that a bladder insult (such as an improperly treated infection) may cause a defect in this protective layer, allowing the submucosal leakage of urinary solutes and irritants. The muscle and nerve fibres of the submucosal layer then become stimulated by the noxious substances, resulting in inflammation. This, in turn, leads to the common IC symptoms, and eventually remote pain secondary to the upregulation of spinal nerve fibres. In many patients, release and activation of mast cells with the concomitant histamine release and other secondary side effects also occurs.

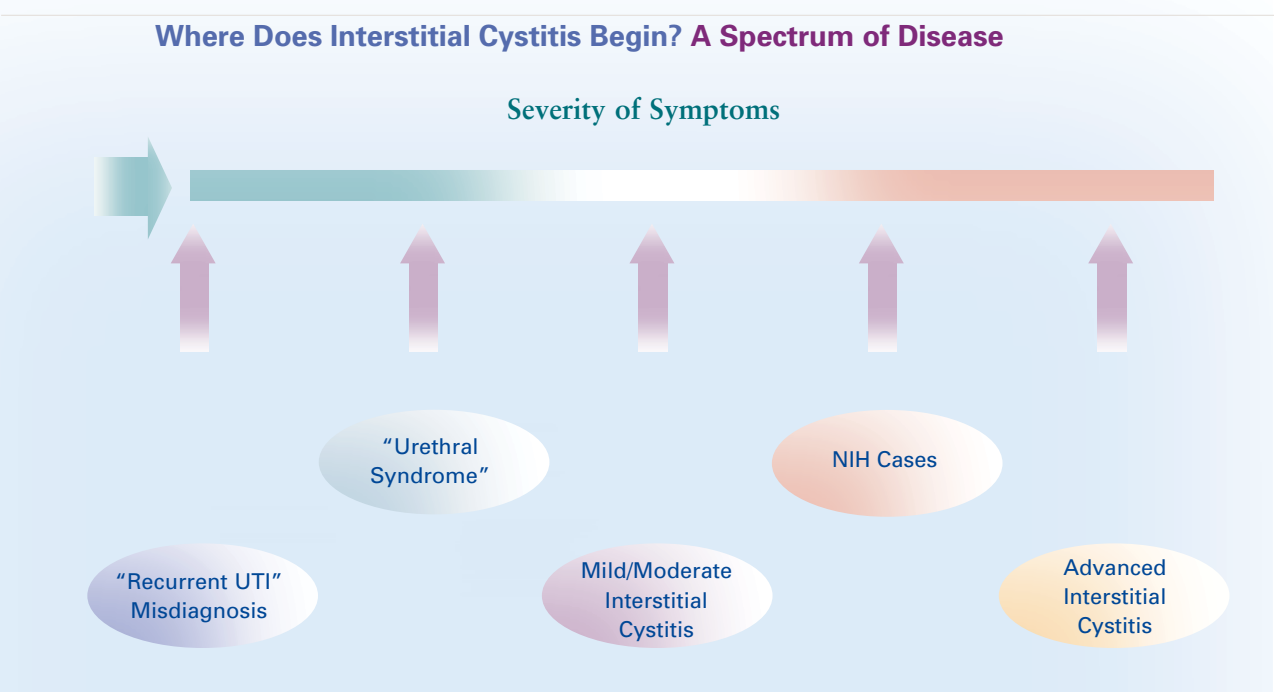
Diagnosis

The estimate today is that there are between .5 and 1 million sufferers in the U.S. and a proportionate number in Canada, although there are tens of thousands that have probably not been diagnosed.[1] Because the criteria for and diagnosis of IC are not yet totally standardized or accepted, the prevalence of the disease has been hard to accurately estimate. If we rely on the National Institutes of Health (NIH) diagnostic criteria for IC, a great number of patients will be denied proper diagnosis until their symptoms and signs become very severe. The NIH criteria were developed as a tool for clinical trials rather than for diagnostic use. Instead, consider that any patient with abdominal/pelvic pain, urinary frequency and urgency, and negative urine cultures has IC until proven otherwise.

An apparent continuum in the development of IC makes the diagnosis confusing, especially early on when the symptoms may be mild. It is at this stage that a myriad of labels are used, such as chronic cystitis, urethral syndrome, chronic pelvic pain syndrome, prostatitis, vaginitis and so on. Figure 1, page 3 illustrates the spectrum of disease.

The earlier the diagnosis of IC, the faster the response to treatment. To prevent escalation of the condition, the goal is to make this determination sooner rather than later. Specific tools (see Table 1, page 4) are used to rule out other problems, and make it relatively easy to make the diagnosis. The approach is to do a proper

Figure 1 Continuum of Interstitial Cystitis



history, physical examination, appropriate investigations and, in some cases, the potassium sensitivity (KCl) test. Cystoscopy is only necessary in certain situations, such as when bladder cancer is suspected. Hydrodistension can be both diagnostic and therapeutic, in the short term.

Methods of investigation

Voiding log

The voiding log is a very simple and useful tool for the clinician and the patient, providing a basis for diagnosis and measurement of response to therapy. Studies have shown that there is difference in the voided volume and frequency in IC vs normal patients. Most "normal" people average 6.5 voids per day while the IC patient averages 16.5.[2] If an IC patient starts with a daily voiding frequency of 24 and nocturia times 8, they will be very grateful to recover to the level where that they are getting up only 2 to 3 times at night and voiding 8 to 12 times in the day — a good therapeutic response. Patients only have to record their intake and output for 48 hours, so it is not a burden to complete the log.

Urodynamic testing

Urodynamics are usually unnecessary unless there is concern that the patient has a neurogenic bladder. This is unusual, especially in the younger or middle-aged patient. There can be some confusion with the "overactive bladder" diagnosis, but in that situation there is usually no pain and no response to KCl. Urodynamics often reveal small bladder capacity and a sense of urgency. The average bladder capacity is 110 mL with over 95% of IC patients feeling increased sensory urgency at <100 mL.[3]

O'Leary-Sant IC Problem and Symptom Indices

It is always important to try to quantify the patient's symptoms — such as pain and voiding complaints — as well as determine how bothersome these are. The O'Leary-Sant Interstitial Cystitis Problem Index and the Interstitial Cystitis Symptom Index (Table 2, page 5) were developed to do this — and they help evaluate if IC is present. In the O'Leary et al study, almost all patients with IC had a score greater than 5 for each test.[4] Results of these self-administered questionnaires provide a way of grading the patient with respect to severity of symptoms. Patients can then be stratified by total score, which will help guide appropriate treatment.

Quantifying results also allows a baseline comparison for assessing response to therapy.

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Table 1 Diagnosing IC

Several tests are useful in determining whether IC is present — not only can they lead to a proper diagnosis, but they may help rule out other causes of the patient's symptoms, such as bladder cancer or urinary tract infection.

Diagnostic tools

- Urine: urinalysis, culture, cytology
- Voiding log
- O'Leary-Sant IC Symptom and Problem Indices
- Potassium sensitivity (KCl) test
- Urodynamics
- Cystoscopy/Hydrodistention/Biopsy

They are complementary and important — it is often the problem index that will dictate the need for treatment and the inclusion of more modalities rather than the symptoms themselves.[5]

Potassium sensitivity test

Dr. C.L. Parsons, who first promoted the concept of epithelial permeability, devised a simple potassium sensitivity test to assess the integrity of the GAG layer.[6] IC patients show a tendency towards mucosal leaking, which allows the urinary solutes, such as potassium, to reach the submucosal layer where it can irritate the sensory nerves and muscles, causing pain and urgency.

Two solutions, first sterile water and then a KCl solution (40 mEq KCl to 100 cc of sterile water), are placed in the bladder at separate times. The response of pain and urgency to each solution is measured on a scale from 0 to 5, with 5 being the worst. A score of 1 to 2 is mild, 3 to 4 moderate and 5 severe. The test is considered positive if the patient reports an increase in pain and/or urgency of 2 or more to the KCl preparation. Between 70% and 90% of IC patients test positive.7 More pain is usually experienced as the disease progresses.

Cystoscopy and hydrodistension

Studies have shown that hydrodistension can increase the bladder capacity of patients and provide some symptomatic relief, but it only lasts about 6 months. Even under anesthesia, IC patients have a much lower bladder capacity compared to normal (575 mL vs 1,115 mL).[8]

If a Hunner's ulcer is found, the patient is usually suffering from more severe symptoms and will have a smaller bladder capacity. Glomerulations may be seen, but their absence does not preclude the diagnosis of IC if the symptoms and history are suggestive. In the major study of the Interstitial Cystitis Data Base (ICDB), 75% of the patients had bloody effluent and over 91% had at least some glomerulations. This did not correlate to the degree of symptoms.[9]

In a recent study, 379 women who met the ICDB criteria were evaluated. Almost 90% of these patients were believed by experienced clinicians to have clinical IC. However, if the clinicians applied strict NIH — and not the ICDB — criteria, including cystoscopy, more than 60% of the patients felt by the clinicians to "definitely or likely" have IC would not have been diagnosed with IC.[10]

This is another example of how the NIH criteria are not practical when trying to diagnose IC. Cystoscopy can be helpful to rule out bladder cancer and other significant pathology, but a negative result should not rule out IC.

Treatment and management

The principles of IC therapy are directed at the three areas of major pathology:

- address epithelial/mucosal dysfunction
- modulate neural activity
- stabilize mast cells

The treatment of IC is based on the stage of disease and the duration, multiplicity and severity of symptoms. The key is to recognize it early so that the symptoms do not become too severe and bladder damage is minimized. The type of therapy often depends on how far the condition has progressed.

Lifestyle

Patients must modify their lifestyle to help manage IC. In general, tea, coffee, alcohol, spicy foods, smoking, stress, travel, high potassium foods and lack of rest can aggravate IC and should be avoided. Patients need to be aware of what foods or activities cause their flare-ups.

Oral medication

Pentosan polysulfate – PPS (Elmiron®)

Pentosan polysulfate (Elmiron®), or PPS, is the only approved oral medication for the treatment of IC. At least 5 double-blinded placebo

controlled studies have proven its efficacy, all of which demonstrated that with 100 mg tid, the patients were able to achieve significant pain relief over placebo.[10-14]

Although its mechanism of action is still unknown, the theory is that PPS rebuilds the damaged bladder wall and acts as a buffer to prevent permeability, preventing the inflammatory response.

Since Elmiron proved effective in managing the pain and bladder discomfort of IC, the next question was whether a higher-than-standard dose (100 mg tid) would first, be safe, and second, provide for a more rapid or greater response in symptom relief without increased side effects. This spawned the Elmiron dose-escalation study. Over 300 patients were evaluated in a blinded manner as to their daily dose of 300, 600 or 900 mg of PPS per day for 8 months.

The results were interesting. Improvement in IC symptom scores occurred as early as 4 weeks. At the end of the trial, almost 80% of the patients had achieved a significant response — however, the response curve had not yet plateaued. This emphasizes the need for the patients to stay on Elmiron as long as possible. They should not be discouraged if there is no improvement for up to 6 months, and once symptoms start easing, maximum response will be obtained beyond 8 months. The duration of therapy is more important than the dose. There was no significant difference, except for the incidence of diarrhea, in the side effect profile regardless of the dosage.[15]

Other drugs

Antihistamines: If there is a significant history of allergies, or if the flares seem to be worse during allergy season, the use of histamines may be appropriate. This will inhibit the mast cell release of histamines and may diminish bladder wall inflammation. Antihistamines can also have a sedative effect, which might improve patients' sleep.

Antidepressants: Two different families of antidepressants have been utilized for IC — tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Both have antihistaminic activity, provide some sedative effects, block the reuptake of serotonin, have anticholinergic actions, and may ease pain. There have been no controlled, blinded studies on either family of drugs.

Table 2 The O'Leary-Sant IC Indices[4]

Problem Index

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

Q1: Frequent urination during the day?
Q2: Getting up at night to urinate?
Q3: Need to urinate with little warning?
Q4: Burning, pain, discomfort or pressure in your bladder?

____ no problem = 0
____ very small problem = 1
____ small problem = 2
____ medium problem = 3
____ big problem = 4

Total score: ____/16

Symptom Index

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

Q1: Felt a strong need to urinate with little or no warning?

____ not at all = 0
____ less than 1 time in 5 = 1
____ less than half the time = 2
____ about half the time = 3
____ more than half the time = 4
____ almost always = 5

Q2: Urinate less than 2 hours after urinating?

____ not at all = 0
____ less than 1 time in 5 = 1
____ less than half the time = 2
____ about half the time = 3
____ more than half the time = 4
____ almost always = 5

Q3: Get up at night to urinate?

____ not at all = 0
____ 1 time = 1
____ 2 times = 2
____ 3 times = 3
____ 4 times = 4
____ 5 times = 5

Q4: Experienced pain or burning in your bladder?

____ not at all = 0
____ a few times = 1
____ fairly often = 2
____ almost always = 3
____ always = 4

Total score: ____/19

Adapted from O'Leary MP, Sant GR, Fowler FJ Jr. et al. The interstitial cystitis symptom index and problem index. *Urology* 1997;49(suppl. 5a):58-63.

Anticholinergics: If the problem is urinary frequency, anticholinergics or bladder relaxant drugs may be helpful. Usually the pain must be controlled before these drugs will work. A combination of medications may be used to gain more of an effect. If, however, the pain of urgency has not been controlled, the urge to void will still be there, and the drugs may slow the process, which could also be uncomfortable.

Neuroleptics: It has been postulated that there is an upregulation of the sensory nerve fibres in IC. Neuroleptics — such as gabapentin (Neurontin®), phenytoin sodium (Dilantin®) and carbamazepine (Tegretol®) — may "down-regulate" the overstimulated nerve fibres, resulting in less pain and urinary frequency. They are usually added in very severe cases.

Analgesics (Systemic/Urinary): It is crucial to relieve the pain of IC. Pain and urgency prevent patients from working and can destroy their quality of life. Combinations of anti-inflammatories — sometimes coupled with the narcotics and stronger analgesics — often provide relief. For flares that occur on a chronic basis, urinary analgesics, such as phenazopyridine (Pyridium®), may be helpful.

The key to managing IC is to treat it early and appropriately — a multimodal approach is usually necessary

Narcotics should only be used in severe acute situations and ultimately tapered if possible. These strong analgesics are sometimes used in combination with skeletal muscle relaxants.

Miscellaneous agents: Patients sometimes get a reflex type of retention or dysfunctional voiding where they want to void but feel some resistance. They may also develop detrusor-sphincter dyssyneria, voiding against a tight or spastic sphincter; alpha blockers may help reduce bladder neck and/or sphincter spasms. Potassium citrate can actually bind up some potassium and alkalinize the urine which may decrease acid and the resulting burning or irritation in the bladder.

Other therapy

Intravesical agents: Intravesical therapy, unfortunately, has no proven long-term efficacy but may be helpful initially. Agents commonly used include dimethyl sulfoxide (DMSO), heparin, hyaluronic acid, hydrocortisone, lidocaine and sodium bicarbonate. Intravesical heparin continued after DMSO therapy prolongs the initial response to DMSO. One of the only studies to address this suggests that continued heparinoid therapy (such as heparin intravesically or perhaps pentosan polysulfate orally) can prolong the initial — and usually quick — response obtained with intravesical DMSO.[16] This underlines the rationale behind starting and continuing Elmiron in patients treated with intravesical agents.

Some studies on Bacillus Calmette-Guerin (BCG), however, have been interesting, showing a reasonable symptom response after 6 weeks without significant side effects.[17] At this time, BCG should be considered experimental therapy only until the real risks and benefits are assessed in an ongoing clinical trial.

Bladder hydrodistention: Under general anesthesia, the bladder is distended using water pressure to a level of 100 cm. The bladder remains full for 2 minutes and then emptied. A Hunner's ulcer, glomerulations or a bloody effluent may be present, any of which suggests IC. Sometimes a biopsy is performed at that time to look for inflammation and mast cells. The process can sometimes temporarily relieve the symptoms of urgency and frequency, but is short-lived.

Nerve stimulation: The upregulation of the sacral nerve fibres causes the pain to be referred beyond the bladder. Stimulation of the sacral nerves may alleviate pain and frequency. Temporary sacral nerve stimulators (SNS) can be implanted and tested. In one study, 13 out of 15 patients (87%) had a positive response with a decrease in nocturia, frequency and urgency with a concomitant increase in volumes.18 This is the only clinical trial in which the results are outlined in detail; however, it is only a pilot study. For very severe symptoms, a permanent SNS may be considered.

Physical therapies: Other methods of managing symptoms include physiotherapy, such as pelvic floor massage, trigger point therapy, bladder retraining and instruction in muscle strengthening (e.g. Kegel and pelvic floor exercises). Biofeedback, ultrasound, acupuncture, yoga and other adjunctive techniques can often ease patient discomfort.

Surgery: If symptoms cannot be relieved with a combination of any of the above modalities, surgery — cystectomy and some type of urinary diversion — may be offered as a last resort.19 These patients must be experiencing debilitating levels of discomfort. Even after surgery, however, pain may still be present because of the upregulation of the spinal nerves distant from the bladder.

The right treatment at the right time

The key to managing IC is to treat it early and appropriately — a multimodal approach is usually necessary. This can be tapered after 8

months if the patient is stable. It is crucial that patients taking Elmiron stay on therapy for at least 6 months before gauging response. With time, most IC patients know what works best for them.

Interstitial cystitis can be easily diagnosed: the symptom complex of pelvic pain, urinary frequency and urgency, combined with negative urinary cultures and cytology is IC until proven otherwise. With the right medications or combinations of therapy for the proper length of time — and with early intervention — the chances of symptom control and possibly cure are very high.

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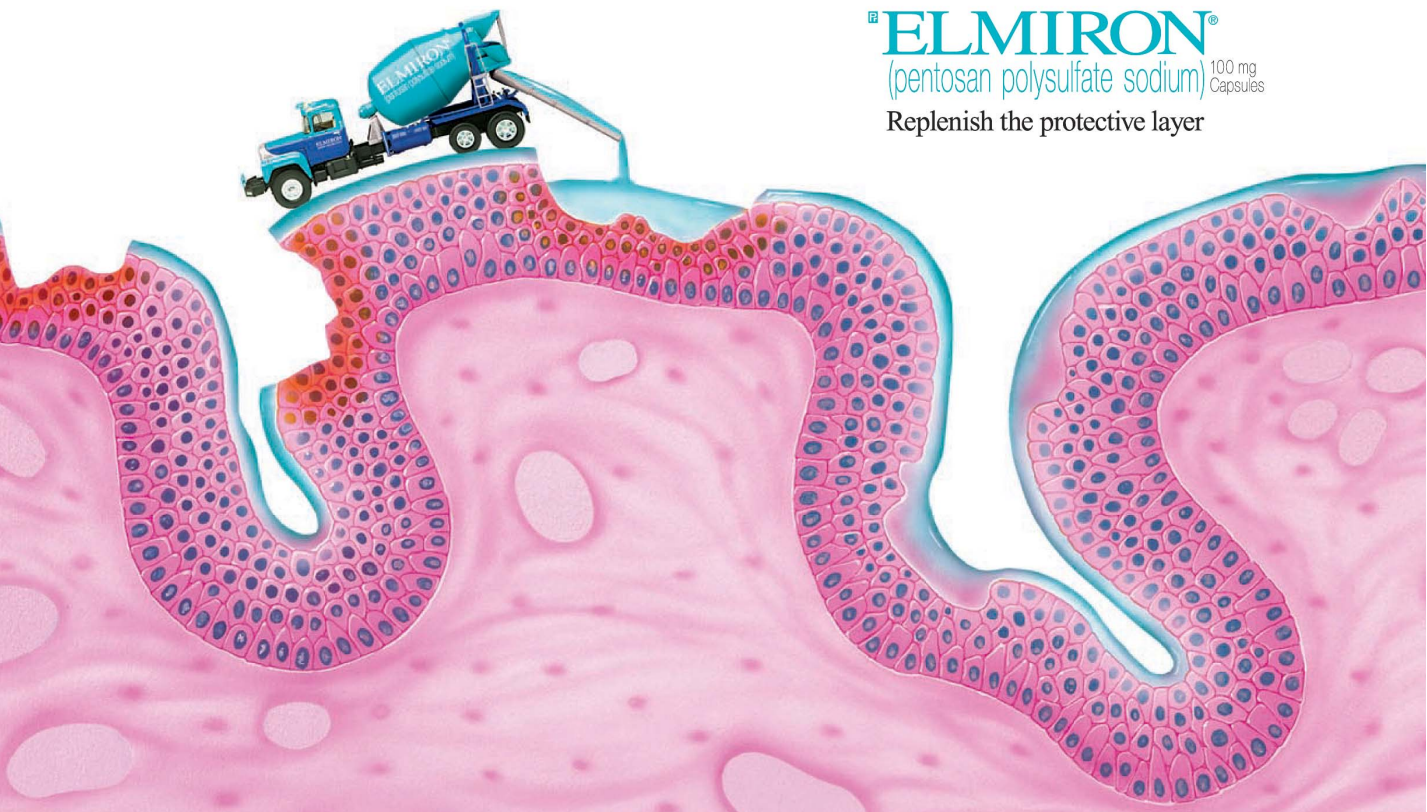

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