

Interstitial Cystitis

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1. What is Interstitial Cystitis

What is Interstitial Cystitis?

- Skene (1887)-inflammation that destroyed the urinary bladder “mucous membrane partly or wholly and extended to the muscular parietes.” Skene coined the term “interstitial cystitis.”

Continued.....

- Hunner (1915) popularized the disease with the description “a peculiar form of bladder ulceration.”
- Hand (1949) gave the 1st epidemiological description of IC as “widespread, small, submucosal bladder hemorrhages and significant variation in bladder capacity.”

Continued.....

- Messing and Stamey (1978) – “nonspecific and highly subjective symptoms of around the clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia” (included those without ulcerations.

Continued.....

- NIDDK (1990) Pain associated with the bladder or urinary urgency and glomerulations or Hunner's ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids/day, 1 void/night and capacity <350cc.

Continued.....

- NIDDK (revised in 1997)- unexplained urgency or frequency (7 or > voids/day) or pelvic pain of at least 6 months in duration in the absence of other definable etiologies.
- NIDDK study indicated that >60% of IC cases could be missed if strict criteria are followed.

Continued.....

- NIDDK/International Cystitis Association (ICA) (2003) joined and begin to establish new criteria based on extensive clinical evidence.
- 3rd International Consultation on Incontinence (2004) terms Painful Bladder Syndrome and IC as same.

And now.... NIDDK/ICA

- A diagnosis of exclusion based on H&P, Urinalysis and culture, and the use of IC symptom and bother questionnaires.
- A symptomatic diagnosis based on the presence of three key symptoms: pain, urgency, and frequency. Pain is the most consistent and disabling for IC patients.

How do you define IC?

- IC can present with many faces.
- Urgency and frequency vary.
- Pain thresholds vary among patients.
- Pain may be described as pressure.
- Dyspareunia is often present.

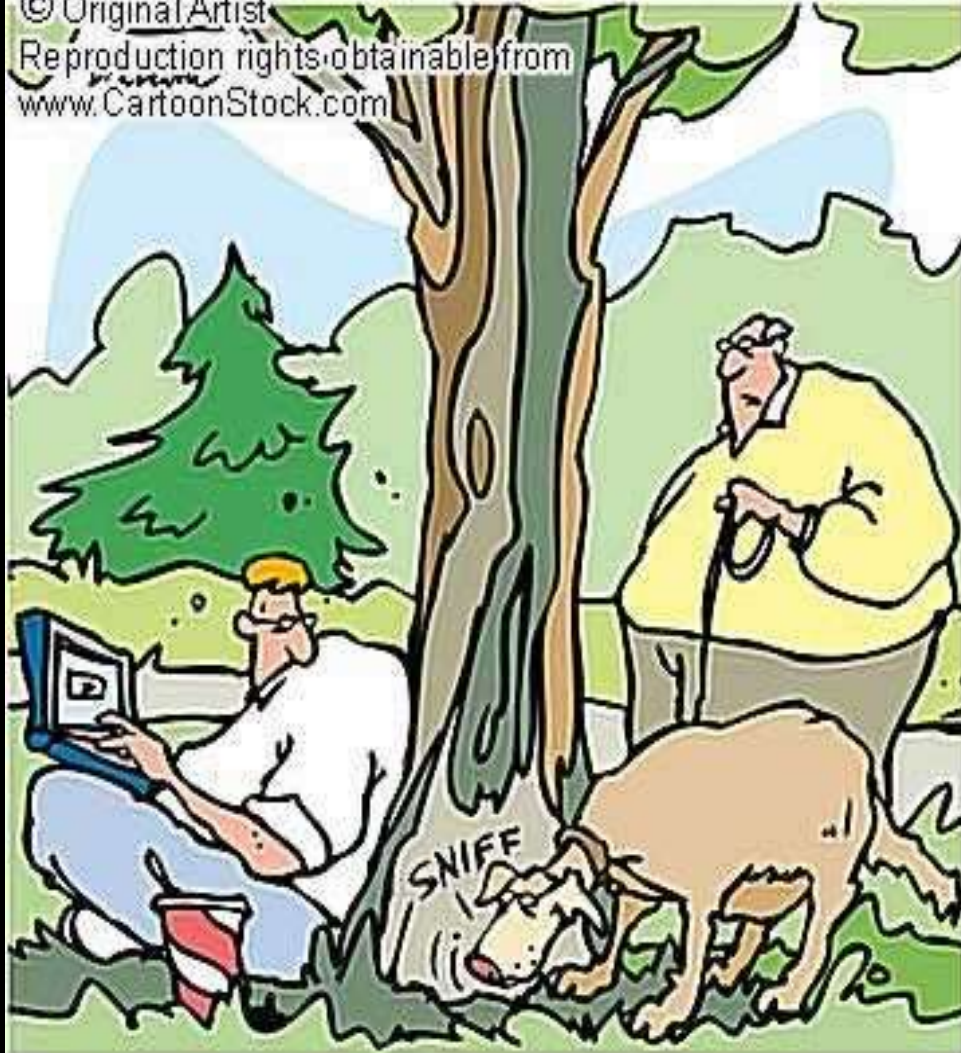
PBS and IC defined by International Continence Society and European Association of Urology

- PBS: Suprapubic pain related to bladder filling, accompanied by day and night frequency in the absence of infection and other pathology.
- IC: Same as above but also with typical cystoscopic and histologic features.

(American Journal of OB/GYN (2002) , 187(116-126)

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"Relax, he's just checking his p-mail."

2. The Challenges of Interstitial Cystitis

Challenges of IC

- No universal definition
- Lack of markers such as radiographic, lab, biopsy or serologic findings for IC.
- Unknown etiology!
- Often misdiagnosed as OAB, endometriosis, recurrent UTI's.
- Usually negative UA and C&S –may or may not respond to antibiotic therapy.

Major Problems

- Diagnosis of exclusion
- Lack of consensus
- Overlapping conditions
- Inconsistent symptoms
- Lack of understanding by healthcare providers – no interest, frustration, outdated training.

Incidence

- 700,000 to 1 million people diagnosed with IC, but many go undiagnosed.
- 90% of diagnosed are women
- 25% presenting to OB/GYN for CPP/PID may have IC.
- Related to fibromyalgia, IBS, Type I Diabetes, Parkinson's, autoimmune disorders.
- Average patient is not diagnosed for 5-7 yrs.

(Parsons, J; Roth, K; and Sant, G (2007) Urology 69 Suppl 4A)

Etiology

- UNKNOWN
 - Uncertain pathophysiology
 - Lack of standardized methodology, study sizes and demographics due to variations in signs and symptoms.
-
- Parsons, J; Roth, K; and Sant, G (2007) Urology 69 Suppl 4A

Proposed Etiologies

- Altered bladder mucosal permeability or deficiency of glycosaminoglycans (GAG layer)
- Immunological/Autoimmune Disorder
- Mast cell activation (Primary or concurrent)
- Neuroinflammatory condition
- Pelvic floor muscle dysfunction
- Genetic Predisposition

Possible Initiators of IC

- Allergic Triggers
- Immunologic Triggers
- High tone Pelvic Floor Dysfunction
- Occult Infection (e.g. H-pylori)
- Recurrent UTI's
- High acid system

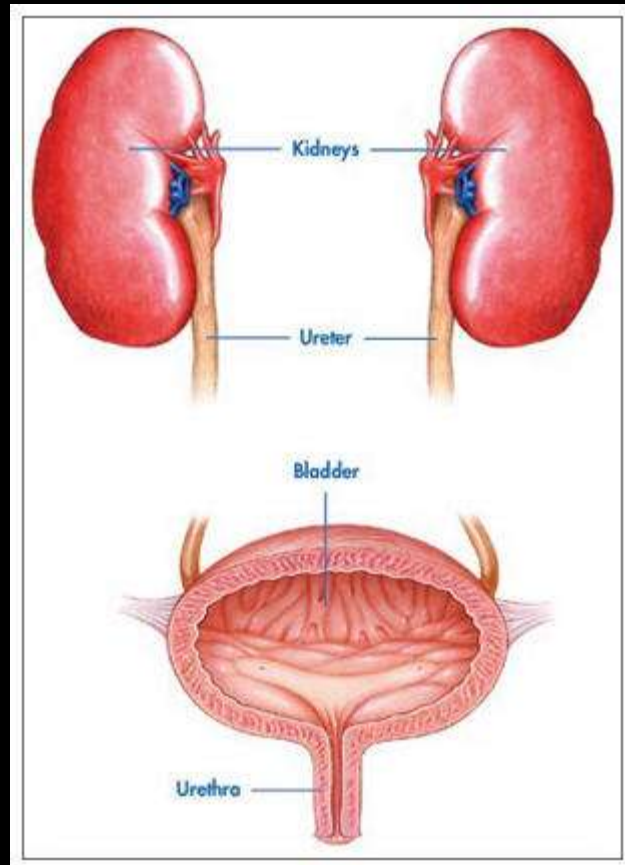
Impact of IC on the Patient

- Quality of life is significantly impacted – the patient, family, friends and work.
- Frustration and feeling of not being believed or not mattering.
- Sleep deprivation and increased incidence of depression.
- Average age of dx is 40, 25% of women with IC now under 30. But, men and women, and all ages.

3. Anatomy

- Anatomy of the Bladder
- Associated Anatomy

The urinary System



- The kidneys produce urine, a fluid containing toxic substances and waste products. From each kidney, the urine flows through a long thin tube, the ureter, to the bladder, a pelvic organ that stores and empties urine. The external urinary sphincter is the primary muscle that prevents urine from accidentally leaving the urinary bladder -- it is the muscle you squeeze to stop the flow of urine in midstream. The bladder funnels into another tube, the urethra.

How urine affects the bladder.

- The bladder is a muscular sac for storing urine. Urine is made of waste products, or chemicals, that have been filtered from the blood by the kidneys. Some of these products, such as potassium, can be quite high in concentration and can irritate certain body tissues. Since the bladder may store urine for several hours, it has a protective lining to shield its wall from these chemicals. This protective mucous lining is called the glycosaminoglycan (GAG) layer.

GAG Layer

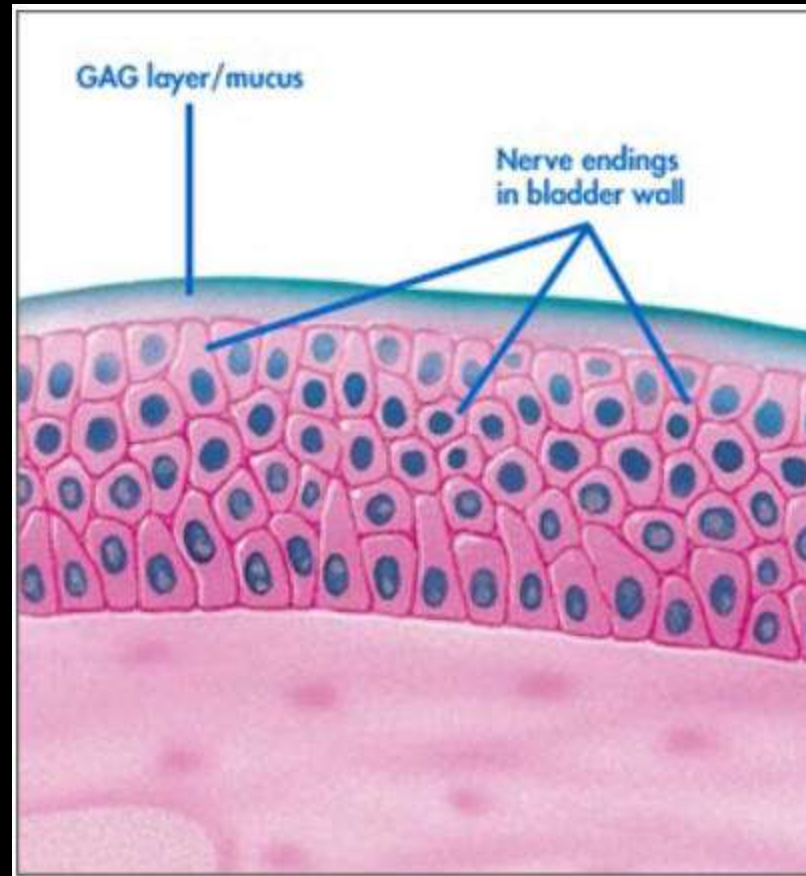
- ***The protective GAG layer***

The GAG layer is a lining of the inner bladder wall that protects it from the natural waste products found in urine.

How does the bladder differ in women with IC?

- In many patients with interstitial cystitis symptoms, it is thought that the protective GAG layer inside the bladder may be damaged, inflamed or defective.
- As a result, chemicals in the urine may irritate or leak out of the bladder wall, causing bladder muscle injury, inflammation, and pain.

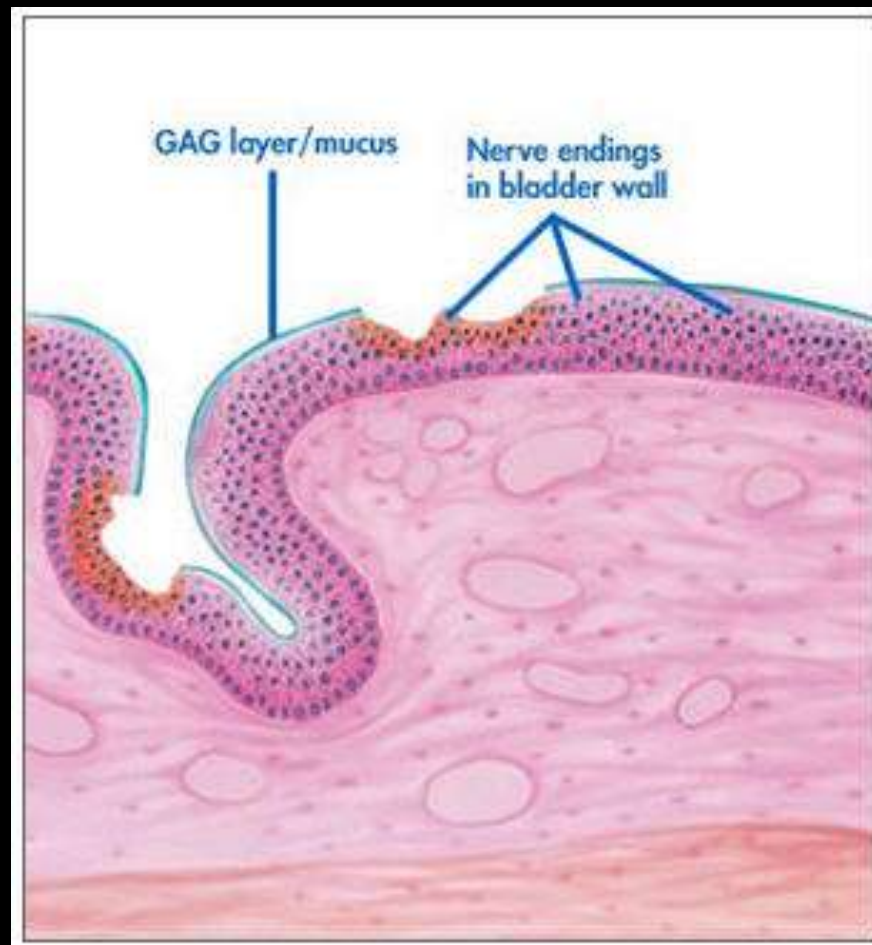
Normal Function



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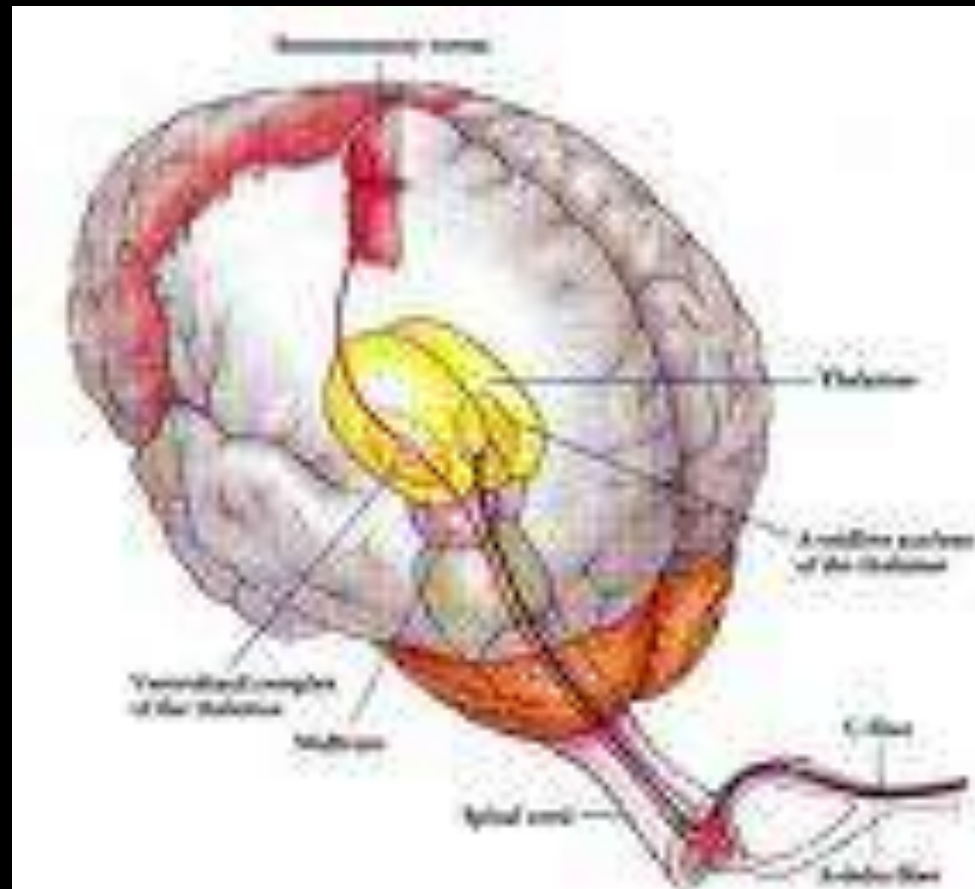
- It is thought that even inflammation can cause urine to leak through and come in contact with nerve endings causing pain.

IC



Professor J-J Wyndaele, urologist, of Antwerp University Hospital says,

- The brain plays an important role in pain with messages passing to and from the brain and other parts of the body, including the bladder. Neurotransmitters send nerve impulses from one cell to another. Specialized nerve cells called nociceptors at the end of nerve fibers are activated by external events such as pain or injury to body tissues and relay this information via peripheral nerves to the central nervous system where it is interpreted as pain.



Limbic system

- The brain's limbic system, which includes the hypothalamus, hippocampus and amygdala, lies on both sides of and below the thalamus. The thalamus forwards the pain signals to the cerebral cortex and the limbic system.

Continued.....

- It is the limbic system which produces manifestations of pain, including the physiological signs of palpitations, stress and anxiety or crying in response to pain. This means that there is a very close relationship in the brain between pain sensation, emotion and stress.

4. Signs and Symptoms

Symptoms of IC

- Triad: Urgency, frequency and pain. But, some patients only have pain or pressure, or only frequency or urgency.
- Often dyspareunia.
- Symptoms may gradually increase in intensity, tend to occur in cycles or flares.

"Hello, incontinence helpline - can you hold?"



IC Flares and Triggers

- Allergies
- Stress
- Week before menses
- Certain food and drinks
- Sexual activity (during or after)
- Trigger points of hypersensitivity – vagina, umbilicus, abdomen, upper thighs.

The Belgian Interstitial Cystitis Patient

Association (ICPB) conference 18 February 2006,
Vilvoorde, Belgium described symptoms as:

- The hallmark symptoms of PBS/IC – bladder pain with urgency/frequency, pain increasing as the bladder fills and alleviated when the bladder is emptied - cause a change in the normal pattern of urination. The patient urinates small amounts frequently. In other words, the bladder can no longer store urine in the normal way.

"You just keep going and going?"



Continued.....

- Many patients may experience pain with sexual relations. And some patients have pain throughout the pelvic floor. Although painful urination is considered to be typical of bacterial cystitis, PBS/IC patients may also experience burning pain as urine comes into contact with irritated urethral or vulvar tissues.

Continued.....

- A study of 589 patients (Fitzgerald et al ICDB Study group ICS/IUGA 2004 abstract 417) showed that patients also had intermittent, moderately severe pain in places other than the bladder as follows:

Continued.....

- 74 % urethra
- 51 % vagina
- 53 % perineum
- 65 % lower back
- 80 % lower abdomen
- 24 % rectum
- 27 % elsewhere

**(The Belgian Interstitial Cystitis Patient Association (ICPB)
conference 18 February 2006, Vilvoorde, Belgium)**

5. Evaluation of the IC Patient

- History
- Physical Exam

Workup

- Extensive History
 - Associated conditions, look for lower back/nerve problems; OB/GYN history
 - LUTS
- Comprehensive Physical
 - Spasticity of levator muscles, bladder spasms, rigid bands of muscle at bottom of vagina (3-5 o'clock and 7-9 o'clock with distinct focus of pain.
 - Tenderness or pain at bladder base and posterior urethra
- Questionnaires – need baseline
 - O'Leary Symptom & Problem or PUF Questionnaire

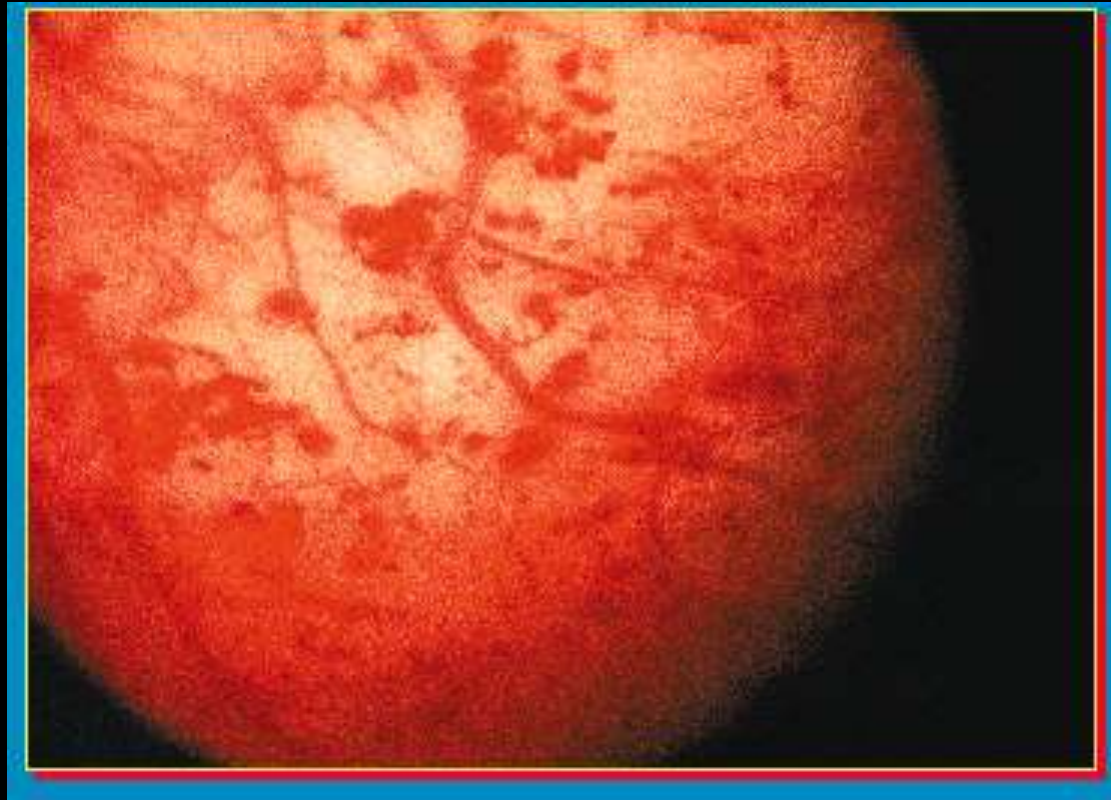
Laboratory Tests

- Urinalysis and Urine Culture and Sensitivity
- Cytology in smokers and patients >40

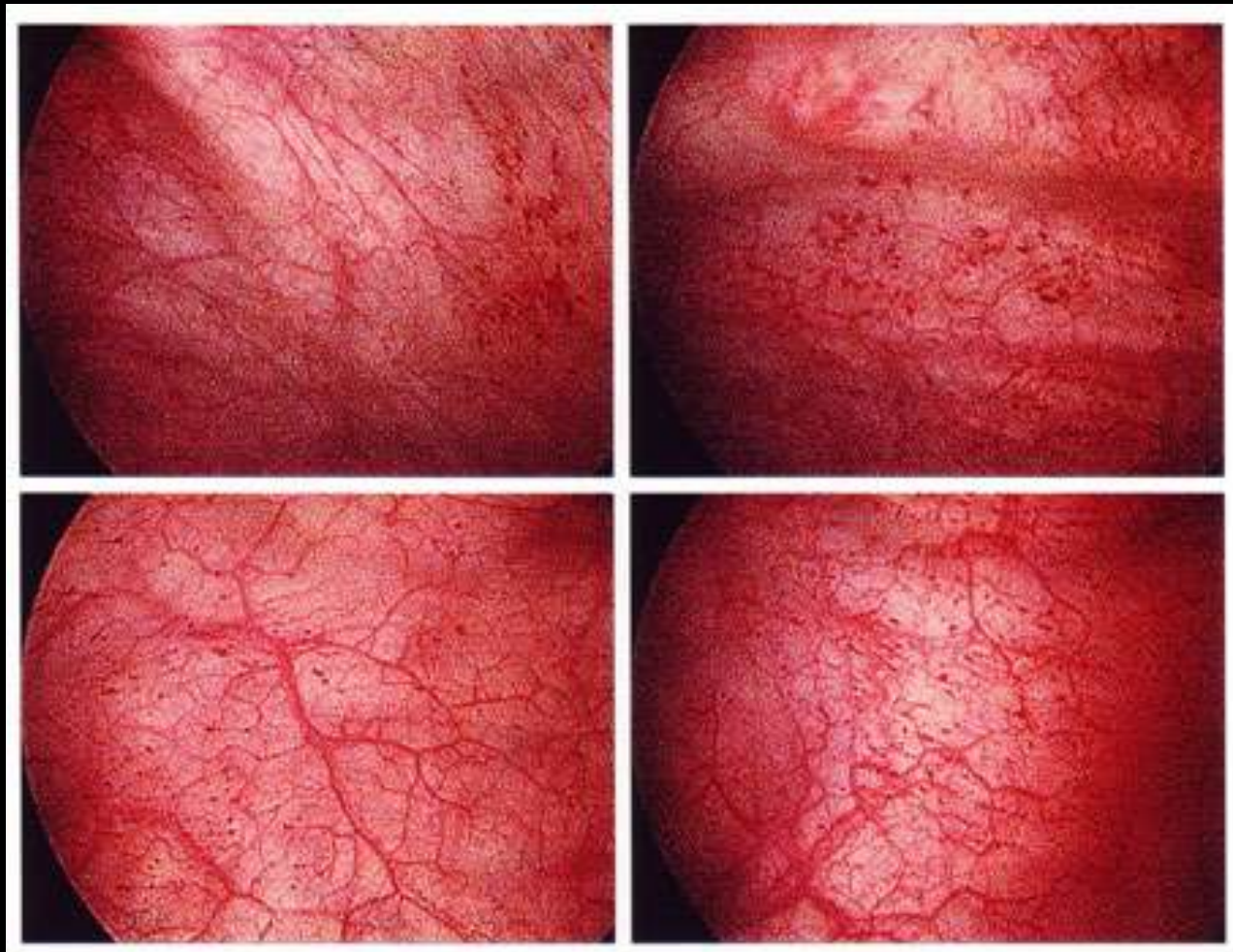
Procedures that may be performed

- Cystoscopy – cannot effectively establish diagnosis of IC but can often visualize glomerulations/ulcers and evaluate bladder capacity
- Biopsy with suspicious findings
- Voiding Diary
- CMG
- KCL Challenge Test or Lidocaine Test

Glomerulations Seen in Most Bladder Inflammation

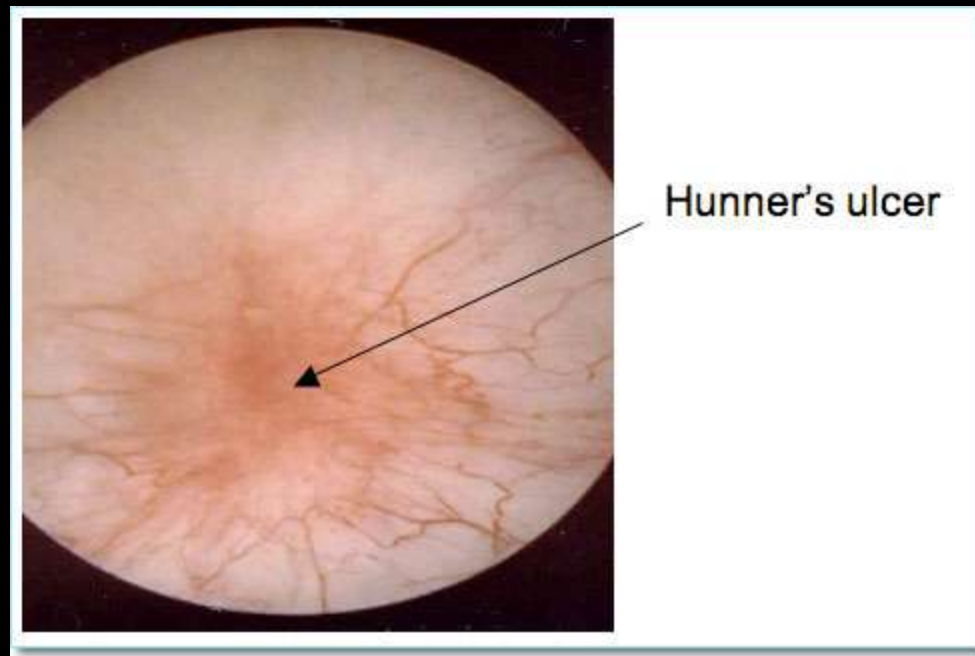


Interstitial Cystitis

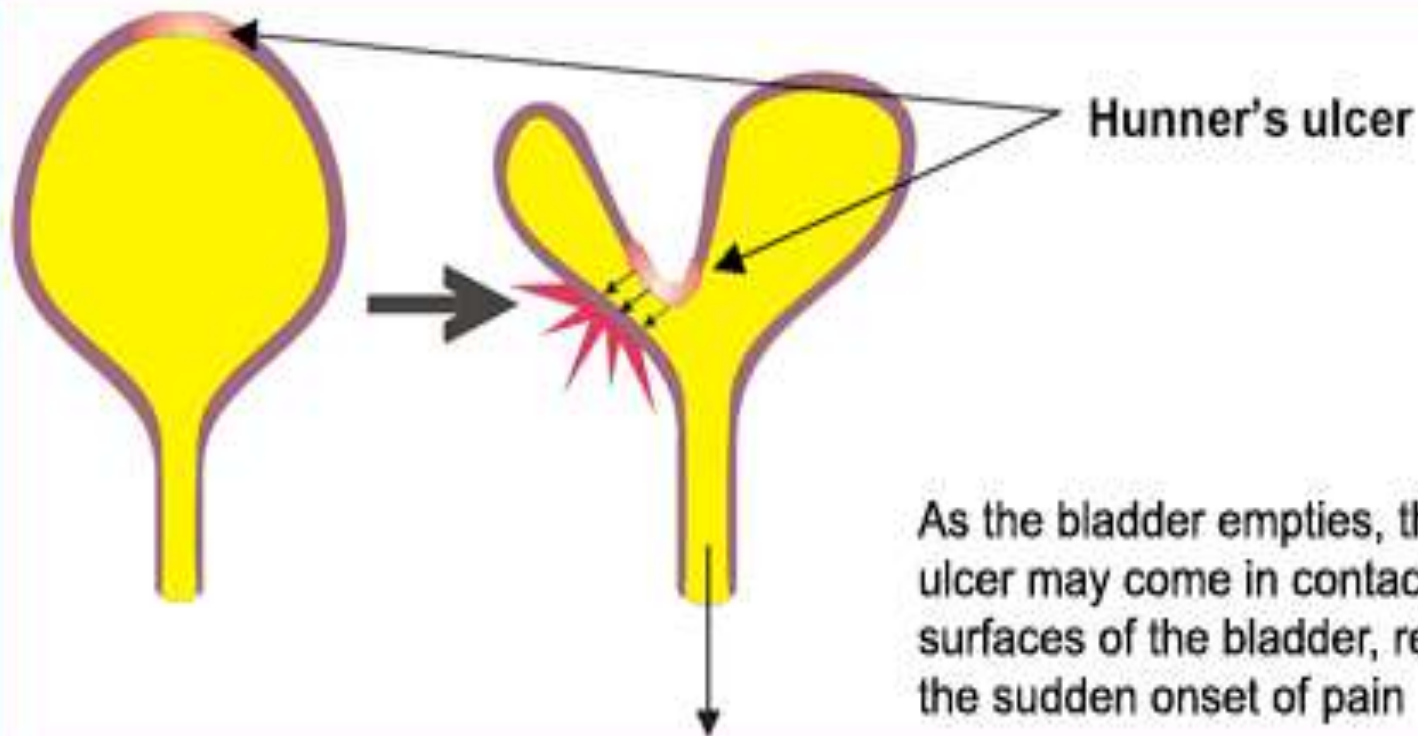


Hunner's Ulcer – only in 10% of patients

The Belgian Interstitial Cystitis Patient Association (ICPB) 18 February
(2006)



Incidence of severe pain



As the bladder empties, the Hunner's ulcer may come in contact with other surfaces of the bladder, resulting in the sudden onset of pain

6. Diagnosis and Treatment

So -Diagnosis may be currently based on:

- The exclusion of other possible diseases
- Urine tests to rule out infection and hematuria
- Varying symptoms :pain, frequency and urgency
- Cystoscopy for additional information
- A biopsy may reveal mast cells in the detrusor muscle, lamina propria and epithelium.
- KCL Challenge Test or Anesthesia Bladder Lidocaine Challenge
- Urodynamics for more info on SUI and UI
- Laparoscopy if OB/GYN deems it necessary

KCL – Potassium Stimulation Test

- Detects abnormal bladder epithelial permeability in 78% of patients with IC
- Demonstrates this defect by provoking urinary urgency and/or pain
- Negative – may trigger pain response for extended period and be difficult to reverse
- Parsons, C. (2003); Urology, 62-976-982, Moldwin, R & Bretschneider, N. (2003).

Anesthetic Bladder Challenge Test

- Accepted alternative to KCL
- Anesthetic Solution instilled into bladder to evaluate significant pain relief
- Buffered Lidocaine more appropriate than Marcaine for this test d/t concerns regarding potential absorption and cardiac toxicity. Small amts of Marcaine are very safe and effective in treatments, however.
- Parsons, C. (2003); Urology, 62-976-982, Moldwin, R & Bretschneider, N. (2003).

Possible Urinary Biomarkers

- Antiproliferative Factor (APF)
 - Present in 94% of IC patients
 - 94% sensitivity and 95% specificity for IC
 - APF shown to normalize after hydrodistention and Sacral nerve stimulation
 - Thought to be related to pathogenesis of epithelial thinning or ulceration

(Erickson, D. (2001) *Urology*, 57 (suppl 6A): 15-21, Keay, S., Szekeley, K., Conrads, T., Et al (2004); Hurst, R., Moldwin, R., & Mulholland, S. (2001) *Urology* 69 (suppl 4A) 17-23.)

Continued.....

- GP51

- Major component of mucin lining of urinary tract
- May be strategic mechanism of defense of bladder
- Significantly lower in IC patients than in controls
- Erickson, D. (2001) *Urology*, 57 (suppl 6A): 15-21, Keay, S., Szekley, K., Conrads, T., Et al (2004); Hurst, R., Moldwin, R., & Mulholland, S. (2001) *Urology* 69 (suppl 4A) 17-23.

Treatment

- There are many different facets to treatment of IC patients. It is essential to take time to listen to the patient, explain everything carefully and provide the patient with support. IC patients take a lot of time.
- Patient support groups can be helpful.
- Start with conservative treatment and progress to more invasive treatment if the conservative treatment fails. IC is not considered a curable disease, but sometimes subsides of its own accord.

Treatments

- Start with the least invasive and least expensive treatment and most reversible.
- Surprisingly, many patients get relief with minimal change.
- Patients greatly vary in what works for them so no treatment is uniformly effective – thus there is no definite standard of treatment.
- Trial and error.

Continued...

- Treatments are applied in progression.
- If you start one drug/treatment at a time, you can determine its effectiveness.
- Treatment goal: Reduce symptoms and improve the patient's quality of life.
- Education is crucial – disease explanation, dietary/fluid management, time and stress management, behavioral modification
- Empowerment – through knowledge and interactive management.

Dietary Modifications

- IC Diet – Find the major triggers. If you can, you won't have to eliminate everything.
- Acidic Foods – coffee, citrus, concentrated tomato products
- Smoking
- High potassium – Bananas, ETOH, Aged cheeses/meats/yogurt/chocolate/most nuts
- Allergens – grains, dairy, nitrites/nitrates, MSG.
- Reintroduce foods one at a time.

Behavioral Modifications

- Education
- Read labels
- Water intake and dilution of urine
- Bladder training/timed voids
- Biofeedback
- Pelvic floor exercises
- Walking
- Stress Management

Pharmacological Therapy

- Tricyclic Antidepressants – Amitriptyline
 - Relief of dyspareunia, pain and frequency in some patients
 - Mechanism of analgesia unknown – thought to inhibit reuptake of serotonin or norepi, inhibit histamine secretion, anticholinergic effect sedative effect, and ability to increase bladder capacity.

(Hanno, P. (1994) Urology Clinic North America, 21 (89-91); Yashimora, N. (2003), Urology (suppl 3A).

New research with Cymbalta and Celexa

Antihistamines

- Postulated intravesical histamine release may cause increase in IC symptoms
- Off label
- Sedative
- H2 receptor blocker – e.g. Hydroxyzine 10-50 mg qhs, Cimetidine. H1's may also help.
- Inhibits release of mast cells

Elmiron -pentosan polysulfate sodium –
100 mg tid, po

- Oral formulation of heparin analogue
- Theory of epithelial permeability barrier
- Only FDA approved oral medication
- Efficacy at 3 months; up to 12 months for severe cases – compliance issue; > 50% reduction in pain after 3 months.
- Expensive, side effects

Analgesics/Anti-inflammatory Agents

- Chronic pain
- Narcotics are not very effective for IC pain, but patients can become reliant on them.
- Try NSAIDS, ASA, Gabapentin (titrate up and then down).
- IC is more related to nerve pain so Amitriptyline, Celexa and Cymbalta may be most effective.
- Pyridium, Prosed DS, Urelle, Hyomax

Anticholinergics/Antispasmodics

- Used to reduce frequency and urgency
- Vesicare, Enablex, Detrol LA, Oxybutynin, Ditropan XL, Sanctura, Oxytrol patch
- Education regarding dry mouth, difficulty swallowing
- Mentation issues - use Enablex or Sanctura- do not cross BB barrier.

Muscle Relaxants

- Use only in severe spasms
- Relaxation of skeletal muscles
- Diazepam 2mg-10 mg tid
- Baclofen 10 mg bid
- Clonazepam 0.25 mg – 1 mg tid

Non Prescription Therapies

- Preliief
- Cysto-protect (now contains seafood an allergen!)
- Cysta Q
- Algonot
- Desert Harvest Aloe Vera

Intravesical Therapies

- AKA (Bladder Instillation)

Rescue Solutions

- Numerous rescue bladder “cocktails” based on patient
 - Always use a rescue instillation following KCL challenge test
 - Lidocaine/Marcaine/Sodium Bicarb/Heparin/Kenalog – Caution with Marcaine (cardiac toxicity), Heparin and Kenalog (can be irritating in some patients)
 - Can instill Elmiron intravesically as well

Continued....

- Heparin
 - Mucopolysaccharide
 - Beneficial anti-adherence action
 - Anti-inflammatory and surface protective action
 - May mimic activity of bladder mucous glycosaminoglycans (GAG)

DMSO Treatments

- Administered in office/hospital if > pain
- DMSO – only FDA approved for instillation
 - Mechanism of action unknown
 - Muscle relaxant and anti-inflammatory
 - 6-8 week course recommended
 - Garlic taste and smell

Continued.....

- Intravesical treatment occasionally used is Chlorpactin (Sodium oxychlorosene) 0.4%.
- A very old treatment still occasionally used is silver nitrate.
- A new treatment is Botulinum Toxin (Botox). Trials are in progress with IC patients in Europe 9/13 improved/Cleveland clinic trials had 0% improvement. Botox injected into lining through cystoscope.

Sacral nerve Stimulation

- Interstim
- Staged procedure
- S3 electrode wire placement
- Refractory urgency, frequency and urge incontinence
- Often significant decrease in pain and frequency in IC patient

Percutaneous Tibial Nerve Stimulation

- Neuromodulation of tibial nerve as used to treat urgency, frequency and urge incontinence.

Hydrodistention

- Extreme distention of bladder with or without the addition of Chlorpactin
- Increases the bladder capacity and decreases “stretch” pain
- Needs to be done in OR for sedation
- Extremely painful for IC patients

Other procedures

- Ablation of ulcers- The beneficial effects are short-term. Laser treatment is used to seal ulcerated or raw patches in the bladder. It is temporary but can be repeated.
- Neuromodulation implantation- is an expensive form of treatment involving implantation of devices usually reserved for patients who have failed all other treatments.
- BCG – experimental, results of studies are not conclusive at this time

Continued.....

- Modified Thiele massage and other forms of pelvic floor relaxation can be tried once the pain is under control.
- Hyperbaric oxygenation is similar to the type of treatment given to divers who develop the bends and comprises breathing pure oxygen in a special chamber.
- Cystectomy/Urinary Diversion/Neobladder only in extreme pain with no relief

Other

- Neurontin/Lyrica – neuropathic pain
- Opioids – short and long acting for refractory cases
- Hyaluronic acid (Cystistat®)
- Chondroitin sulfate 0.2 % (Uracyst®)-
40 ml intravesically, once a wk for 4
wks.

Other

- Acupuncture works for some.
- Cyclosporine in relation to nitric oxide (NO) levels (Sweden). NO in urine is a marker for inflammation. NO levels decreased to almost zero in Swedish trials.
- Quercetin – a flavinoid, 500 mg bid x 4 wks.

And, on the horizon

- Liposomes- enhance urothelium layer to absorb other medications
- EMDA- Facilitates the transport of water soluble drugs by the use of electrical current (studied with oxybutynin and local anesthetics)
- Sativex – mouth spray for MS and neuropathic pain, 2.7 mg THC, 2.5 mg CBD.

- New Pfizer drug for IC pain – test drug is an antibody targeting nerve growth factor that affects pain.
- Miniaturio – I – Electromodulator from Israel, now used for stress and urge incontinence. SubQ in pubic area with lead to urethral sphincter.

References

- Interstitial Association www.ichelp.org
- Interstitial network www.ic-network.com
- International Painful Bladder Foundation www.painful-bladder.org
- www.urotoday.com
- www.clinicaltrials.gov

The End

