INTERSTITIAL CYSTITIS (IC)

----- "Bladder Pain Syndrome", "Myofascial Pelvic Pain", "Chronic Pelvic Pain", "Over-Active Bladder", "Vulvadynia", "Urethritis", "Yeast Vaginitis", "Endometriosis", and "Prostatitis"

There is considerable research and clinical evidence that all the medically named conditions listed above are simply variations of a single primary disease process in the lower urinary tract. Which of the above diagnoses a patient receives depends on the location and character of the symptoms, as well as the medical specialist from which the patient seeks help. If the patient goes to a Urologist, the diagnosis is more likely to be IC, or Bladder Pain Syndrome or Over-Active Bladder --- whereas if the patient goes to a Gynecologist, the diagnosis is more likely to be Chronic Pelvic Pain, Vulvadynia, or even Endometriosis. If the patient is a male, the diagnosis will undoubtedly be Prostatitis.

Classic or traditional IC is an ulcerative condition. So, many physicians, in the absence of detectable ulceration, will select from among the diagnoses listed above. But classic ulcerative IC represents only the severe and quite rare form of the IC disease process. Far more common are those who manifest symptoms of urinary frequency, urgency, incontinence, or, urinary tract or genital tract pain --- with no evidence of ulceration. ----- Defining a disease by its symptoms rather than by its pathophysiology is often done in medicine when there is a lack of scientific evidence. The tendency to call IC "Painful Bladder Syndrome" illustrates this. But if the pathophysiology is understood, then, regardless of the individual patient's symptoms, an all-inclusive label such as IC, which represents the common pathophysiology, is more appropriate.

A major source of confusion leading to misdiagnosis of IC is that the pain generated by visceral origin such as from the lower urinary tract (UT) does not localize well. In fact, UT inflammation can refer to any location --- from the umbilicus and low back to the knees. It is this referral of UT pain that is responsible for most of the "educated guess" misdiagnoses made by both Urologists and Gynecologists. The confusion between Urologists and Gynecologists is made worse in that very often urinary tract symptoms are exacerbated during menstruation, or during sexual intercourse, or with hormone changes over the course of the menstrual cycle.

IC tends to be of insidious onset, with mild, intermittent vague symptoms. 80% of those with IC show initial symptoms by age 30 --- with 81% showing urinary frequency, and 59% pain.

What exactly is the pathophysiology underlying IC? There are three considerations:

1. Dysfunctional Urinary Tract Epithelium. The epithelial lining in one or more locations of the UT has lost its integrity, and lost its protective mucous layer. The uroepithelium thus becomes excessively permeable to urine solutes, and as these solutes leak into the epithelium they cause irritation and inflammation.

2. Activated Mast Cells. In some individuals, either as a result of or as a cause of the IC, there is an excess presence of Activated Mast Cells in the urothelium. The Mast Cells release pro-inflammatories including Histamine, Tryptase, and Prostaglandin D2. These pro-inflammatories initiate a cascade of inflammation that provokes increased Eosinophilic Cationic Protein, as well as Vascular Endothelial Growth Factor (VEGF), C-Reactive Protein (CRP), and Inflammatory Cytokines including IL-1B, IL-6, IL-8, and TNF-Alpha.

3. Organ "Cross-Talk". There is extreme comorbidity between IC and other immuno-neurological inflammatory conditions. Organ Cross-Talk involves irritation initiating in a distant organ reflexly activating inflammation in the UT.

We will elaborate on those elements of the IC pathophysiology below. But first we will summarize foods that tend to irritate and those that do not irritate IC, and then provide a list of therapeutic interventions that are shown to be beneficial.

IC non-irritating foods

- Meat, Fish, Poultry, Shrimp
- Eggs
- Milk, Cheese
- Bananas, Pears, Raisins, Watermelon, Honeydew Melon
- Cabbage, Broccoli, Cauliflower, Brussels Sprouts
- Carrots, Celery, Cucumber, Zucchini, Mushrooms, Radishes
- Peas, White Potatoes, Sweet Potatoes, Yams, Squash
- Oats, Rice, Pretzels

Common IC Food Irritants

- Citrus fruits → irritate by a mechanism not related to pH of urine → perhaps the irritant is citric acid (--- Also note that citric acid as a food additive is derived from mold)
- Tomatoes & Tomato products
- Vitamin C

- Artificial Sweeteners (--- ALL = Aspartame, Xylitol, etc.)
- Coffee/Tea increase IC frequency & urgency, but not pain (includes decaf!!)
- Carbonated Beverages (includes cola, non-cola, decaf & diet)
- Alcohol – 75% of IC patients suffer increased pain & 94% increased urgency/frequency
- Spicy foods; vinegar; MSG
- Oxalate-containing foods, or foods from which the liver produces oxalates.

  • Foods containing oxalates: There is an IC support group that advocates the total elimination of oxalate-containing foods from the diet. They have many success stories to tell, one of whom was a past patient in our office who experienced a miraculous cure of IC upon eliminating oxalates from the diet, and immediate excruciating pain anytime she inadvertently consumed oxalates. --- High oxalate foods include cashews, most nuts, most berries, leafy greens, beets, and cocoa/chocolate.

IMPROVE IC SYMPTOMS:

- Maintaining normal microbiota is critical in IC patients for several reasons. First, the maintenance of normal microbiota will decrease any tendency to immune system reactivity, whether from autoimmunity, allergy, or mycotoxins. Second, a healthy microbiota will decrease the tendency to urinary tract infections of either bacterial or yeast origin, which, if not a cause of IC, are certainly a common irritant. Finally, apart from any specific microbiota-associated pathologies, an abnormal microbiota is a powerful immune trigger that increases inflammatory cytokines in a non-specific way, which certainly exacerbates IC symptoms.

  • IMMUNO-SYNBIOTIC = Immune X-Flam, Immune Restore, Immune Power

- Calcium Glycerophosphate → would neutralize UT acidity --- but --- so many studies show that symptoms do not relate to UpH, so, the mechanism is uncertain.

- Cocoa = high in polyphenols (especially flavonoids), (15 g, 3X daily) increases Neurotransmitters phenyl-ethylamine, serotonin and anandamide in the brain --- probably via brain cannabinoids in cocoa.

- CBD

- Baking Soda

- Sodium Citrate → enough to maintain UpH > 6.2 → decreases # of pain episodes, decreases urgency/frequency --- and increases sleep & energy

- Chiropractic --- normalizes by sacral nerve stimulation

- Elimination Diet --- Wait 3 days between re-introduction of each new food.

- (Amitriptyline = no better than a placebo)

  • Antidepressants have long been prescribed for IC. The rationale seems to be that IC pain is neurogenic inflammatory and that the antidepressant calms down the neurogenic pain. The literature shows, however, that the only antidepressant that consistently benefits symptoms of IC is amitriptyline/Elavil and subsequent studies have shown it to be no better than a placebo, especially after the first few weeks. Since amitriptyline has gone out of fashion and been replaced by SSRIs, that is the drug most IC sufferers are now given, even though there is no substantial evidence that the SSRIs do any good.

- IC can be associated with almost any of the NUTRI-SPEC Imbalances (--- with almost any source of ImmunoNeuroEndocrine stress). There is either bladder tissue Acidosis or Alkalosis associated with the pain sensitivity. If you are fortunate to be able to test the patient without the influence of drugs commonly given for this condition, you should do quite well. Look for a chance to administer Oxy Tonic, Oxy D+, sodium bicarbonate, sodium citrate or Phos Drops. In other words, if you can correlate the pHs, particularly the urine pH, with the severity of pain, use that information for pain control.

THE PATHOPHYSIOLOGY OF IC:

1. DYSFUNCTIONAL URINARY TRACT EPITHELIUM -> induced by Antiproliferative Factor, and by cationic urinary toxic factors capable of injuring superficial epithelial cells.

- Glycosaminoglycans (GAGs) & glycoproteins constitute the “mucous layer” designed to regulate epithelial permeability to small molecules & ions.

Among those who suffer from IC, there may be “leakers” and “non-leakers” as regards urine solutes penetrating UT epithelium. Leakers experience pain, while in non-leakers, frequency and urgency may be more significant symptoms than pain. (However, there may be an alternative distinction when viewed from a NUTRI-SPEC perspective. Pain may predominate in those who are Sympathetic (= vasoconstriction) while frequency/urgency “Over-Active Bladder” (OAB) may be the major symptom in those who are Parasympathetic.)

- Initial Cause of Epithelial Damage?

  - Vascular insufficiency (vaso-constriction) → localized tissue nutrient deficiency
  - Vasculitis from autoimmune disease or Reflex Sympathetic Dystrophy
  - Inflammatory/allergic reactions in the interstitium (Tissue Acid/Alkaline, Anaerobic/Dysaerobic Imbalances)

- Normalized by sacral nerve stimulation = chiropractic and pelvic floor exercises

- Potassium → concentration in normal urine = 24-133 m.eq. --- and studies show 8 m.eq. is irritating in some IC cases → epithelial leak

- IC patients have a much higher urine concentration of cationic metabolites

- Despite evidence of K+ (per Sensitivity Testing) as an irritant = that evidence may be questionable since IC patients do not typically suffer exacerbation from high K+ foods such as potatoes, yams & milk.

  • The K-challenge → Is irritation due to the K+, or, to the KC1 used as the source of potassium? ----- KC1 is the most tissue acidifying (Anaerobic pain) of all the electrolytes.

- Vascular permeability is increased (= increased VEGF)

- Cations in urine other than K+, Na+ & Ca++ are protein & nucleic acid metabolites that contain amino groups → potentially bind to the anionic UT surface mucous

- Urine contains a protective factor, THP, a glycoprotein highly anionic because of sialic acid → neutralizes by binding toxic cations. IC patients = defective THP, w/ decreased sialic acid content.

- HC1 (dilute) removes epical cell GAG layer within 24 hours → increases permeability to K+ and other cations.

2. ACTIVATED MAST CELLS in urothelium release pro-inflammatories including Histamine, Tryptase and Prostaglandin D2.

- IC is always associated with elevated Mast Cells --- (excess Mast Cells are indicated by a red Dermographics reaction in your NUTRI-SPEC Testing). The Mast Cells release Histamine, increase inflammation, and prevent healing of the inflamed urinary tract epithelium.

- Increased Eosinophilic Cationic Protein + Mast Cell density + IL-8 & IL-6

- IC bladders fail to release PGE2 in response to tryptase (--- Do not use Motrin or Aspirin as they further suppress PGE2)

- Urine = increased IL-6, IL-8, VEGF. Serum = increased IL-6, IL-8, IL-1B, TNF-alpha, & CRP

  • VEGF (Vascular Endothelial Growth Factor, aka, Vascular Permeability Factor) involves a vicious cycle: Initial damage to UT → VEGF increases as a survival mechanism → increased vascular permeability → inflammation, edema → increased VEGF.

- Tryptophan/Serotonin metabolites as cationic irritants = Kyneurine & Quinolinic Acid.

- Instilled Chondroitin Sulfate binds preferentially to damaged urothelium and restores the impermeability barrier to an acid damaged bladder → Chondroitin decreases recruitment of Mast Cells and Neutrophils (but not CD-45-positive lymphocytes).

- Instillation of urine ranging from pH 5.0-7.5 into IC women's bladders showed no change in pain scores → UpH does not have a sensory effect on nerves of the UT.

3a. IC COMORBID CONDITIONS:

- IC most often occurs in individuals who also suffer from ImmunoNeuro-Endocrine stress as evidenced by Fibromyalgia Syndrome, Chronic Fatigue Syndrome, Irritable Bowel Syndrome, and several of the autoimmune diseases.

- IBS = 39% - 70% (vs. 5% in the general population) → Recommendations = X PUFA, alcohol, fructose, lactose, sugar alcohols, wheat, citrus, corn, beans, cabbage family, lettuce

  • IC – IBS comorbidity is neurally mediated.

- H Pylori Gastritis/Ulcerations

- Fibromyalgia Syndrome = 19%

  • NUTRI-SPEC to reduce ImmunoNeuroEndocrine Stress

  • Cocoa decreases fatigue & pain, increases residual function, decreases anxiety, decreases depression

- Chronic Fatigue Syndrome = 9%

  • NUTRI-SPEC to reduce ImmunoNeuroEndocrine Stress

  • Cocoa decreases fatigue & pain, increases residual function, decreases anxiety, decreases depression

- Vulvadynia = 50% (vs. 16% in the general population) = Anecdotal evidence of oxalate sensitivity → but --- IC + Vulvodynia women show no difference in urine oxalate concentration compared to normals --- so--- it is not quantity, but sensitivity (--- no increased risk of developing Vulvodynia with increased oxalate intake).

- Neuropathic Pain

- IC tends to occur in association with excess estrogen and/or insufficient thyroid. It is not known whether the estrogen stress or thyroid insufficiency are causes of IC, but there is a definite correlation that needs to be considered. There is a strong correlation between IC and endometriosis in women.

- [Occasionally, we hear of women with IC being warned about complications during pregnancy. There is no basis for such concern. Mild to moderate cases of IC do not increase during the first two trimesters of pregnancy, but do increase, but only slightly, in the third trimester. In cases of increased IC symptoms during pregnancy, it is almost always the frequency of urination that increases, but not the pain. Patients with severe IC symptoms prior to pregnancy actually have an improvement of their symptoms for most of pregnancy, with only a slight increase in frequency but no increase in pain in the third trimester.]

3b. ORGAN "CROSS-TALK" = stimuli from one organ lead to physiological response in another organ via integrated sensory pathways.

- For example --- Colon irritation → Sensitizes mechanical & chemical receptive properties of bladder fibers to noxious stimuli. Sensitization is mediated largely by Mast Cells.

- 24 hours after bladder exposure to protamine sulfate → Both bladder urothelium leakage increases & colon uptake of contrast agent increases → Cross-Talk causes comorbid increased bladder and bowel permeability = IC & IBS comorbidity

  - Does the bowel – bladder communication arise from cellular communication by migratory Mast Cells – or – via info transmitted through neural communication, then release of neurosecretory proteins that alter one organ according to the status of the other?

    - Mast Cells & Macrophages respond directly to neural signals = The Inflammatory Reflex

CHRONIC PELVIC PAIN (CPP) = involves bladder, bowel & other pelvic visceral structures. Cross-Sensitization follows acute or chronic pelvic visceral irritation or stimulation = facilitated by:

- Anatomic apposition
- Coordinated physiologic & reflex pathways (Cross-Talk)
- Convergent sensory input of pelvic viscera (sphincters, muscles, epithelium)
- Neurogenic Inflammation = Facilitated Afferents reflexly causes Facilitated Efferent to uninsulted organ = functional changes.
- Colonic distension = increased CPP
- Chronic irritation of the colon causes increased Mast Cell infiltration of the bladder → Mast Cells release adenosine phosphates, bradykinin, histamine, prostaglandins, leukotrienes, K+, TNF, lymphokines, cytokines IL-6, IL-8 = bladder Afferent sensitization via c-fibers – bladder & urethra – Also – increased Nitric Oxide & iNOS.
- Bladder irritation increased by colonic administration of capsaicin

- Visceral Cross-Talk is uni-directional = colon & uterus to bladder, but not bladder to colon --- or --- it is bi-directional, but the gut has greater anti-inflammatory capacity to protect itself.

- Dietary improvements in IC may actually act via the gut = modulating the sum of visceral inputs contributing to IC permeability.

Neural Up-regulation, peripherally or centrally = amplifies symptoms & food effects on symptoms.

Neurogenic Inflammation → efferent sensitization/facilitation causes pain with little or no evidence of organ inflammation

- Signaling through the Vagus releases neurotransmitters & cytokines that activate Mast Cells & Macrophages that then increase bladder permeability.

- Sacral nerve stimulation is beneficial

- Feline IC = excess Sympathetic, increased plasma NE, with no increase in ACTH, cortisol or dopamine

- Increased Sympathetic activity in IC → mediated via chronic alpha IA adrenoreceptor activation

- Positive Feedback Loop = Substance P-containing peripheral nerves stimulate Mast Cells = release inflammatory mediators = inflammation, including histamine = increased Substance P = increase Mast Cell activation

- Bladder distension → release of ATF from urothelial cells → activates purinergic P2X3 receptors = signaling factor in bladder sensation reflexes.

- Neural up regulation occurs both peripherally & centrally → neural up regulation = major facilitation of pain

- Bladder Pain Syndrome (BPS) vs. Myofascial Pelvic Pain (MPP) ("Fibromyalgia of the pelvis") --- and --- consider that Fibromyalgia Syndrome = Sympathetic Stress.

  - BPS = primary Vagal deficiency. (Sympathetic Imbalance) Comorbidities = IBS, dyspepsia, chronic nausea

  - MPP = primary Sympathetic deficiency (Parasympathetic Imbalance) Comorbidities = migraine & dyspepsia

  - Both BPS & MPP are usually preceded by one or more of PTSD, anxiety, depression, migraine, fibromyalgia, chronic fatigue, IBS

  - BPS & MPP in the same individual = greater comorbidity

  - Chronologically = PTSD – migraine – dysmenorrhea – IBS

  - Orthostatic Intolerance (but clinical signs of POTS decrease with chronicity even though POTS symptoms persist) but no orthostatic failure or POTS in IC/BPS/MPP

- Elevated Heart Rate

- Decreased HRV (Sympathetic Stress or Parasympathetic Deficiency) in Both BPS & MPP, but more in BPS

- Both Sympathetic & Parasympathetic tone are reduced in BPS, but Parasympathetic decreased more = Sympathetic symptoms

    - But --- There is a Parasympathetic connection to IC. The first Connection here is that elevated Mast Cells (and Fosinophils) are typical of a Parasympathetic Imbalance. Secondly, neurogenic sensitivity of the bladder is a Parasympathetic phenomenon since the Parasympathetic nervous system controls the bladder.

- Quercetin is a powerful Mast Cell inhibitor (and is found in your Oxy D, but particularly in your Complex P). Some patients may benefit from quercetin supplementation beyond what is contained in NUTRI-SPEC supplements.

- IC/BPS = Pelvic Floor hypertonicity = short Levator muscle (= Chiropractic → sacral nerves)

- Paradox? = Sympathomimetic Dextroamphetamine 15-30 mg extended release relieves pain in severe pelvic pain & in IC, and a variety of pain syndromes (including FMS) in women with Sympathetic Neural Hyperalgesia Edema Syndrome. ----- Amphetamine improves symptoms:

    - Amphetamine for paroxysmal tachycardia + hypertension, with abnormal Water Load Test (= excrete less than 75% of a 1500 ml water load in 4 hours standing (--- rule out hypothyroid; renal or liver disease; CHF)

    - Edema + FMS Case History = Amphetamine = decreases pain, and in one case = 27 pound weight loss as edema decreased

    - migraines; chronic urticaria; eczema; dyspareunia, back ache; cold-induced urticaria; idiopathic orthostatic edema decreased capillary permeability = all respond well to Amphetamine

    - Symptoms are not relieved by the decreased edema, since diuretics decrease edema but do not improve symptoms → the cause of the edema is corrected = --- excess epithelial (capillary) permeability

- Sympathetic Dysfunction in FMS, CFS, IBS & IC review of case-control studies: {2012} ----- 65% of studies showed Sympathetic Dominance, 7% of studies showed Parasympathetic Dominance.

  • IC = decreased foot skin temperature → cold stress test = foot skin temperature drops more rapidly & is slower to recover

  • Is the Sympathetic Dominance in IC a contributing cause, or is it an attempted defense? → It is a cause, since administering alpha IA adrenergic stimulation increases pain

  • Norepinephrine is elevated in IC, but does not fluctuate with symptoms.

    ○ IL-8 promotes Sympathetic pain
    ○ IL-8, IL-6 & IL-2 = elevated in IC urine
    ○ IC bladder bladder muscles have increased Sympathetic neurons & those neurons are positive for (VIP) Vasoactive Intestinal Polypeptide & Neuropeptides = similar to Crohn's, RA, & ulcerative colitis