

# UNDERSTANDING AND MANAGING INTERSTITIAL CYSTITIS: A PERSONALIZED APPROACH

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### INTRODUCTION:

Patients diagnosed with interstitial cystitis are angry. Physicians managing IC are frustrated. Multiple etiologies have been proposed, studied and debated. Each theory has sound theoretical basis, usually some animal model confirmation and evidence from epidemiological studies. Yet we have come to accept that there will likely be no one unifying etiology for all patients diagnosed under the umbrella of IC. Many small treatment trials have shown promising results, only to have our hopes dashed when those interventions were subjected to large well designed multi-center placebo controlled clinical trials. We have come to accept that we will likely never discover a single treatment that will "cure" all patients diagnosed with IC.

IC remains an enigma [1]. We continue to argue what to actually call a syndrome characterized by pelvic pain perceived to be of bladder origin associated with variable urinary frequency and urgency [2]. Does the name interstitial cystitis do it justice? Or are the recently introduced terms of painful bladder syndrome or bladder pain syndrome more reflective of who these patients are? Or is the name

of the syndrome really important all? While clinicians and researchers understanding of this condition continues to improve, the two most important concepts that have evolved over the last several years is that the patients with this diagnosis have more than just an organ (bladder) centric disorder and that patients with IC are not a homogenous group of similar patients (even though they may share the main symptoms of bladder pain and urinary symptoms).

### THE SNOW FLAKE HYPOTHESIS

We have hypothesized each patient presenting with the characteristic symptoms of perceived bladder pain and urinary frequency/urgency is actually a completely unique individual [3,4]. Each patient likely has a slightly different etiologic mechanism or even multiple mechanisms, different symptom complexes, different progression trajectories, different flare triggers and different medical associations. This would account for why we have not been able to find a single universal theory that satisfactorily explains every case of IC/PBS. It also vindicates to some extent our many large, complex

and expensive treatment trials that have not shown major benefit to the majority of patients while a reasonable number do improve. It therefore becomes clear, that because patients are different, we should never have expected them to respond to a single therapeutic strategy. In fact, most of our treatment regimes are directed towards bladder pathology. Was this a mistake as well?

### BEYOND THE BLADDER

It has only been in the last several years that researchers and now clinicians are moving beyond an organ centric (in this case bladder) understanding of interstitial cystitis. All patients must have pelvic pain perceived to be from the bladder as well as at least one irritative voiding symptom (frequency, urgency and/or nocturia) to be diagnosed with painful bladder syndrome or bladder pain syndrome, but it has become evident that the majority of patients experience much more than just bladder related symptoms.

We have noted that patients diagnosed with interstitial cystitis have a number of distinct presentations that are made up of a number of broad

clinical categories, other than bladder pathology and voiding symptoms. Many IC patients experience pelvic floor neuromuscular dysfunction which can be further related to pelvic pain, voiding problems and dyspareunia. Others are noted to present with other local chronic pelvic syndromes such as vulvodynia, irritable bowel syndrome which further exacerbates the pelvic pain and dyspareunia. Others have diagnoses or symptoms of systemic pain syndromes such as fibromyalgia and chronic fatigue syndrome. In fact, recent observations strongly suggest that patients with an initially organ centric bladder pain syndrome may progress over time to a local then systemic chronic pain syndrome [5]. Patients with IC further have a number of psychosocial and cognitive difficulties which include depression, stress, anxiety, maladaptive coping (inappropriate catastrophizing and/or pain resting) and/or dysfunctional social interactions [6]. It appears that there may also be a progression of psychosocial deterioration as patients progress from a local organ centric to a regional and then finally a systemic chronic pain condition [5].

If patients are much more complicated than we originally believed and each is different in clinical presentation and potential response to therapy, how can we diagnose, categorize and manage them?

## CLINICAL PHENOTYPING USING UPOINT

We have recently described a clinical classification system for urologic chronic pelvic pain syndromes [3] and have validated the approach in both chronic prostatitis [7] and Interstitial Cystitis [4]. In developing this classification system, we knew that the specific phenotypic domains must be discrete, clinically relevant and identifiable, must be associated with potentially effective therapy and should be flexible enough to incorporate new advances in our understanding of mechanisms or

development of new biomarkers. The 6-point UPOINT (**U**rinary, **P**sychosocial, **O**rgan Specific, **I**nfection **N**eurologic/systemic and **T**enderness) Phenotypic classification system fulfills these criteria (Figure 1).

We have shown that patients with a clinical diagnosis of IC (or Painful Bladder Syndrome or Bladder Pain Syndrome) can be successfully categorized into two or more of the UPOINT clinical domains [4]. Urinary domain includes patients reporting bothersome urinary frequency, urgency, nocturia, incontinence and/or dysuria. It is expected that most, if not all patients, would be included in this domain due to the criteria we use clinically to make the diagnosis of IC.

Psychosocial domain includes patients identified as clinically depressed (or with recent history of depression), those with identifiable maladaptive coping mechanisms (e.g. catastrophizing) or problems with social interactions. This can be based on a simple clinical assessment with standard history and focused interview.

Organ specific domain includes patients who report pain with bladder recycling (typically pain with bladder filling and temporary relief with voiding), pain on bladder filling detected with low volumes of irrigation fluid, glomerulations and/or Hunner's ulcers noted during cystoscopy (either local or general anesthesia) and/or patients with typical inflammation confirmed on bladder biopsy. It is likely that future studies will confirm our impression that there will be definite subcategories of this domain based on cystoscopic, pathologic or clinical testing results. Some researchers and clinicians suggest the potassium sensitivity test for confirmation however that particular test causes more pain and distress in patients already suffering. In our clinic, patients with equivocal findings (usually those patients with severe pelvic floor pain in whom it is difficult to decide if the problem is bladder pain, pelvic muscle pain/spasm

or both) are assessed before and after an anaesthetic challenge test (200 mg of lidocaine alkalized with 8.4% sodium bicarbonate for a final solution volume of 10 cc instilled in an empty bladder and then drained by catheter after 10-15 minutes) [4,8]. We expect most patients, would be included in this domain due to the criteria used to make the clinical diagnosis of IC/PBS, however a significant proportion of patients end up with a diagnosis of pelvic floor dysfunction without a diagnosis of IC specifically. This is an important clinical consideration since treatment directed towards the bladder will only benefit those patients with an Organ Specific problem. Infection domain includes patients who have confirmed significant bacteriuria with typical uropathogenic bacteria within the previous year or so associated with an exacerbation in baseline symptoms and return to baseline symptoms following appropriate antimicrobial therapy. It must be emphasized that a diagnosis of IC can only be made when symptoms persist in the face of sterile urine. Neurologic/Systemic domain includes patients with a concurrent diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, vulvodynia or any other condition that suggested neuropathy or neural up regulation. Tenderness domain includes patients who are noted to have pelvic floor muscle/ligament tenderness and or pain, including but not restricted to specific trigger points during standardized pelvic examination.

## FAILURE OF TRADITIONAL THERAPY.

Critical review of the literature reveals that even the most promising therapies fail to live up to their expected potential when subjected to large multicenter prospective randomized placebo controlled clinical trials [9,10]. For example, clinicians continue to employ oral therapy with pentosanpolysulfate, amitriptyline, hydroxyzine, antibiotics and various

intravesical therapies despite recent randomized placebo controlled trials that suggested no significant efficacy. In fact the large NIH clinical trials evaluating pentosanpolysulfate [11], hydroxyzine [11], BCG [12] and amitriptyline [13] all failed to show efficacy based on primary endpoint analysis. Where does that leave the patient suffering from IC and the clinician attempting to manage such patients?

Let's re-look at those interventions and "negative" trials again. If we start with antibiotics, which many use to treat bacteriuria in IC patients with variable success, the only randomized placebo controlled trial did show statistical improvement in patients treated with long term sequential antimicrobial therapy [14]. However the treatment created many side effect problems and would not be universally applicable to all patients. There have been conflicting results regarding pentosanpolysulfate efficacy, with some trials showing that this compound is effective and some not [15]. In fact in the large, but underpowered NIH trial with its complicated 2X2 factorial design and enrollment of previously treated patients, the group treated with pentosanpolysulfate achieved a marginally significant improvement over those who did not ( $p=0.06$ ) [11]. In the same trial, patients treated with hydroxyzine did not appear to improve compared to those not treated, however in real life clinical practice only those patients with an allergic history or findings on cysto and biopsy would be expected to improve. The NIH intravesical BCG therapy trial was reported as negative even though twice as many patients improved on BCG compared to placebo ( $p=0.06$ ), suggesting that some patients may benefit from this therapy [12]. The NIH amitriptyline trial was similarly reported as negative, however a sub-analysis clearly showed that patients who attained a study drug dose of 50 mg had significant benefit over those treated with the same dose of placebo [13]. Another trial shows

what appears to be clear benefit with amitriptyline when compared to placebo [16]. Other recently reported trials have suggested benefits with intravesical alkalized lidocaine [8], chondroitin sulfate [17] and physiotherapy [18] in IC patients (not necessarily the majority of patients, but at least a significant number).

So perhaps our traditionally therapies are not really complete failures after all. It might be that we are using our therapies incorrectly. How can we then learn from our past experiences?

## TARGETED THERAPY

We believe that the key to the management of IC patients is to appropriately clinically phenotype them and then employ a therapeutic strategy in which specific treatments are directed against individual phenotypes. The UPOINT phenotyping system that we have developed will support this clinical phenotyping of patients with IC, using standard clinical assessment, hopefully promoting this targeted therapy. It is important to realize that the majority of patients have more than the two usually targeted phenotypes (Urinary and Organ Specific) [3] and other identified clinical phenotypes must be treated in order to achieve a successful therapeutic outcome.

**Urinary:** For the Urinary domain, treatment could include an empiric trial of anticholinergics or pyridium. (note that some treatments may be considered for multiple domains).

**Psychosocial:** We believe that targeting and management of psychosocial parameters will improve not only patient adjustment, but also symptoms and quality of life. Depression can be treated medically, maladaptive coping can be modified with Cognitive Behavioral Therapy and social dysfunction with counseling.

**Organ Specific:** Therapies for the most common domain would include

traditional IC bladder centric therapies including oral and intravesical heparinoids (such as chondroitin sulphate), hydroxyzine for those with allergic history, hydrodistension under general anesthesia and perhaps surgical ablation of Hunner's ulcers. It is very likely that future treatment trials will show a differential treatment effect for subsequent subcategories of the Organ Specific domain (e.g. based on cystoscopic and/or biopsy findings).

**Infection:** We believe that more women with IC may suffer from IC exacerbations secondary to uropathogenic bacteriuria than previously recognized [3]. Antimicrobial therapy should be restricted for documented uropathogenic bacteriuria, which may be associated with a flare-up of baseline symptoms.

**Neurologic/Systemic:** Suggested therapy would include medical neuromodulation (amitriptyline, gabapentinoid therapy), surgical neuromodulation (implantable nerve stimulator) and/or therapy specifically directed towards an identifiable associated medical condition (for example directed therapy for irritable bowel syndrome, vulvodynia etc).

**Tenderness:** Therapy for this domain would include counseling, focused exercises, muscle relaxants and various forms of physical therapy (probably most importantly directed pelvic floor physiotherapy).

The therapeutic suggestions outlined above are not based on prospective randomized placebo controlled trials but rather are only "best-evidence" based. This approach to therapy awaits further confirmation, and this will likely come from prospective "real-life" clinical practice studies. The UPOINT system of classifying patients according to phenotypes and then directing tailored therapies to individual patients, really just formalizes and guides what many clinicians are already doing.

## THE FUTURE

We believe that this approach to clinically phenotyping patients is the future for IC research and patient management. Clinicians, particularly urologists have no problem identifying the Urinary, Organ Specific, Infection and probably the Tenderness Domains, however because of our profession is essentially a surgical one, we do have problems with the Psychosocial and Neurologic/Systemic domains. Our group plans to develop clinically simple and applicable questionnaires to better quantify these domains, but

until those are developed domain identification has to be based on standard clinical assessment.

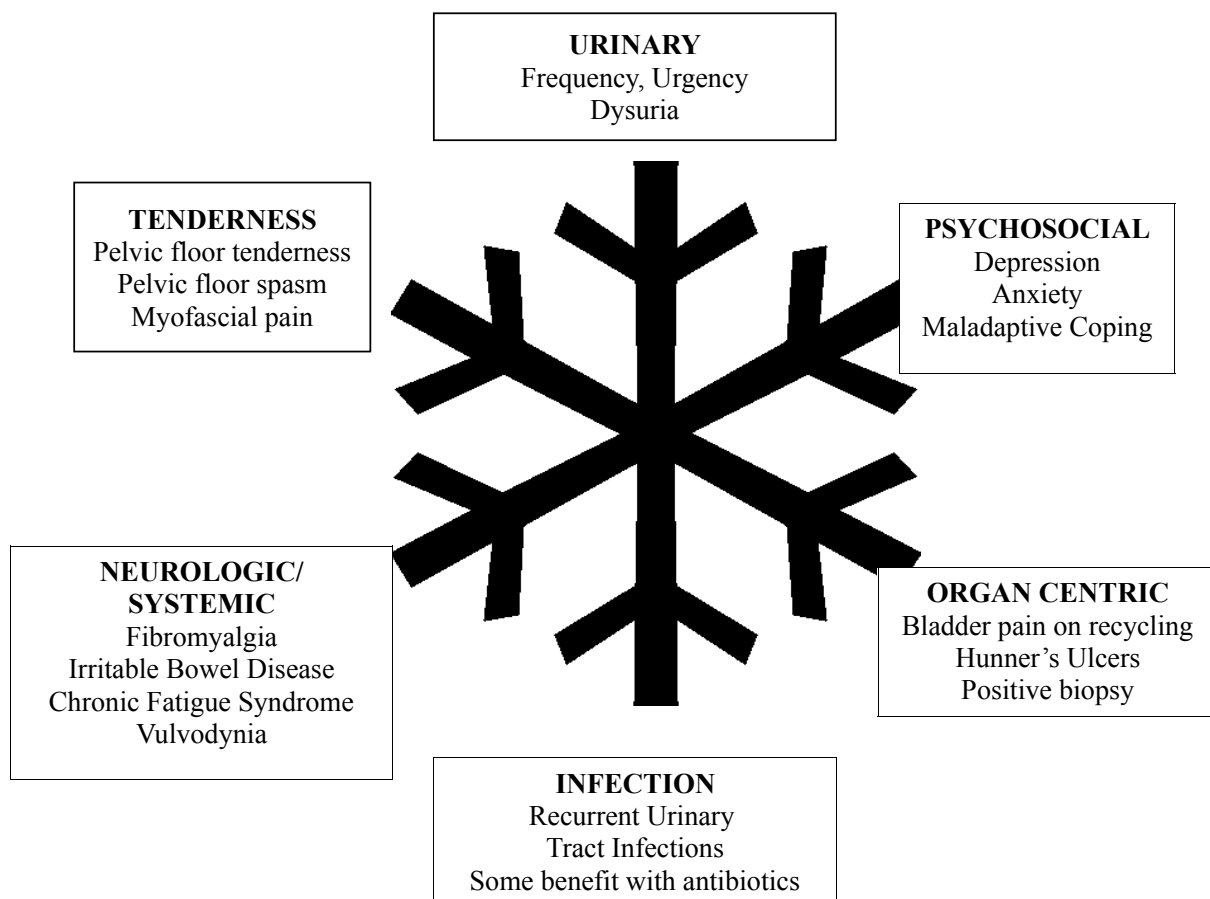
The UPOINT approach to IC will not be static, but rather extremely flexible. It should easily incorporate new epidemiology and basic science findings (including biomarkers). We believe that some of the domains should incorporate more categories as future research in etiological mechanisms, epidemiology and biomarkers will allow sub categorization in the specific UPOINT domains (for example validation of

cystoscopic findings to differentiate organ specific subdomains).

Finally the entire concept of clinical phenotyping and targeted therapy awaits confirmation in terms of improving patients' symptoms and quality of life. We are currently undertaking a "real-life" clinical practice study to determine if our hypothesis will lead to better IC management.

*Figure: UPOINT phenotypic domains ("the Snow Flake" Hypothesis)*

## UPOINT: THE SNOW FLAKE HYPOTHESIS Clinical Phenotyping of Patients with Interstitial Cystitis/Painful Bladder Syndrome



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