# *Improving the utility of clinical phenotyping in interstitial cystitis/painful bladder syndrome: from UPOINT to INPUT*

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***Introduction:*** *The phenotyping system UPOINT has proven effective in classifying patients with Urologic Pelvic Pain Syndromes in a clinically meaningful way and to guide therapy. While highly successful in men with chronic pelvic pain syndrome (CPPS), UPOINT is more limited in patients with interstitial cystitis/painful bladder syndrome (IC/PBS) since by definition all patients have the urinary and organ specific phenotype. Furthermore, AUA guidelines recommend a sequential tiered approach to therapy rather than the multimodal UPOINT scheme. We sought to modify UPOINT to be more practical and efficacious for IC/PBS.*

***Materials and methods:*** *We developed a new phenotype by removing the urinary and organ specific domains from UPOINT and adding a Hunner's ulcers (U) domain, since these patients benefit from phenotype specific therapies (fulguration, cyclosporine). This yields "INPUT": infection, neurologic/systemic, psychosocial, ulcers and tenderness of muscles. We applied this system retrospectively to our previously validated upointmd.com IC/PBS database. Symptoms were measured by the Genitourinary Pain Index (GUPI) (valid for men and women). The database was searched for patients with complete data to assess the INPUT domains and include GUPI. Men were included if they reported pain relieved by voiding and/or presence of Hunner's ulcers. Groups were compared with ANOVA, Mann-Whitney, t test or chi squared when appropriate and correlated with Spearman r.*

***Results:*** *There were 239 patients, 154 female (64%) with age range 18-79 (mean 41.8). Incidence of domains was infection 11%, neurologic/systemic 51%, psychosocial 81%, ulcers 18% and tenderness 85%. Mean total domains was 2.46 (range 0-5) and 65% had 2 or 3 positive domains while only 5% had none. There was a stepwise increase in GUPI score with increasing number of positive INPUT domains (ANOVA for differences between groups $p < 0.0001$. Correlation by Spearman $r = 0.355$ $p < 0.0001$). Presence of Hunner's ulcers increased mean symptom score (25.7 versus 29.7, $p = 0.004$) and indeed each of the domains significantly increased total GUPI score except for Infection.*

***Conclusions:*** *The INPUT phenotype in IC/PBS appears to replicate the validity and potential clinical utility of UPOINT in CPPS. Patients have a diversity of phenotypes and more positive domains correlate with more severe symptoms. Since 95% of patients have at least 1 positive domain it may benefit patients to receive multimodal therapy up front for these extra domains (eg. pelvic floor physical therapy, fulguration of ulcers) rather than relying on a sequential tiered approach.*

**Key Words:** interstitial cystitis/painful bladder syndrome, UPOINT, INPUT

## Introduction

Urologic pelvic pain syndromes comprise a heterogeneous group of patients, many of whom do not have an easily identifiable underlying etiology of their symptoms. Monotherapy often fails as each available modality may only be effective for a certain subgroup of patients. This leads to patient and clinician frustration and delay in effective care.

Men with chronic pelvic pain syndrome/chronic prostatitis (CP/CPPS) and men and women with interstitial cystitis/painful bladder syndrome (IC/PBS) make up the two main symptom complexes under the umbrella of urologic chronic pelvic pain syndromes (UCPPS). IC/PBS is defined by the Society for Urodynamics and Female Urology (SUFU) as "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes".[1] Because there is no objective biomarker for

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diagnosis of either syndrome, there remains a need for categorizing patients into distinct phenotypic sub-groups both for research and development of efficacious therapy.

The phenotyping system UPOINT (urinary, psychosocial, organ specific, infection, neurologic/systemic and tenderness) has proven effective in classifying patients with CPPS in a clinically meaningful way, allowing the implementation of multimodal individualized therapy.[2-5] However, while highly successful in men with CPPS, UPOINT has been less successful in patients with interstitial cystitis/painful bladder syndrome (IC/PBS). Diagnostic discrimination is lessened since by definition all patients have the urinary and organ specific domains. While still showing some modest improvement over a stepwise "one-size-fits-all" algorithmic approach, unlike UPOINT in CPPS patients, an increasing number of positive UPOINT domains was not correlated to increasing symptom score[6] and UPOINT driven therapy in IC/PBS did not show the same efficacy as for CP/CPPS.[6]

We sought to modify UPOINT to be more practical and efficacious for IC/PBS. We developed a new phenotype by removing the redundant urinary and organ specific domains from UPOINT and adding a Hunner's lesions (U) domain, since patients with these lesions benefit from specific therapies (fulguration, cyclosporine). This yields the acronym "INPUT": infection, neurologic/systemic, psychosocial, Hunner's lesions and tenderness of muscles. We hypothesized that each patient with IC/PBS population would have at least one positive INPUT domain and that the number of INPUT domains would directly correlate with the symptom severity as measured by the Genitourinary Pain Index (GUPI). We also hypothesized that these patients would be heterogenous, with separation of different populations into one or more phenotypic categories based on positive domains.

## Materials and methods

To investigate the clinical utility of the proposed INPUT framework, we applied this system retrospectively to our previously validated upointmd.com IC/PBS database and measured symptoms by the GUPI.[7] This previously-gathered web-based cohort consisted of men and women who submitted data on the UPOINT (http://www.upointmd.com) IC/PBS database between May 7, 2009 and Jan 2014. Symptoms for this IC/PBS cohort were measured by the validated GUPI. The study was approved by the Cleveland Clinic Institutional Review Board.

In generating this cohort, we searched the database for patients with complete data to assess the INPUT domains. We excluded those records with significant missing data that would not allow for the utilization of the INPUT classification scheme. Both male and female patients were included, but to enter the cohort, men had to report pain relieved by voiding and/or the presence of Hunner's lesions.

For comparison between groups, ANOVA, Mann-Whitney, Student's t-test and chi-squared tests were used as appropriate. For correlation analysis, Spearman's correlation coefficient was used. All analyses were performed using the statistical software package Prism version 5.0. Normalized data visualization generated with Orange open source data visualization package (https://orange.biolab.si/).

TABLE 1. **Diagnostic criteria and available treatment modalities. Web-based questionnaire asks both presence of given diagnosis in "yes/no" format (ie "depression", "fibromyalgia") as well as symptoms (ie "Does the patient feel helpless or hopeless about their condition" "Is there pain outside the pelvis and genitals") Please refer to Tran et al[7] for a full representation of the web-based questionnaire.**

| Domain | Defining characteristics | Available therapies |
|---|---|---|
| Infection | Positive cultures in prostatic fluid in absence of UTI (men)<br>Atypical bacteria in the urine (eg. mycoplasma, ureaplasma) | Antibiotics |
| Neurologic/systemic | Pain outside the pelvis<br>Systemic pain syndromes | Pregabalin<br>Amitryptyline |
| Pyschosocial | Clinical depression<br>Catastrophizing | Psychological or psychiatric referral |
| HUnner's lesions | Cystoscopic confirmation | Fulguration, cyclosporine |
| Tenderness | Pelvic floor spasm<br>Muscle trigger pain | Pelvic floor physical therapy<br>Myofascial release |

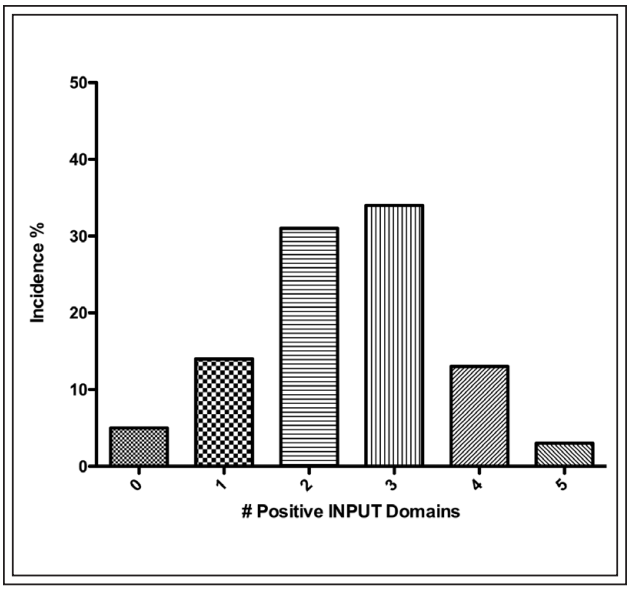


**Figure 1.** Percentages of the total population (n = 239) by number of positive INPUT domains (0-5). Mean total domains was 2.46. Five percent of patients had zero positive domains. Sixty-five percent had 2-3 positive domains.

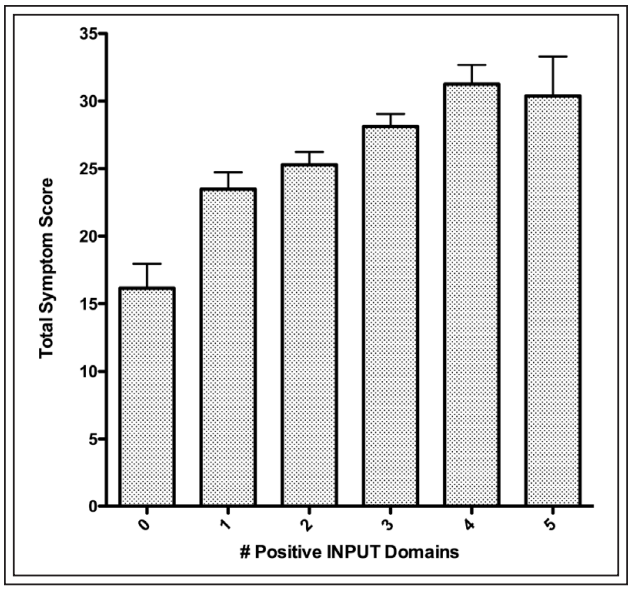


**Figure 2.** The number of positive INPUT domains plotted against increasing symptoms score. There was a stepwise increase in GUPI score with increasing number of positive INPUT domains (ANOVA for differences between groups $p < 0.0001$).

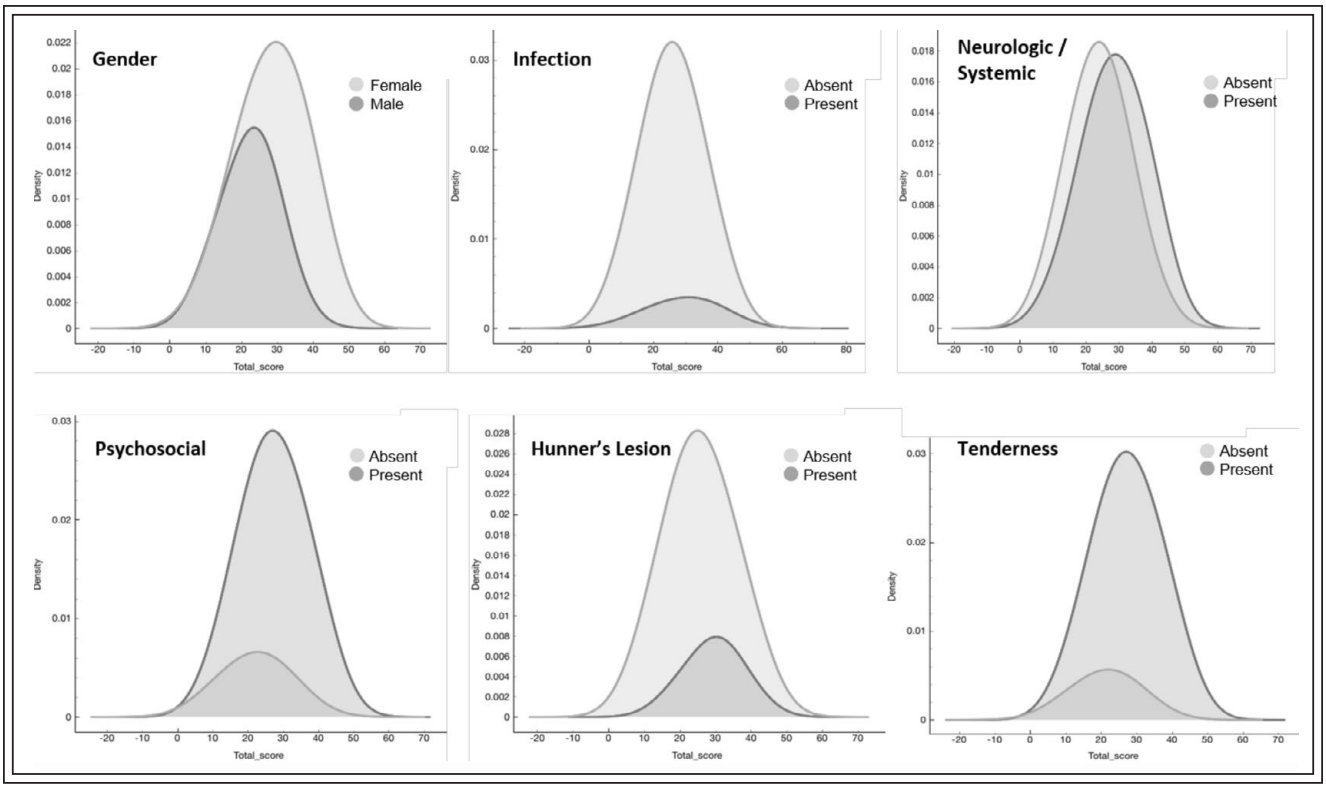


**Figure 3.** Visualization of the frequency of symptom severity by each domain and by gender. Gaussian kernel density estimation.

## Results

Of about 1200 patients in the database, 239 met our inclusion criteria for IC/PBS and had sufficient data. Of these, 154 were female (64%), with an age range of 18-79 years (mean 41.8). The 83 men had a mean age of 40.4 years (range 21-79). Definition and representative symptom-directed therapies for each of the five INPUT domains are shown in Table 1.

The incidence of the INPUT domains was infection 11%, neurologic/systemic 51%, psychosocial 81%, Hunner's Lesions 18% and tenderness 85%, Figure 1. The mean total domains per patient was 2.46 (range 0-5) and 65% had 2 or 3 positive domains while only 5% had none. There was a stepwise increase in GUPI score with increasing number of positive INPUT domains (ANOVA for differences between groups $p < 0.0001$, correlation by Spearman $r = 0.355$ $p < 0.0001$; Figure 2).

Visualization of normalized data is shown in Figure 3 representing frequency of increasing symptom severity by gender and by each INPUT domain. Woman had a slightly increased frequency of greater symptom severity than men. Presence of infection did not correlate with greater symptom severity while each other domain did significantly correlate with more severe symptoms. The presence of Hunner's lesions increased mean GUPI score (25.7 versus 29.7, $p = 0.004$).

## Discussion

IC/PBS is a clinically challenging syndrome encompassing an overlapping range of phenotypes. It is difficult to estimate the prevalence of IC/PBS due to the variability in presentation but large-scale studies have estimated that it affects approximately 83,000 men and 1.2 million women across the United States.[8] Patients with IC/PBS have significantly decreased quality of life compared to controls as well as an increased incidence of co-morbid conditions including depression and systemic chronic pain disorders with up to 75% of patients reporting pain outside the pelvis in the literature.[9-11] These patients also often have impaired coping mechanisms with catastrophizing being particularly common.[12,13] The existence of systemic and psychiatric symptoms further decreases the quality of life in large subset of patients with multiple co-morbidities.[14,15] The multi-factorial nature of the syndrome reinforces the need for multi-disciplinary care. In fact, among a cohort of women with IC/PBS originally phenotyped under the UPOINT system, just 13% of patients had only organ-specific and urinary domains positive.[16] This implies that effective care will almost always be multi-modal in nature for this patient population with bladder-centric treatments alone destined to fail or only be of partial effectiveness in a majority of patients.

We refined the original UPOINT system to exclude the urinary and organ-specific domains because close to 100% of patients have criteria for these domains and they therefore lose any discriminative function. We added the Hunner's lesion domain for IC/PBS because these patients are known to respond differently to certain therapies (eg cyclosporine, fulguration). With this revised system we found an increasing symptom severity score with increasing number of positive INPUT domains in our patient population. In addition, each domain except infection independently significantly correlated with an increase in GUPI score. Although, particularly in women, concurrent infection is often considered not compatible with a true diagnosis of IC/PBS, a true co-existing infection with a uropathogen may acutely exacerbate underlying symptoms and should be treated. However, infection may not have correlated with increased symptom severity on its own, perhaps because of its transient nature, at least in the case of acute cystitis. It is also possible that reporting of the infection domain is the most susceptible to patient misinterpretation.

Due to the difficulty in individualization of treatment care paths for these patients, there is a need for a reliable clinical phenotyping system. The INPUT phenotype in IC/PBS appears to replicate the validity and potential utility of UPOINT in CPPS. Since 95% of patients have at least one positive domain we believe that it will benefit patients to receive multimodal therapy up front for each positive domain (eg. pelvic floor physical therapy, fulguration of ulcers) rather than relying on a sequential tiered approach. The current AUA guidelines for IC advocate a stepwise approach to patient management with division of treatments into first to sixth-line therapies. However, the guidelines also state that multimodal therapy is left up to the discretion of the provider and should be individualized to each patient.[17] For an example of how phenotyping may help guide the appropriate point of entry for evidence-based treatments, a patient with positive Hunner's lesion domain alone would likely not benefit from proceeding through pelvic floor physical therapy while fulguration and cyclosporine are recommended as third and fifth line treatments, respectively. With the aid of clinical phenotyping tools such as the INPUT stratification system, the ability to implement the appropriate patient-directed and multimodal therapy will become much easier.

Limitations include the retrospective nature of the study and the reliance on patient-reported diagnoses and symptoms. Prospective validation of INPUT in a clinical setting is needed. From there, the impact of phenotype-directed treatment on patient symptom severity and quality of life can be investigated and the model refined as needed. Also, there currently is no level I evidence for phenotype driven specific therapy. However, the INPUT phenotype classification lays the groundwork for directed care and provides a more refined best guess on which therapies to start with for a given patient. Prospective studies remain needed to elucidate the most appropriate targeted therapy strategy. □

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