

Phenotype-directed Management of Interstitial Cystitis/Bladder Pain Syndrome

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OBJECTIVE	To assess a flexible therapeutic strategy for patients referred to a specialized interstitial cystitis/bladder pain syndrome (IC/BPS) clinic using an individualized phenotype-directed treatment plan based on clinically based urinary, psychosocial, organ-specific, infection, neurologic or nonbladder, and tenderness of pelvic floor (UPOINT) categorization, instead of the traditional algorithmic stepwise approach.
METHODS	Consecutive patients referred to a specialized tertiary IC/BPS clinic with at least 1 follow-up posttreatment visit were categorized according to their UPOINT status and treated according to previously published individualized phenotype-based treatment plan. Patients were assessed at baseline and up to 2 years with validated symptom scores (interstitial cystitis symptom score [ICSI]; and pain urgency frequency questionnaire) as well as pain and voiding assessments.
RESULTS	Follow-up visit data were available for 93 patients (mean age, 45.2 years; median age, 44 years; mean ICSI, 13.2 ± 3.6). Patients reported a median of 4 UPOINT domains (mean, 3.7 ± 0.94) with the following distribution: U = 100%; P = 31.2%; O = 97.8%; I = 45.2%; N = 39.8%; and T = 55.9%. The mean decrease in ICSI was 3.4 points. Significant clinical improvement (>30% decrease in ICSI) was observed in 46.2% compared with initial baseline visit. Pain urgency frequency, and pain and urgency scoring changes were comparable. No correlation between severity of symptoms and number of domains and ICSI decrease was observed.
CONCLUSION	Almost 50% of patients referred to a tertiary IC/BPS clinic, regardless of the complexity or severity of condition, experienced clinically significant improvement using an individualized phenotype-directed therapeutic approach. UROLOGY ■: ■-■, 2014. © 2014 Elsevier Inc.

Our goal, as physicians managing interstitial cystitis/bladder pain syndrome (IC/BPS) is to find the ultimate best treatment for our patients suffering from this painful and debilitating enigmatic condition. Careful analysis of the available evidence can only lead to the conclusion that there is no single ideal therapy or a combination of therapies that will benefit all patients.¹ The American Urological Association (AUA) IC/BPS guidelines² provide a best evidence stepwise single therapy approach to treat patients with IC/BPS. Unfortunately, this approach does fail in some patients who continue to be impacted by this condition despite our best efforts. For those patients who do not improve using our standard or traditional approach, we have

suggested designing individualized therapeutic strategies based on each patient's unique clinical phenotype.^{3,4} We have adapted the UPOINT (urinary, psychosocial, organ-specific, infection, neurologic and/or extrapelvic/systemic pain, and tenderness of pelvic floor) phenotype classification system, which has worked so well in managing men with chronic pelvic pain syndrome⁵ to patients diagnosed with IC/BPS. We have validated the concept of using this classification system to patients in our IC/BPS clinic.^{6,7} We have since adapted the current IC/BPS guidelines into this individualized phenotype-directed (individualized multimodal plan rather than usual first, second, and third line therapy approach) therapeutic strategy for treating refractory patients referred to our tertiary specialized IC/BPS clinic. The purpose of this study was to prospectively determine clinical improvement in difficult, mostly treatment-refractory patients treated by a multimodal approach driven by their UPOINT phenotype. We hypothesize that the results would be superior to published results of monotherapy trials.

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PATIENTS AND METHODS

Patients

Consecutive patients (n = 100) diagnosed with IC/BPS referred to a specialized tertiary IC/BPS clinic, excluding patients assessed for consultation only, were followed prospectively until

Table 1. UPOINT domains: patients were categorized into the following clinical domains and treatments were chosen accordingly (details have been described previously⁷ and are outlined in text)**U—urinary**

Categorization: patients report bothersome urinary frequency, urgency, nocturia, incontinence, and/or dysuria. It was expected that most, if not all patients, would be included in this domain because of the criteria used to make the clinical diagnosis of IC/PBS.

Treatment: antimuscarinics, pyridium, and bladder retraining.

P—psychosocial

Categorization: patients determined to be clinically depressed (or with recent history of depression), those with identifiable maladaptive coping mechanisms (eg, catastrophizing), or problems with social interactions. This is a clinical assessment based on history and focused interview.

Treatment: education, coping, Cognitive Behavioral Therapy, tricyclic antidepressants, and anxiolytics.

O—organ specific

Categorization: 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 ulcers noted during cystoscopy (either local or general anesthesia), and/or patients with typical inflammation confirmed on bladder biopsy. 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) were assessed before and after an anesthetic challenge test (200 mg of lidocaine alkalized with 8.4% sodium bicarbonate for a final solution volume of 10 mL instilled in an empty bladder and then drained by a catheter after 10-15 min). It is expected that most patients would be included in this domain because of the criteria used to make the clinical diagnosis of IC/BPS.

Treatment: pyridium, intravesical GAGs, DMSO, lidocaine, pentosan polysulfate sodium, and quercetin.

I—infection

Categorization: patients confirmed to have significant bacteriuria with typical uropathogenic bacteria within the previous 2 y associated with an exacerbation in baseline symptoms and return to baseline symptoms after appropriate antimicrobial therapy.

Treatment: antimicrobials

N—neurologic/systemic

Categorization: patients with a concurrent diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, vulvodynia, or any other condition that suggests neuropathy or neural upregulation.

Treatment: amitriptyline, gabapentinoids, system specific therapies, and referral.

T—tenderness

Categorization: patients have pelvic floor or lower abdominal muscle/ligament tenderness and/or pain, including but not restricted to specific trigger points during standardized abdominal and pelvic examination.

Treatment: physiotherapy, exercise, muscle relaxants, and injection therapy.

DMSO, dimethyl sulfoxide; GAG, glycosaminoglycan; IC/BPS, interstitial cystitis/bladder pain syndrome; UPOINT, urinary, psychosocial, organ specific, infection, neurologic or nonbladder, and tenderness of pelvic floor.

last visit or a maximum of 2 years. Patients were diagnosed on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least 1 other urinary symptom, such as urgency or frequency. All other diseases that could cause pelvic symptoms were excluded with our standardized diagnostic algorithm. Patients, therefore, would have mostly fulfilled the diagnostic criteria described in the AUA IC/BPS guidelines.²

UPOINT Phenotyping

Patients were categorized according to their UPOINT status and were treated according to our previously published diagnostic workup.⁷ In summary, this consisted of general and disease-specific history, focused physical examination, including pelvic examination, urinalysis, urine culture, urine cytology and, if indicated, cystoscopy (typically under local anesthesia with bicarbonate-lidocaine bladder challenge testing at the same time⁷). This categorization is therefore based on standard evaluation of symptoms, history, physical examination, urine studies, and other traditional tests, such as cystoscopy (if indicated). [Table 1](#) describes how this evaluation was used to phenotypically categorize the individual patients.

Individualized Treatment Plan

An individualized phenotype-based treatment plan was developed for each patient based on the general outline described in [Table 1](#). Our clinic treatment algorithm, based on best evidence

principles, involves initial management with a conservative approach that includes education, diet and exercise modification, and relaxation or stress reduction. Almost all patients present with urinary symptoms undergo a trial of anticholinergics and urinary analgesics. All patients with bacteriuria are treated with a short course of an antibiotic.⁸ Those patients who have bladder-specific pain (by history, but if in doubt, we usually confirm with an anesthetic challenge test⁷) are managed with bladder-centric therapies, which include intravesical dimethyl sulfoxide, heparin, chondroitin sulfate,⁹ hyaluronic acid, and/or alkalized lidocaine¹⁰ as mono or combination therapy or, alternatively, oral pentosan polysulfate ± hydroxyzine (if has an allergic history).^{11,12} Those with refractory organ-specific problems (eg, Hunner lesion-related pain) are considered for hydrodistention under general anesthetic, cauterization of lesions, experimental treatments (such as continuous lidocaine infusion¹³ or Bacillus Calmette-Guerin therapy¹⁴), and more recently cyclosporine A for selected patients.¹⁵ Pelvic floor tenderness, painful trigger points, and myofascial pain are managed with local heat therapy, exercises, and/or physical therapy.¹⁶ Neuropathic pain is treated with amitriptyline¹⁷ and/or gabapentinoids¹⁸ and/or analgesics (with an attempt to limit opioid use¹⁹). Patients identified with nonbladder-associated pain syndromes such as irritable bowel syndrome, vulvodynia, fibromyalgia, and chronic fatigue syndrome²⁰ may be referred for specialist therapy. We carefully assess our patients for psychological^{6,21} and social problems,^{22,23} including suicidal ideation,²⁴

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