Review Article

Novel research approaches for interstitial cystitis/bladder pain syndrome: thinking beyond the bladder

Chris Mullins, Tamara Bavendam, Ziya Kirkali, John W. Kusek

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA

Contributions: (I) Conception and design: All Authors; (II) Administrative support: NIDDK, NIH; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chris Mullins, PhD. Director of Basic Cell Biology Programs in Urologic and Kidney Disease, Division of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 2 Democracy Plaza, Room 637, 6707 Democracy Blvd., Bethesda, MD 20892-5458, USA. Email: mullinsC@extra.niddk.nih.gov.

Abstract: Despite years of basic and clinical research focused on interstitial cystitis/bladder pain syndrome (IC/BPS), including clinical trials of candidate therapies, there remains an insufficient understanding of underlying cause(s), important clinical features and a lack of effective treatments for this syndrome. Progress has been limited and is likely due to many factors, including a primary focus on the bladder and lower urinary tract as origin of symptoms without adequately considering the potential influence of other local (pelvic) or systemic factors. Traditionally, there has been a lack of sufficiently diverse expertise and application of novel, integrated methods to study this syndrome. However, some important insights have been gained. For example, epidemiological studies have revealed that IC/BPS is commonly associated with other chronic pain conditions, including fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome. These observations suggest that IC/BPS may involve systemic pathophysiology, including alterations of the central nervous system in some patients. Furthermore, there may be multiple causes and contributing factors that manifest in the symptoms of IC/BPS leading to multiple patient sub-groups or phenotypes. Innovative research is necessary to allow for a more complete description of the relationship between this syndrome and other disorders with overlapping symptoms. This report provides examples of such innovative research studies and their findings which have the potential to provide fresh insights into IC/BPS and disorders associated with chronic pain through characterization of broad physiologic systems, as well as assessment of the contribution of the bladder and lower urinary tract. They may also serve as models for future investigation of symptom-based urologic and non-urologic disorders that may remain incompletely characterized by previous, more traditional research approaches. Furthermore, it is anticipated a more holistic understanding of chronic urologic pain and dysfunction will ensue from productive interactions between IC/BPS studies like those described here and broader cutting-edge research endeavors focused on potentially related chronic pain disorders. A more comprehensive vision for IC/BPS inquiry is anticipated to yield new insights into basic disease mechanisms and clinical characteristics that will inform future research studies that will lead to more effective therapies and improved clinical care for these patients.

Keywords: Interstitial cystitis (IC); bladder pain syndrome (BPS); urologic chronic pelvic pain syndrome (UCPPS); research models; translational science

Submitted Jul 29, 2015. Accepted for publication Aug 03, 2015.
doi: 10.3978/j.issn.2223-4683.2015.08.01
View this article at: http://dx.doi.org/10.3978/j.issn.2223-4683.2015.08.01

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined by the hallmark symptom of chronic pain described by patients as being localized to the pelvic organs, pelvic floor myofascial support, or external genitalia often accompanied by urinary symptoms, such as urgency or frequency (1-3). IC/BPS occurs in both males and females over a broad age range and across ethnic/racial groups (4). The morbidity of IC/BPS is substantial and often leads to poor quality of life for both patients and their partners (4). IC/PBS diagnosis is primarily based on patient reported symptoms and exclusion of other disorders, due to the lack of consistent physical findings. The wide spectrum of symptoms found in IC/BPS suggests that this syndrome may have subgroups which manifest in a similar way clinically but have differing underlying etiologies.

The prevalence estimates of IC/BPS vary considerably likely because of differences in source populations and case ascertainment (1). The RAND Interstitial Cystitis Epidemiology (RICE) Study, through a probability sample of U.S. women contacted by telephone, estimated IC/BPS prevalence between 2.7% and 6.53% among person age 18 or older using case definitions of high specificity and high sensitivity, respectively (5). This represent between 3.3 and 7.9 million affected individuals. The RICE Study also estimates IC/BPS prevalence in men between 1.9% and 4.2% (6) while community-based prevalence estimates from the Boston Area Community Health (BACH) Survey suggest 1.3% of U.S. men between the ages of 30 and 79 report symptoms of IC/BPS (7).

The bladder has historically been thought to be the origin of IC/BPS symptoms based primarily on patient-reported pain, pressure, or discomfort related to filling of this organ. However, this dogma is challenged by observations by the absence of an identifiable bladder pathology in many IC/PBS patients and patients without bladders can continue to report symptoms consistent with this syndrome (8-11). In addition, numerous studies have shown IC/BPS is associated with various conditions characterized by chronic pain, such as vulvodynia, endometriosis, fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome [for a review see (12)]; suggesting that central sensitization mechanisms contribute to the manifestation of IC/PBS, at least in some patients.

Here we provide an overview of research efforts to characterize IC/BPS and evaluate therapies; when appropriate the possible limitations of this prior work are highlighted. A rationale for developing new strategies to address longstanding and fundamental questions for IC/BPS is also proposed and a number of research and clinical programs that have employed such novel approaches are cited. The importance of collaboration between IC/BPS-focused studies and wider research efforts to promote a more holistic understanding of this syndrome in the context of other urologic and non-urologic disorders is also stressed. These research directions are expected to foster new insights into IC/BPS that may inform future clinical studies and treatment. In this article we restrict our terminology to IC/BPS except in cases where the original reports used other nomenclature.

Limitations of past approaches

Numerous research studies and clinical trials of IC/BPS have been conducted since the early 1990's to identify etiology, describe clinical course and risk factors, and identify effective therapies for this syndrome.

Efforts to describe fundamental IC/BPS pathophysiology have addressed a broad set of hypotheses of underlying mechanisms, primarily because of the wide variation in clinical presentation in these patients. Studies have focused on the contribution of inflammatory mediators and the immune system, for example autoimmunity; urothelial cell structural and function abnormalities, such as maintenance of the bladder barrier function and cellular signaling controlling proliferation, respectively; alterations in pain sensation and voiding due to disruptions in bladder sensory neurons and/or central nervous system involvement; and establishment of visceral pain resulting from prior microbial infection, such as urinary tract infections (13-18). Many studies of possible disease mechanism have been performed in animal models with features of the clinical condition. A diversity of induced and naturally occurring animal models, primarily rodent and feline, has used to assess neuronal, inflammatory, and infectious processes, among others. While these efforts have certainly provided new insights into relevant biological events and allowed for *in vivo* testing of possible therapeutic interventions the relevance of these *in vivo* findings to human IC/BPS is the subject of long debate (e.g., potential confounders of genetic/strain differences and the absence of key features of the syndrome) (19).

Concurrent with attempts at defining biologic aspects, epidemiological studies have addressed IC/BPS definition, impact, course, and risk factors. For example, the Interstitial Cystitis Database (ICDB) Study revealed

a greater heterogeneity in patient characteristics than previously thought (20). Both the RICE Study (5,6) and BACH Survey (4,7,21) developed improved case definitions for IC/BPS; more accurate estimates of prevalence; and further characterized symptoms, impact, and risk factors in community-based populations. Importantly, as noted a number of epidemiological studies have shown an association of conditions that share chronic pain as a major symptom with IC/BPS (22-27).

A number of large, multi-center clinical study groups, many supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), have examined the efficacy of a wide range of interventions for IC/BPS in placebo/sham controlled clinical trials. These include the Interstitial Cystitis Clinical Trials Group (ICCTG); Interstitial Cystitis Collaborative Research Network (ICCRN); and in light of proposed similarities between IC/BPS and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), the Urologic Pelvic Pain Collaborative Research Network (UPPCRN) [for a more detailed review see (28)]. Of the large number of therapies evaluated by these studies perhaps the most encouraging findings were observed for pelvic floor myofascial physical therapy among women with IC/PBS and pelvic floor tenderness. This intervention resulted in an improvement in an overall symptom measure versus global therapeutic message in a cohort of newly diagnosed IC/PBS (29,30). However, assessments of pain and urologic dysfunction (e.g., urgency and frequency) were not significantly different between treatment groups and information on duration of the benefit is lacking, suggesting further studies are needed to define the longer-term clinical benefit and generalizability of this treatment.

Although new insights have been gained from previous studies there remains an incomplete understanding of the natural history of UCPPS, including risk factors for development and variation of pain and urologic symptoms and the nature of symptom fluctuations over time ("flares"); a lack of major insights into fundamental pathophysiology; no consensus on diagnostic or prognostic criteria or a consensus clinical definition; and no generally effective treatment options or prevention strategies for patients. The relationships between IC/BPS and co-occurring disorders and with other urologic conditions with overlapping symptoms have not yet been defined. In addition, there is a strong likelihood that patients with IC/PBS may possess differing clinical phenotypes that likely influence their course of illness. Such sub-groups, if present, will need to be considered in the design of future clinical trials.

This inadequate progress on understanding this syndrome is likely due to a number of limitations in previous approaches, including an over emphasis on identifying pathologies in the bladder without consistent consideration of other pelvic conditions or systemic contributions, insufficient collaborations between basic and clinical researchers and with disciplines beyond urology, over-interpreting data from animal models that are insufficiently validated relative to patient symptomatology, and too few innovative and integrated research strategies. In addition, it is possible that due to the inclusion criteria defining IC/BPS some clinical trials have examined efficacy in cohorts comprised of heterogeneous patient phenotypes with differing etiologies, but overlapping symptom profiles. This has the potential to mask true efficacy of treatments (i.e., reduce statistical power) that may be specific to certain phenotypes.

Stepping back to move forward: advancing new views of IC/BPS

Following the outcome of the above studies it became apparent that traditional approaches had not yielded sufficient new insights. New perspectives and novel study designs were clearly needed to expand our understanding of the pathophysiology underlying IC/BPS and ultimately to improving clinical care for patients. These would be expected to involve diverse urologic and non-urologic expertise and new methodological approaches to promote a comprehensive description of IC/BPS cause and patient phenotype. Studies must also be informed by recent insights that open new avenues of research. For example, findings that IC/BPS in some patients is found in association with other pain conditions suggesting systemic involvement beyond the bladder, such as central nervous system contributions seen in other chronic pain disorders (31-33).

In the following sections we briefly describe the design and selected findings from recent, and in our view, novel research studies that have addressed key clinical questions for IC/BPS. These efforts employ unique methodology, study designs, and expertise that extend beyond traditional basic science or clinical investigations and promote new views of IC/BPS beyond solely a "disorder of the bladder". Common to these studies is the growing realization that to make meaningful improvements in clinical management it is first necessary to take a step back and develop a more comprehensive and fundamental understanding of IC/BPS.

Events Preceding Interstitial Cystitis (EPIC)

As noted above, a large number of epidemiological studies of IC/BPS have been conducted over the past two decades. Many of these have reported prevalence and incidence estimations but few have been prospective and none have focused exclusively on new cases. While useful to describe the burden of IC/BPS in diverse settings, prior studies have provided only limited information to assess the important characteristics of this syndrome and possible etiologic or inciting factors. EPIC study was designed to identify risk factors for interstitial cystitis/painful bladder syndrome (IC/PBS) (the term used by investigators) and prospectively characterize its clinical features (34). This unique U.S.-wide case-control study followed prospectively 312 "incident" cases (defined as a history of IC/PBS of 12 months or less) of IC/PBS in women and has provided important new information for this syndrome. Such studies of newly diagnosed/recent onset cases provide unique opportunities to inform on inciting etiology and evolving pathogenesis. Highlights of this investigation are described below.

The treated natural history of IC/PBS remains uncertain and remains of great interest to both patients and health care providers and its study may provide information to predict clinical course. Approximately one-third of EPIC participants reported symptom improvement from baseline to the 48-month end of follow-up (35). However, less than 10% reported complete remission of their symptoms.

In a case-control analysis (controls were matched on sex, age and region of the country) more IC/PBS cases than controls had surgeries prior to date of symptom onset than controls (36). However, when presence of chronic pelvic pain was included in the statistical model the association between surgeries and IC/PBS was attenuated and was not statistically significant. This suggests that the apparent indications for surgeries, not the surgeries themselves were stronger risk factors for this syndrome. Infection as a cause of IC/PBS has long been postulated with scant epidemiologic evidence to support or refute this hypothesis. Using urine culture, urinalysis and symptoms separately and in combination to define infection and inflammation between 18% and 36% of the participants were found to have evidence of a UTI at the onset of IC/PBS. Studies using state-of-the-art methods such as those used in the MAPP Research Network (37) (described below) will be necessary to more definitively define the importance of infectious agents. As noted earlier, there is strong epidemiological evidence of an occurrence of non-bladder syndromes with IC/PBS. The importance of this clustering of syndromes remains uncertain; for example whether non-bladder syndromes are present prior to ("antecedent") onset or are identified post-diagnosis of IC/PBS is not known. Among EPIC cases, using the most stringent definition (symptom based diagnoses) the antecedent prevalence of chronic fatigue syndrome, chronic widespread pain, irritable bowel syndrome, migraine and panic were higher than in controls (23), about three-fourths of the cases had at least one non-bladder syndrome, and these non-bladder syndromes were found to be strong risk factor for IC/PBS (38), suggesting that these patients may have a systemic syndrome. The prognostic importance of non-bladder syndromes was shown subsequently during follow-up as self-report of chronic fatigue syndrome at baseline was associated with worsening of IC/PBS symptoms (39). Whether the occurrence of a non-bladder syndrome resulted from or initiated IC/PBS or there is shared common pathogenesis between them remains to be elucidated (22).

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

The NIDDK initiated the MAPP Research Network in 2008 as a novel effort to address clinically relevant questions of natural history, patient phenotype, the relationship between associated pain conditions, and underlying mechanisms for urologic chronic pelvic pain syndrome (UCPPS) (http://www.mappnetwork.org/) (28). UCPPS is a term adopted by the MAPP Research Network to encompass both IC/BPS and CP/CPPS, which could be related based on overlapping symptoms (3). The MAPP Research Network has developed a highly collaborative and integrated research designs that views IC/BPS (in the larger context of UCPPS) as a systemic disorder involving not just the urologic system (e.g., bladder) but also diverse non-urologic physiological systems and processes. Studies incorporate novel methodological approaches conducted by a broad range of investigators including urologists experienced with IC/BPS patients, as well as expertise in neurobiology, pain research, the microbiome, biomarker discovery and validation, animal model systems, epidemiology, psychology and psychosocial measures, immuno-biology, quantitative sensory testing, and many others. The Network's primary goal is to inform the design of future clinical studies/trials and ultimately to advance clinical care for patients.

The MAPP Research Network includes nine Discovery Sites that conduct cross-site (i.e., Trans-MAPP) studies; a Data Coordination Core (DCC) that provides centralized data management and bio-statistical analyses and administrative support for network efforts; and a Tissue Analysis and Technology Core (TATC) that provides oversight for bio-specimen collection and sample banking, annotation, and distribution for the network (40). The network's initial, central scientific protocol, the Trans-MAPP Epidemiology/Phenotyping (EP) Study, was a prospective observational study of the treated natural history of UCPPS. This study employed extensive urologic and non-urologic measures at baseline and during 12-month follow-up period in conjunction with concurrent characterization of diverse physiological systems for IC/BPS participants and control cohorts (40). The MAPP Research Network has also developed new strategies to improve the translational significance of animal model studies by validating models based on key features of human IC/BPS (41).

A novel feature of the MAPP Research Network's design is the highly integrated nature of the diverse approaches. This is accomplished through common clinical phenotyping of all IC/BPS and control participants, who then are further evaluated by most and often all of the Discovery Sites; the collection and assay of common biological samples; and centralized data management, quality control and analysis by the DCC. In addition, neuroimaging parameters are standardized across sites and neuro-scan data is managed centrally by the University of California at Los Angeles (UCLA) Discovery Site's Central Nervous System (CNS) Data Core. In this way complementary, this permits data from the various studies to be combined for a single participant or group to provide a comprehensive assessment of important features of IC/BPS.

MAPP Research Network studies are yielding new insights into IC/BPS pathophysiology and clinical phenotypes. Findings from a neuroimaging study of 82 IC/BPS patients and 85 healthy controls at five sites suggest alterations in sensorimotor components of the central nervous system known to mediate bladder function, which differs from abnormalities observed in more classic pain regions reported for other persistent pain conditions (42). Biomarker studies suggest a loss of inflammatory control linked to hypothalamic-pituitary-adrenal (HPA) dysregulation and Toll-like receptor (TLR)-4 is associated with pain severity in IC/BPS patients (43). Analysis of self-report data reveals IC/BPS patients report diverse non-urological chronic pain syndromes and an association between the presence of these conditions and urological and psychosocial symptom severity (44). Qualitative studies of symptom flares have revealed a much wider spectrum of symptom exacerbation characteristics and patient experiences than previously appreciated (45). Ongoing analyses of the MAPP Research Network data also suggest multiple, clinically relevant sub-groups of IC/BPS patients exist that may be differentiated by their pain and urologic dysfunction profiles. Furthermore, preliminary analyses reveal that some phenotypes are at a higher risk of symptom worsening. Further exploration of these and many other insights are ongoing by network investigators.

In 2015, the MAPP Research Network initiated a second phase of integrated, collaborative studies designed to expand upon insights from initial efforts and continue to address the network's central goals. Studies will further describe changes in UCPPS (i.e., IC/BPS and CP/CPPS) symptoms over time and identify corresponding, underlying biological factors associated with symptom profiles; examine the contributions of the microbiome; examine the relationship between treatment response (in the setting of usual clinical care) and phenotype; and further define clinically significant patient sub-groups; as well as other questions.

The Interstitial Cystitis: Elucidation of Psychophysiologic and Autonomic Characteristics (ICEPAC)

The ICEPAC study was initiated in 2009 as a multi-site, multi-disciplinary effort to assess the autonomic nervous system (ANS) and other potential psychophysiologic contributors to IC/BPS symptoms (46). The ICEPAC study hypothesized that IC/BPS has abnormalities in the ANS different from those in other female chronic pelvic pain disorders, such as myofascial pelvic pain (MPP), not characterized by bladder dysfunction. The investigators also proposed that previous findings in animal models and patients together suggest a correlation between increased sympathetic system (the "urgent response" branch of the ANS) outflow, dysregulation of the hypothalamic-pituitary-adrenal axis (e.g., lower circulating cortisol), and symptoms (e.g., pain and urgency) in IC/BPS, thus further supporting this scientific direction (46).

ICEPAC investigators assessed female chronic pelvic pain subjects, including IC/BPS, MPP, and IC/BPS+MPP cohorts, and healthy controls through a cross-sectional study design that included measures of urologic function (e.g., voiding diaries, ultrasound, and uroflow measures), abdominal and pelvic floor tenderness, and patient report

measures of psychological and stress factors. Broad quantitative assessments of neurophysiology were also collected with a focus on the ANS, including both the sympathetic and parasympathetic systems (e.g., tests of cardiac and vasomotor function as indicators of ANS function). While no ANS structural abnormalities were observed in IC/BPS patients versus healthy controls, differences in heart rate variability (HRV) were observed between individuals with IC/BPS, MPP, and IC/BPS + MPP (47,48). These findings suggest abnormal ANS function is not simply a consequence of the presence of pain and HRV may serve as a functional biomarker for patient sub-grouping (48).

Insights gained during ICEPAC are now being used to develop the follow-on Interstitial Cystitis: Examination of the Central Autonomic Network (ICECAN). The multi-site ICECAN, to be initiated in 2015, will conduct a longitudinal study of IC/BPS, MPP ± IC/BPS, and healthy control cohorts to address questions of ANS functional causality in IC/BPS and the potential for ANS modulation in moderating IC/BPS symptoms. It will also include a detailed examination of ANS functional indices through fMRI. ICECAN expands on the novel foundation set by ICEPAC to break from traditional investigations of IC/BPS through emphasizing subgrouping of IC/BPS from other pelvic pain conditions (e.g., MPP) in hypothesis testing, a focus on ANS function as key contribution to pathophysiology, a hypothesis-driven longitudinal design versus a discovery-based approach, and an emphasis on brainstem function (i.e., HRV). In addition, ICECAN has adopted a number of clinical phenotyping measures employed in the MAPP Research Network. This and other ongoing efforts to integrate these complementary studies will allow for significant new insights into IC/BPS from collaborative data analyses.

Urinary, Psychosocial, Organ-specific, Infection, Neurologic/Systemic and Tenderness of Skeletal Muscle (UPOINT)

As noted earlier, it has been suggested that there may be important and distinct sub-groups, or phenotypes, of IC/BPS that may influence treatment response and clinical management. An effort to phenotype patients with IC/PBS (the term used by investigators) and CP/CPPS was proposed in 2009 by Shoskes and colleagues (49). This classification system, termed UPOINT system, is broad in scope and includes six clinical domains: urinary symptoms, psychological dysfunction, organ-specific findings, infection, neurologic dysfunction and tenderness of muscles.

The information used to determine whether patients may be assigned into one or multiple domains is obtained through clinical assessment, questionnaires and other generally performed evaluations for these syndromes. A major goal of UPOINT is to clinically manage individual patients according to subtype classifications. In contrast to CP/CPPS, application of UPOINT to IC/PBS has been somewhat limited and consisted of assessing 100 consecutive female patients seen in a Canadian tertiary IC clinic (50,51). All patients were categorized into at least two domains of UPOINT. The proportion of patients with two, three, four, five and all six domains affected was 13%, 35%, 34%, 13% and 5%, respectively. Not surprisingly, the symptom severity measured by the Interstitial Cystitis Symptom Index (ICSI) and reported pain severity increased as the number of domains experienced by the patient increased.

The utility of UPOINT phenotyping to improve treatment was also studied in the same cohort of female IC/PBS patients described above (51). Women classified with UPOINT received treatments tailored to the domains they experienced. The treatments assigned for the domains were as follows: urinary—antimuscarinic drugs, pyridium and bladder re-training; psychosocial—education, coping cognitive behavioral therapy, tricyclic antidepressants, and anxiolytics; organ specific—pyridium, intravesical instillations that affect the glycosaminoglycan layer of the bladder, dimethyl sulfoxide (DMSO), lidocaine, pentosan polysulfate sodium and quercetin; infection—antimicrobials; neurogenic/systemic—amitriptyline, gabapentinoids, systemic specific therapies and referral; and for tenderness—physiotherapy, exercise, muscle relaxants and injection therapy. Over a follow-up period of at least 1 year, nearly one-half of the participants experienced significant clinical improvement (greater than 30% decrease in the ICSI from baseline). The non-randomized design of the study, the absence of a placebo/sham treatment arm, and the wide array of treatments available for each domain precludes making definite statements about the utility of UPOINT to facilitate matching treatment(s) to IC/BPS patient phenotypes to improve outcomes. An online tool has been developed for UPOINT and tested in men with CP/CPPS but has not been evaluated in patients with IC/BPS (52). The UPOINT classification system is an attractive and novel tool, as it incorporates a wide array of patient factors that may influence clinical management. Further efforts to correlate phenotype and treatment response using the

UPOINT system will add additional information on the broad clinical utility of this approach.

Synergy with other studies and resources

The extensive overlap of IC/BPS symptoms with other benign urologic disorders and findings that numerous, non-urologic chronic pain conditions are found in association with IC/BPS warrant expanded collaboration with diverse research programs addressing complementary clinical questions. Such interaction will synergize efforts and ultimately provide a more comprehensive understanding of the pathophysiological relationships between IC/BPS and other conditions and potentially a more holistic approach to patient care.

Because diverse urologic disorders share similar bladder and lower urinary tract symptomatology, their clinical features and causal determinants may also overlap. This is the basis for interactions between the MAPP Research Network and two other large NIDDK research efforts, the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) (https://nih-lurn.org/) and the Prevention of Lower Urinary tract Symptoms (PLUS) Research Consortium. The LURN was initiated in 2012 as a multi-disciplinary effort to increase our understanding of the nature of broad lower urinary tract dysfunction (LUTD) and symptoms in male and females, which potentially includes both urologic organ-specific and more systemic contributors. Unlike the MAPP Research Network, pain associated with the bladder, a hallmark symptom of IC/BPS, is not a defining criterion for LURN participants; however, overlap in urologic symptoms of interest—particularly frequency and urgency—exist between these studies. The LURN is conducting a 1-year prospective observational cohort study and associated sub-studies to identify important patient sub-types and improve upon symptom measurement for LUTD through development of new questionnaires centered on patient experience. A future goal is to develop and disseminate new research tools and other resources to the community. The PLUS Research Consortium was initiated in 2015 as an effort to establish an evidence base for normal (healthy) bladder function, including behavioral and other risk factors for symptoms of bladder infection, urinary incontinence, voiding dysfunction, overactive bladder, and IC/BPS in women over a wide age range that will provide the foundation for future prevention studies.

These research programs have already developed lines of collaboration in their study of complementary urologic conditions and patient groups. This includes sharing best practice guidelines to promote similar approaches to biosample and data collection; adopting common neuroimaging methodologies and a common neuroimaging core, specifically for the MAPP Research Network and the LURN; and developing a common strategy to disseminate key findings to patients, the community, and practicing clinicians; among others. As the LURN and PLUS develop their datasets and resulting insights, comparative analysis between these three studies will provide unprecedented opportunities for a more global understanding of bladder and LUTD and symptoms across disorders, including IC/BPS.

The growing interest in the relationships between chronic pain conditions often found in association in patients has motivated the National Institutes of Health (NIH) Pain Consortium (http://painconsortium.nih.gov/), a group established to enhance pain research and collaboration across NIH Institutes and Centers, to better integrate existing and future data from relevant clinical studies and data resources and enhance future collaborations through development of common data collection strategies and phenotyping tools. In support of this goal, the NIH Pain Consortium convened the 2014 Investigator's Meeting on Chronic Overlapping Pain Conditions in which investigators from numerous large-cohort studies and research resource projects discussed how to leverage these efforts. Groups represented included the MAPP Research Network; the Collaborative Health Outcomes Information Registry (CHOIR) (http://snapl.stanford.edu/choir/), a collaborative partnership between the NIH and Stanford University to provide an open source platform for outcomes data from chronic pain patients, including IC/BPS; the National Center for Biotechnology Information (NCBI) Database of Genotypes and Phenotypes (dbGaP) (http://www.ncbi.nlm.nih.gov/gap), which serves to archive and distribute results of genome-wide association studies, medical sequencing, molecular diagnostic assays, as well as association between genotype and non-clinical traits and extends well beyond urologic or chronic pain disorders; and the National Institute of Dental and Craniofacial Research's (NIDCR) Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) Study (53) (www.oppera.org), launched in 2005 as a groundbreaking prospective study to identify the biological, psychological, and genetic risk factors for first onset and chronic temporomandibular joint and muscle disorders (TMDs); among others.

Numerous recommendations were developed by

attendees and new interactions between studies were started. For example, the MAPP Network has now adopted an approach to patient-reported mapping of widespread pain utilized by the CHOIR and shared with MAPP Network investigators. This improved approach will allow a much more specific assessment of pain localization and progression in IC/BPS with added potential for comparison to results from other studies. In addition, a dialogue was initiated between the MAPP Network and OPPERA to set a foundation for future data sharing. This is of particular significance, as TMDs are often found in association with IC/BPS, and the OPPERA is addressing many questions complementary to current IC/BPS studies. For example, the OPPERA is assessing the contributions of central nervous system nociceptive processing (e.g., pain sensitivity) and ANS function (e.g., heart rate) (54) and a wide array of other risk factors, including the presence of co-morbid pain conditions (55). In addition, OPPERA is examining approaches focused on risk factors related to the underlying pathophysiology of TMD. The NIH Pain Consortium continues to promote interactions between these researchers, including developing a case-definition for chronic, overlapping pain conditions and a minimal set of common data elements.

Conclusions and future directions

New strategies are clearly needed to address longstanding questions regarding the cause(s) of IC/BPS and to improve clinical management. Such an evolution of approaches that expand beyond a primary focus on the bladder and lower urinary tract is largely motivated by the lack of sufficient progress from more traditional research studies and clinical trial designs, as well as more recent findings suggesting more systemic contributors for some patients.

We described investigations which address important questions regarding IC/BPS etiology and clinical presentation through their unique study designs. These include the role of central mediators, such as the central nervous system, in development of IC/BPS and chronic, widespread pain potentially involving other pain disorders; how IC/BPS progresses over time (symptom patterns) and underlying biological mediators and risk factors that define improvement or worsening; how these patients may be sub-grouped on objective findings and patient-reported outcomes, to better identify therapeutic targets and evaluate treatment strategies; among numerous others.

It is anticipated the efforts we describe combined with the work of other clinical and basic researchers will reshape our views of IC/BPS and ultimately provide significant contributions to improved diagnosis, prognosis, and clinical management of these patients.

Acknowledgements

The authors wish to thank Drs. Thomas Chelimsky, John Kusiak, and Linda Porter and Mrs. Emily Duggan for critical reviews. The authors would like to acknowledge the ongoing dedication of all those conducting and promoting IC/BPS research.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financial Support: Drs. C Mullins, T Bavendam, Z Kirkali, JW Kusek are employed by the NIH and these efforts are thereby supported as part of their regular duties.

References

1. Hanno PM, Erickson D, Moldwin R, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol 2015;193:1545-53.
2. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol 2007;177:450-6.
3. Clemens JQ, Markossian TW, Meenan RT, et al. Overlap of voiding symptoms, storage symptoms and pain in men and women. J Urol 2007;178:1354-8.
4. Clemens JQ, Link CL, Eggers PW, et al. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 2007;177:1390-4.
5. Berry SH, Elliott MN, Suttorp M, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 2011;186:540-44.
6. Suskind AM, Berry SH, Ewing BA, et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. J Urol 2013;189:141-5.
7. Link CL, Pulliam SJ, Hanno PM, et al. Prevalence and psychosocial correlates of symptoms suggestive of

painful bladder syndrome: results from the Boston area community health survey. J Urol 2008;180:599-606.
8. Fall M, Johansson SL, Aldenborg F. Chronic interstitial cystitis: a heterogeneous syndrome. J Urol 1987;137:35-8.
9. Messing E, Pauk D, Schaeffer A, et al. Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology 1997;49:81-5.
10. Erickson DR, Simon LJ, Belchis DA. Relationships between bladder inflammation and other clinical features in interstitial cystitis. Urology 1994;44:655-9.
11. Baskin LS, Tanagho EA. Pelvic pain without pelvic organs. J Urol 1992;147:683-6.
12. McLennan MT. Interstitial cystitis: epidemiology, pathophysiology, and clinical presentation. Obstet Gynecol Clin North Am 2014;41:385-95.
13. Gonzalez EJ, Arms L, Vizzard MA. The role(s) of cytokines/chemokines in urinary bladder inflammation and dysfunction. Biomed Res Int 2014;2014:120525.
14. van de Merwe JP. Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol 2007;4:484-91.
15. Keay SK, Birder LA, Chai TC. Evidence for bladder urothelial pathophysiology in functional bladder disorders. Biomed Res Int 2014;2014:865463.
16. Gonzalez EJ, Merrill L, Vizzard MA. Bladder sensory physiology: neuroactive compounds and receptors, sensory transducers, and target-derived growth factors as targets to improve function. Am J Physiol Regul Integr Comp Physiol 2014;306:R869-78.
17. Birder LA. Urinary bladder, cystitis and nerve/urothelial interactions. Auton Neurosci 2014;182:89-94.
18. Rosen JM, Klumpp DJ. Mechanisms of pain from urinary tract infection. Int J Urol 2014;21 Suppl 1:26-32.
19. Bjorling DE, Wang ZY, Bushman W. Models of inflammation of the lower urinary tract. Neurourol Urodyn 2011;30:673-82.
20. Simon LJ, Landis JR, Erickson DR, et al. The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. Urology 1997;49:64-75.
21. Barry MJ, Link CL, McNaughton-Collins MF, et al. Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. BJU Int 2008;101:45-51.
22. Warren JW, Wesselmann U, Morozov V, et al. Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. Urology 2011;77:313-9.
23. Warren JW, Howard FM, Cross RK, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology 2009;73:52-7.
24. Clauw DJ, Schmidt M, Radulovic D, et al. The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res 1997;31:125-31.
25. Heitkemper M, Jarrett M. Overlapping conditions in women with irritable bowel syndrome. Urol Nurs 2005;25:25-30.
26. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, et al. Case-control study of medical comorbidities in women with interstitial cystitis. J Urol 2008;179:2222-5.
27. Rodríguez MA, Afari N, Buchwald DS, et al. Evidence for overlap between urological and nonurological unexplained clinical conditions. J Urol 2009;182:2123-31.
28. Clemens JQ, Mullins C, Kusek JW, et al. The MAPP research network: a novel study of urologic chronic pelvic pain syndromes. BMC Urol 2014;14:57.
29. FitzGerald MP, Anderson RU, Potts J, et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol 2009;182:570-80.
30. FitzGerald MP, Payne CK, Lukacz ES, et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol 2012;187:2113-8.
31. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states--maybe it is all in their head. Best Pract Res Clin Rheumatol 2011;25:141-54.
32. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2-15.
33. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain 2009;10:1113-20.
34. Warren JW, Brown J, Tracy JK, et al. Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. Urology 2008;71:444-8.
35. Warren JW, Greenberg P, Diggs C, et al. A prospective early history of incident interstitial cystitis/painful bladder syndrome. J Urol 2010;184:2333-8.
36. Langenberg PW, Wallach EE, Clauw DJ, et al. Pelvic pain and surgeries in women before interstitial cystitis/painful bladder syndrome. Am J Obstet Gynecol 2010;202:286.e1-6.
37. Nickel JC, Stephens A, Landis JR, et al. Search for microorganisms in men with urologic chronic pelvic pain syndrome: a culture-independent analysis in the mapp research network. J Urol 2015;194:127-35.
38. Warren JW, Clauw DJ, Wesselman U, et al. Sexuality and reproductive risk factors for interstitial cystitis/painful

bladder syndrome in women. Urology 2011;77:570-5.
39. Warren JW, Clauw DJ, Langenberg P. Prognostic factors for recent-onset interstitial cystitis/painful bladder syndrome. BJU Int 2013;111:E92-7.
40. Landis JR, Williams DA, Lucia MS, et al. The MAPP research network: design, patient characterization and operations. BMC Urol 2014;14:58.
41. Lai H, Gereau RW 4th, Luo Y, et al. Animal Models of Urologic Chronic Pelvic Pain Syndromes: Findings From the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network. Urology 2015;85:1454-65.
42. Kilpatrick LA, Kutch JJ, Tillisch K, et al. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. J Urol 2014;192:947-55.
43. Schrepf A, Bradley CS, O'Donnell M, et al. Toll-like Receptor 4 and comorbid pain in Interstitial Cystitis/Bladder Pain Syndrome: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain research network study. Brain Behav Immun 2015;49:66-74.
44. Krieger JN, Stephens AJ, Landis JR, et al. Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: baseline evaluation of the MAPP study. J Urol 2015;193:1254-62.
45. Sutcliffe S, Bradley CS, Clemens JQ, et al. Urological chronic pelvic pain syndrome flares and their impact: qualitative analysis in the MAPP network. Int Urogynecol J 2015;26:1047-60.
46. Chelimsky T, Chelimsky G, McCabe NP, et al. Interstitial Cystitis - Elucidation of Psychophysiologic and Autonomic Characteristics (the ICEPAC Study): design and methods. J Pain Res 2014;7:243-53.
47. Chelimsky G, McCabe NP, Janata J, et al. Autonomic testing of women with interstitial cystitis/bladder pain syndrome. Clin Auton Res 2014;24:161-6.
48. Williams DP, Chelimsky G, McCabe NP, et al. Effects of chronic pelvic pain on heart rate variability in women. J Urol 2015;194:1289-94.
49. Shoskes DA, Nickel JC, Rackley RR, et al. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. Prostate Cancer Prostatic Dis 2009;12:177-83.
50. Nickel JC, Shoskes D, Irvine-Bird K. Clinical phenotyping of women with interstitial cystitis/painful bladder syndrome: a key to classification and potentially improved management. J Urol 2009;182:155-60.
51. Nickel JC, Irvine-bird K, Shoskes DA. Phenotype-directed management of interstitial cystitis/bladder pain syndrome Urology 2014;84:175-9.
52. Tran CN, Li J, Shoskes DA. An online UPOINT tool for phenotyping patients with chronic prostatitis Can J Urol 2014;21:7195-200.
53. Maixner W, Diatchenko L, Dubner R, et al. Orofacial pain prospective evaluation and risk assessment study--the OPPERA study. J Pain 2011;12:T4-11.
54. Greenspan JD, Slade GD, Bair E, et al. Pain sensitivity and autonomic factors associated with development of TMD: the OPPERA prospective cohort study. J Pain 2013;14:T63-74.e1-6.
55. Bair E, Ohrbach R, Fillingim RB, et al. Multivariable modeling of phenotypic risk factors for first-onset TMD: the OPPERA prospective cohort study. J Pain 2013;14:T102-15.

Cite this article as: Mullins C, Bavendam T, Kirkali Z, Kusek JW. Novel research approaches for interstitial cystitis/bladder pain syndrome: thinking beyond the bladder. Transl Androl Urol 2015;4(5):524-533. doi: 10.3978/j.issn.2223-4683.2015.08.01

