Development, Validation and Testing of an Epidemiological Case Definition of Interstitial Cystitis/Painful Bladder Syndrome

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Abstract

Purpose—No standard case definition exists for interstitial cystitis/painful bladder syndrome for patient screening or epidemiological studies. As part of the RAND Interstitial Cystitis Epidemiology study, we developed a case definition for interstitial cystitis/painful bladder syndrome with known sensitivity and specificity. We compared this definition with others used in interstitial cystitis/painful bladder syndrome epidemiological studies.

Materials and Methods—We reviewed the literature and performed a structured, expert panel process to arrive at an interstitial cystitis/painful bladder syndrome case definition. We developed a questionnaire to assess interstitial cystitis/painful bladder syndrome symptoms using this case definition and others used in the literature. We administered the questionnaire to 599 women with interstitial cystitis/painful bladder syndrome, overactive bladder, endometriosis or vulvodynia. The sensitivity and specificity of each definition was calculated using physician assigned diagnoses as the reference standard.

Results—No single epidemiological definition had high sensitivity and high specificity. Thus, 2 definitions were developed. One had high sensitivity (81%) and low specificity (54%), and the other had the converse (48% sensitivity and 83% specificity). These values were comparable or superior to those of other epidemiological definitions used in interstitial cystitis/painful bladder syndrome prevalence studies.

Conclusions—No single case definition of interstitial cystitis/painful bladder syndrome provides high sensitivity and high specificity to identify the condition. For prevalence studies of interstitial cystitis/painful bladder syndrome the best approach may be to use 2 definitions that would yield a prevalence range. The RAND Interstitial Cystitis Epidemiology interstitial cystitis/painful bladder syndrome case definitions, developed through structured consensus and validation, can be used for this purpose.

Keywords

urinary bladder; cystitis, interstitial; pain; epidemiology; diagnosis

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Interstitial cystitis/painful bladder syndrome is a chronic, poorly understood condition. There is no consensus about the cause of the condition, which has prevented identification of an objective marker and development of a clinical diagnostic protocol. As a result, wide variability exists in the ways in which patients are identified for epidemiological studies. Studies have assessed the prevalence of an assigned physician diagnosis of IC/PBS. However, such research is limited to patients with access to health care and not all physicians may be familiar enough with IC/PBS to assign the diagnosis. Another method is to ask individuals whether they have ever been diagnosed with IC/PBS. However, this is subject to inaccuracies due to recall bias and selection effects since patients who have the condition may be undiagnosed or diagnosed with another condition.

The most common method to estimate IC/PBS prevalence is to assess symptoms indicating IC/ PBS.[1–3] Three epidemiological studies used survey methods to estimate the IC/PBS prevalence in a community population of women. Leppilahti et al used a mailed questionnaire to estimate prevalence[1] using a criterion based on the IC symptom and problem indexes.[4] Clemens et al used mailed questionnaire responses about bladder pain, urgency and frequency to estimate the prevalence of IC symptoms in women sampled from a managed care population.[2] The Boston Area Community Health investigators estimated the prevalence of IC symptoms using questionnaires administered during in person interviews at patient homes.[3] Questions about IC/ PBS symptoms were included in the 2004 version of the United States Nurses Health Study, which was administered to women 58 to 83 years old.[5] In this cohort of elderly women the prevalence of IC/PBS symptoms was 2.3%. Prevalence increased with age from 1.7% of those younger than 65 years up to 4.0% in women 80 years old or older. Finally, in 981 women 19 to 89 years old attending a voluntary health screening project in Vienna, Austria, the prevalence of IC/PBS symptoms was 0.3% (306/ 100,000).[6]

Reported IC prevalence estimates in these various studies vary considerably from less than 1% to 11%. The lack of a standardized method to identify IC/PBS symptoms may be responsible for the different prevalence estimates. Also, to our knowledge no information exists about the ability of various questionnaires to accurately identify women with IC/ PBS (sensitivity) or distinguish them from women diagnosed with other similar conditions (specificity).

We report the systematic development and validation of population screening items for use in the RICE study, a national prevalence study of IC/PBS in women. We examined the sensitivity and specificity of this and other epidemiological definitions of IC/PBS used in the literature.

METHODS

Case Definition Panel

We used an adaptation of RAM, a methodology developed to combine the best available scientific evidence with the collective judgment of a group of experts, to yield a statement about the appropriateness of performing a medical procedure. RAM has been used extensively for appropriateness studies worldwide[7] and has been applied to evaluate the appropriateness of diverse medical procedures, such as Crohn's disease therapy,[8,9] coronary angiography and revascularization,[10–14] colonoscopy[15] and spinal manipulation for low back pain.[16,17] It has also been adapted to develop quality of management criteria for noninsulin dependent diabetes mellitus.[18] However, results depend on the quality of the scientific evidence and on expert judgment.

We adapted RAM to determine the appropriateness of various symptom indicators to diagnose IC/PBS compared with indicators of conditions with overlapping symptoms, such as OAB, endometriosis and vulvodynia. We solicited nominations from relevant medical societies, including the American Urological Association, American College of Obstetrics and Gynecology, and American Urogynecologic Society, and from recognized IC/PBS experts. Nine experts were chosen for the final multidisciplinary panel, including 5 in urology, 2 in gynecology, 1 in nursing and 1 in case definition methodology.

We performed a comprehensive literature review of the best scientific evidence about IC/PBS and related conditions with overlapping symptoms, ie OAB, endometriosis and vulvodynia, using the PubMed® database and pre-defined search terms.[19] The final review included a history of the case definition of each disease and a description of the prevalence of patient reported symptoms within and across diseases. Before the panel meeting we sent to the expert panel members the literature review, a list of 60 possible symptom indicators for the case definition of IC/ PBS and related conditions, and symptom rating forms.

Panel members independently rated the extent to which each indicator was evidence for or against a diagnosis of IC/PBS and each related condition, and sent back their ratings. Ratings were analyzed and a report was presented to each individual panel member on meeting day 1. All symptoms were discussed for each condition separately and the moderators focused the group on the areas on which there was substantial disagreement or a spread of ratings. The strength of evidence was discussed as appropriate to determine reasons for disagreement or agreement.

At the end of this discussion panelists completed a second round of ratings. On meeting day 2 panelists were shown the new ratings. After further discussion a consensus case definition was produced.

Validation Study

Measurement—Based on panel results we developed a screening questionnaire including multiple questions on pain, urgency, frequency, nocturia, symptom triggers and alleviators, and quality of life. These items were combined in various ways to yield candidate IC/PBS definitions for testing.

Enrollment—We contacted 42 urologists and gynecologists around the United States, including those in community and academic medical center practices, with recognized expertise in managing IC/PBS, OAB, vulvodynia and endometriosis. We invited the clinicians to refer female patients with these conditions to the investigative team. Eight urologists and 16 gynecologists participated. A total of 673 participants were recruited, of whom 599 were interviewed. The diagnosis was IC/PBS only in 236, IC/ PBS plus 1 of the other conditions in 101, OAB in 124, endometriosis in 58, vulvodynia in 44 and more than 1 nonIC/PBS condition in 36. Study participants completed a comprehensive 90-minute computer assisted telephone interview done by trained interviewers from the RAND Telephone Survey Center.

Analysis—We used an iterative approach to construct and test different combinations of RICE item definitions that could be used to predict the IC/PBS diagnosis (sensitivity) and differentiate IC/PBS from other conditions (specificity). We compared the sensitivity and specificity of the resulting RICE IC/PBS definition with that of other IC/ PBS definitions reported in the literature, including clinical IC/PBS definitions developed by the International Continence Society[20] and research definitions used to estimate IC/PBS in epidemiology studies.[1,3] For this analysis physician clinical diagnoses served as the reference standard to define IC/PBS.

RESULTS

Panel Ratings

In rating round 1 the 9 panelists rated 240 symptoms, including 60 for each of the 4 conditions. They agreed on 33% of the indicators and disagreed on only 2. Rating spreads were indeterminate for the remaining 67% of conditions. The 2 disagreements were on OAB (pain as pressure/heaviness) and endometriosis (pain worsens during urination). In rating round 2 agreement improved to 58% and there were no disagreements. For IC/PBS 13 and 0, for OAB 4 and 5, for endometriosis 6 and 0, and for vulvodynia 7 and 0 symptoms were rated as consistent and inconsistent with a diagnosis, respectively.

Panel Consensus Statement and Case Definition Refinement

After discussing rating round 2 the panel recommended that the necessary symptom cluster for IC/ PBS should be 1) pain, pressure and/or discomfort in the pelvic area (suprapubic to upper thighs) that worsens as the bladder fills or decreases after the bladder is emptied and 2) frequent urination. Rather than having a separate category for nocturia the group decided to include daytime and nighttime urination in the frequency category, ie frequency was defined as 24-hour frequency. Because urgency in IC/PBS cases is thought to be highly associated with the pain or pressure related to urination, the panel did not require a separate criterion for urgency. IC/PBS pain was distinguished from that of endometriosis, which primarily occurs during menstruation, and of vulvodynia, which is not related to bladder filling. OAB was distinguished from all other conditions, including IC/PBS, in terms of its lack of pain. Although the panel considered other symptoms for inclusion, these symptom clusters were thought to be unique to each listed condition and, thus, they could assist in distinguishing among conditions.

Based on discussion among study team members, and consultation with our internal and external advisory boards the panel case definition was further refined by including urgency to relieve pain as an additional criterion. Urgency to relieve pain in patients with IC/PBS is distinguished from urgency to avoid incontinence in patients with OAB.

Working Epidemiological IC/PBS Definition

We separated the conceptual definition provided by the panel into various components, including 1) pain characteristics, 2) pain site, 3) pain triggers, eg menstruation and bladder filling, 4) urinary frequency, 5) urgency/urge incontinence and 6) quality of life impact of symptoms. Using responses to the comprehensive symptom questionnaire an iterative approach was used to construct and test multiple variations of the RICE definition of the presence of IC/ PBS. Some items identified by the panel were useful predictors, including suprapubic pain that worsens as the bladder fills, urgency and daytime frequency (10 or more urinations). Other symptoms did not help identify IC/PBS, including pain relieved by urination and nighttime frequency. Urgency was a useful predictor of IC/PBS when it was experienced as urgency due to pain, pressure or discomfort rather than to fear of wetting. Responses to the final set of selected items can be used to define a RICE high sensitivity definition and a RICE high specificity definition.

IC/PBS Definition Testing

Sensitivity and specificity of the various epidemiological definitions were 19% to 91% and 42% to 95%, respectively. There was a tradeoff between sensitivity and specificity. No single definition proved to be highly sensitive and highly specific to identify patients with IC/PBS and distinguish them from women with other conditions. The RICE high sensitivity definition identified 91% of IC/PBS cases with 42% specificity and the RICE high specificity definition had 79% specificity and 56% sensitivity. These 2 definitions spanned

the range and each represented the best balance of sensitivity and specificity. In contrast, for example the definition with the highest specificity (95%) had 19% sensitivity.

These sensitivity and specificity values were obtained in a sample of symptomatic women with conditions similar to IC/PBS, including OAB, endometriosis and vulvodynia. Specificity is likely to be much greater in the general population, in which most women are asymptomatic. For example, assuming that approximately 15% of the general population are symptomatic,[21–24] the specificity of most of these definitions in the mostly asymptomatic population would approach 90% or higher.

DISCUSSION

The primary aim of the RICE study is to estimate the national prevalence of IC/PBS symptoms in American women. To accomplish this a suitable questionnaire is required to ascertain the presence of these symptoms with reasonable precision. Our findings clearly show that no single questionnaire based measure of IC/PBS symptoms can simultaneously identify all IC/PBS cases (sensitivity) and distinguish these cases from those of similar conditions, such as OAB, endometriosis and vulvodynia (specificity). Thus, using 2 definitions (1 with high sensitivity and 1 with high specificity) may be the best approach since they provide a prevalence range that brackets the true prevalence. The RICE high sensitivity and high specificity definitions, developed from standardized consensus panel methods and tested using telephone interviews, produce reasonable sensitivity and specificity that are similar to other existing IC/PBS definitions and, thus, are suitable for use in large-scale population based surveys. Furthermore, the 2 definitions use a single set of survey questions (11 items), which also captures a clear description of the symptom experienced, eg the number of daytime urinations. We hope that future IC/PBS epidemiological studies will use the RICE definitions, which will allow more meaningful comparison across samples. For conditions such as IC/ PBS, in which there is often a degree of opinion and subjectivity inclusive in the diagnosis, providing a range of prevalence estimates may be advantageous since it acknowledges the variability inherent in the diagnosis.

The finding that no single definition is associated with high sensitivity and specificity may be related to the true overlap of symptoms across these conditions, and to the accuracy of measurement and clinical diagnoses of these conditions. IC/PBS is a symptom defined condition for which there is no accepted diagnostic protocol or validated test. In the absence of defined diagnostic criteria there is likely to be variability among physicians in how they diagnose IC/PBS and to our knowledge this degree of variability is currently unknown. Validation of our case definition included patients with a limited number of diagnoses and, thus, it may not represent the entire spectrum of patients seen in the community. The effect that this may have on RICE case definition sensitivity and specificity is unclear.

CONCLUSIONS

Previous measures used to identify patients with IC/PBS were primarily developed to track the course of the condition. The RICE measures are designed to identify women with IC/ PBS symptoms and describe their symptoms. They were developed using a rigorous, consensus based protocol and validated against the current gold standard of clinical diagnoses by urology and gynecology experts. We encourage the use of these case definitions in IC/PBS epidemiological studies. Additional testing of the definitions can be done as more objective markers of IC/PBS disease status are developed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations and Acronyms

IC	interstitial cystitis
IC/PBS	IC/painful bladder syndrome
OAB	overactive bladder
RAM	RAND/UCLA Appropriateness Method
RICE	RAND Interstitial Cystitis Epidemiology

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