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## Evidence-based criteria for the pain of interstitial cystitis/painful bladder syndrome in women

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### Abstract

**Objectives**—There are no diagnostic physical signs, urologic findings, or available laboratory tests for interstitial cystitis/painful bladder syndrome (IC/PBS). Its diagnosis is based upon symptoms and exclusion of mimicking diseases. We hypothesized that certain pain characteristics are sensitive criteria for diagnosing IC/PBS.

**Methods**—In women with recent onset IC/PBS recruited in 2004 – 2006 for the case control study, Events Preceding Interstitial Cystitis (EPIC), we identified locations of each case’s pain and in a non-leading way asked about effects of 17 different experiences (criteria) upon it. We identified a set of criteria that described the largest number of EPIC patients. In a secondary analysis of another cohort recruited by others in 1993 – 1997, the Interstitial Cystitis Database (ICDB), we determined the proportion of cases captured by these same criteria.

**Results**—In EPIC, pain that worsened with certain food or drink and/or worsened with bladder filling and/or improved with urination was reported by 151/156 (97%) cases. These were the only three criteria that applied directly to the bladder. The same three criteria described the pain of 262/270 (97%) of women in the ICDB who “definitely” had IC/PBS.

**Conclusions**—An hypothesis generated in one IC/PBS patient group and tested in another, pain that worsened with certain food or drink and/or worsened with bladder filling and/or improved with urination was described by 97% of IC/PBS patients in each cohort. This triad may describe the pain of IC/PBS and contribute to a sensitive case definition. Estimating specificity awaits comparison with other diseases with similar symptoms.

### Keywords

interstitial cystitis; painful bladder syndrome; bladder pain; diagnosis

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## Introduction

In interstitial cystitis/painful bladder syndrome (IC/PBS), physical signs are few, bladder biopsy often reveals meager findings, the role of urodynamics remains unclear, and usable laboratory tests are not commercially available. Therefore, the diagnosis is based on symptoms<sup>1–3</sup>. However, reliance upon the characteristic quartet of pain, frequency, urgency, and nocturia may be problematic because common conditions such as overactive bladder, vulvodynia, endometriosis, and urinary tract infection have overlapping symptoms<sup>2</sup>.

Pain is an important feature of IC/PBS. The term “painful bladder” goes back to at least 1951<sup>2</sup>. At pivotal IC meetings in 1988, pain was a prominent part of the discussions<sup>4</sup>. In 1990, Held et al, reported that urologists ranked pain as the most common criterion to diagnose IC<sup>5</sup>. In 2002, the International Continence Society (ICS) described the pain of “painful bladder syndrome (PBS)” as “related to bladder filling” and suggested that IC was a subcategory of PBS<sup>3</sup>. Recently, numerous international groups concurred that pain was a necessary part of the disease<sup>1,6–8</sup>.

We hypothesized that changes in pain with the voiding cycle and other activities might describe and be a sensitive measure of IC/PBS. We generated such data in an ongoing case-control study, Events Preceding Interstitial Cystitis (EPIC) and, serendipitously, confirmed our findings in a completely separate sample, the Interstitial Cystitis Database (ICDB)<sup>9,10</sup>.

## Material and Methods

### Events Preceding Interstitial Cystitis

EPIC is an ongoing case-control study to identify risk factors for IC/PBS. To avoid confounding by prostate disease we recruited women and to enhance recall of antecedent exposures we sought recent onset patients. Enrollment criteria were women  $\geq 18$  years old with a syndrome beginning  $\leq 12$  months earlier comprising pain that they perceived to be of bladder origin and  $\geq 2$  of frequency, urgency, or nocturia. Pertinent medical records were required and were reviewed for onset date confirmation, other causes of these symptoms, and initial management. Exclusion criteria were 12 diseases mimicking IC/PBS symptoms<sup>4</sup> and, to avoid neurogenic bladder, selected neurologic diseases<sup>11</sup>. Enrollees underwent telephone interviews at baseline and every 6 months. Detailed methods have been published<sup>11</sup>.

After the baseline interview we mailed to each case a questionnaire that included anterior, posterior, and perineal views of the female body and asked each to shade and number locations of her worst and any other “pain, pressure, or discomfort as a result of IC”, up to a total of 5. For each pain, “when your symptoms are at their worst...” she noted whether each of 17 experiences, derived from the literature and focus groups, caused that particular pain to “get worse”, “get better”, or “remain the same”.

### Interstitial Cystitis Data Base

The ICDB (now publicly available)<sup>9</sup> was developed by urologists experienced in IC/PBS from nine centers in the U.S. who from 1993–1997 uniformly studied IC/PBS cases in their practices<sup>10</sup>. Participants were asked “Over the past four weeks, how often have you had any of the following” and among experiences queried were “pain increasing when your bladder fills” and “pain relieved by urination”. We accepted “sometimes”, “frequently”, or “always” as positive responses. The ICDB questions about diet were quite detailed: “If eaten, what effect do the following foods have on your urinary symptoms?” and 35 foods and drinks were queried. We accepted either of two responses: “causes my symptoms to worsen” or “triggers an onset of my symptoms”. Of the 637 ICDB cases, we assessed the 280 women judged by ICDB investigators to “definitely have the ‘IC complex’”.

Analyses included Chi square and Fishers' exact tests when categorically coded variables were analyzed and Students' t-test when continuously coded data were used.

## Results

### EPIC

In this ongoing study, 766 individuals were screened to yield the first 209 cases who met enrollment criteria; of the latter, 158 (76%) completed the mailed questionnaire. Respondents and non-respondents were not significantly different in race, symptoms, history of hydrodistention, presence of glomerulations or Hunner's ulcer, or diagnosis of IC/PBS by a urologist or gynecologist. Respondents did slightly differ in age (43.7 vs 39.1 years,  $p = 0.02$ ) and in receipt of standard IC medications before the baseline interview (90% vs 76%,  $p = 0.01$ ). Table 1 indicates that respondents had a pelvic pain syndrome with urinary symptoms, urologic findings, medication use, and chronicity consistent with IC/PBS<sup>1,2,5,10</sup>.

Of the 158 cases, 109 (69%) reported pelvic pain in multiple locations (mean, 2.2 locations/case). Three pain affectors were prominent, each reported by  $\geq 84\%$  of participants (Table 2). We consolidated these three and found that 151/156 cases (97%) reported that IC/PBS pain was worsened with diet and/or worsened with bladder filling and/or improved with urination (Table 3).

Our data allowed several variations on questions and answers. In Table 3, "improves with urination" includes pain that improved "during urination", "immediately after urination", and/or "a half hour after urination". Those reporting improvement "during urination" were 82/155 (53%) and those reporting improvement "during" and/or "immediately after urination" were 112/157 (71%). Substituting these more restrictive definitions in Table 3 resulted in changes in the last three lines to 94%, 88%, and 97% and to 96%, 90%, and 97%.

### ICDB

In the preceding 4 weeks, 270 ICDB women had pain; Table 3 displays the proportions who reported it worsened with diet, worsened with bladder filling, or improved with urination. Distributions for each experience were not significantly different from those reported in EPIC. Moreover, combinations were even more similar, e.g.  $\geq 1$  of these experiences described the pain of 262/270 (97%) of these ICDB women who "definitely" had IC/PBS. Even if we omit those who answered "sometimes" to the voiding cycle questions, 254/270 (94%) still met  $\geq 1$  criterion.

### Comment

The lack of a usable definition for IC/PBS has been universally lamented<sup>1,6-8</sup> and has had sequelae. The estimated prevalence of IC/PBS ranges widely, pathogenesis(es) remains unknown, diagnosis is characteristically delayed, natural history is unclear, treatment is empiric, and preventive techniques have not even been considered<sup>1</sup>. Hanno et al, summarized: "The lack of universally accepted clinical diagnostic criteria for IC/PBS affects all aspects of making progress in understanding this disease"<sup>1</sup>.

But development of a case definition for IC/PBS has been deceptively challenging. The absence of objective findings relegates IC/PBS to a symptom-based diagnosis. The classic quartet of pelvic pain with urgency, frequency, and/or nocturia is sensitive for IC/PBS, i.e. describes the great majority of cases<sup>2</sup>. However, it may or may not be specific, i.e. exclude patients who have other diseases with similar symptoms. For instance, overactive bladder (OAB) is quite prevalent, about 15% of adults reporting this syndrome comprising urgency and frequency<sup>12</sup>. Moreover, even if OAB does not include pain<sup>13</sup>, the co-occurrence of OAB with

another common condition, i.e. chronic pelvic pain, which also occurs in about 15% of American women<sup>14</sup>, could lead to confusion. Multiplying their prevalences suggests that about 2% of women at any given time have both conditions and thus symptoms which mimic IC/PBS. Finally, some reports indicate that 45% – 60% of women with vulvodynia<sup>15</sup>, hydrodistention-negative pelvic pain<sup>16</sup>, and even irritable bowel syndrome<sup>17</sup> have urgency, frequency, and/or nocturia.

We hypothesized that practical and non-leading questions might probe subtleties of IC/PBS pain and yield a set of criteria sensitive for the disease. These criteria were generated in one population of IC/PBS patients (EPIC) and, importantly, confirmed in a second (the ICDB). The ICDB was developed by urologists expert in IC/PBS<sup>10</sup> and has become the reference standard<sup>18</sup> for the disease. Despite different recruitment techniques, enrollment criteria, study years, symptom duration, question phrasing, and response options, combinations of these criteria captured 93 – 98% of cases in both EPIC and the ICDB.

One might ask whether we are simply reporting a tautology. This would be an issue if these affectors led to selection bias. However, enrollment criteria for neither ICDB<sup>10</sup> nor EPIC included these pain affectors. During ICDB recruitment, the existing definition for IC/PBS did not mention effects of diet, bladder filling, or urination<sup>4</sup>. During EPIC recruitment, meetings addressing IC/PBS definition<sup>1,6–8</sup> were reported but none commented upon these effects. It is possible that the ICS definition of 2002<sup>3</sup> (“pain related to bladder filling”) and criteria used in a prevalence study by Clemens et al<sup>19</sup> in 2005 (“pain increasing when your bladder fills ... (or) ... that is relieved by urination”) could have affected types of patients recruited for the EPIC study – but not for the earlier ICDB. Finally, for the 158 EPIC cases, we reviewed 545 medical records and recall no templates that included these pain affectors and only occasional comments about them. Nevertheless, we recognize the possibility that such patient comments might go undocumented and yet still elicit or confirm in the clinician’s mind the diagnosis of IC/PBS.

Indeed, this may be the point: these features are so common that they characterize IC/PBS pain. Based upon the primary bladder function of storage and elimination of urine and its solutes, these three criteria appear to represent logical, or face validity<sup>20</sup>. It perhaps is not surprising that, of the many possible pain affectors in Table 2, the three most commonly experienced by EPIC patients were the only three directly related to the bladder lumen.

Perception of a full bladder and the disappearance of this sensation with voiding is of course normal. Interestingly, we found no published data detailing proportions of IC/PBS patients experiencing worsened pain with bladder filling. However, our ICDB review revealed supportive (but unpublished) data<sup>9</sup>. During urodynamic studies, ICDB patients were asked “Does this feeling or sensation feel like your symptoms?”. At first sensation to void 224/269 (83%) and at maximal cystometric capacity 250/268 (93%) answered yes. IC/PBS pain that improves with urination has been reported. Held et al stated that 57% of 902 female Interstitial Cystitis Association members noted “pain relieved by voiding”<sup>5</sup>. Koziol observed that 73% of 565 patients (89% female) reported that “urinating reduced or relieved IC pain”<sup>21</sup>.

Others have reported that certain food and drink worsen the pain of IC/PBS<sup>21–23</sup>. The types of foods prominent in these studies are alcohol, citrus fruits, coffee, carbonated drinks, tea, chocolate, and tomatoes. Shorter et al report that 92/102 (92%) respondents to a mailed questionnaire noted that at least one food or drink worsened their IC/PBS symptoms. This experience perhaps can be explained by effects of food-based urine solutes upon the abnormal bladder mucosa of IC/PBS. Tomaszewski et al revealed that in IC/PBS cases only two of 48 histopathologic features studied were associated with pain severity; one of these was the percentage of mucosa denuded of urothelium<sup>24</sup>.

Variants of these three pain criteria may contribute to a sensitive case definition of IC/PBS. We could not find relevant published data for vulvodynia or endometriosis and so even estimating the specificity of these criteria in excluding patients with these and other diseases that might mimic IC/PBS is difficult. Although outside the purview of EPIC, a venerable method to develop and validate a case definition with high sensitivity and specificity entails four steps: 1) clinical experts select potential diagnostic criteria; 2) other clinicians recruit patients with IC/PBS, overactive bladder, vulvodynia, endometriosis and IBS; 3) the set of criteria which maximizes sensitivity and specificity is identified for IC/PBS; and then 4) these criteria are confirmed in additional samples of cases and symptomatic controls. A similar stepwise process for developing a case definition for IC/PBS has been recommended by van de Merwe<sup>25</sup> and Hanno<sup>26</sup>. This rigorous methodology was used in 1982 to develop a set of diagnostic criteria for systemic lupus erythematosus<sup>27</sup>, an even more bewildering disease than IC/PBS, that has been successfully used for the last quarter century.

There are several caveats for this study. That pain is a necessary component of IC/PBS is a recent view; previous studies reported only 63 – 92% of IC patients with pain<sup>2</sup>. Whether this is a function of changing perceptions, different definitions, or variables in symptoms as the disease progresses in an individual etc., is unclear. Understanding the pathogenesis of IC may reveal that some patients do not perceive pain. Nevertheless, one can say that the participants studied here represent an important group of IC cases, i.e. those with pain. Finally, many features of EPIC differ from those of the ICDB. We believe this to be a strength rather than a weakness: that the overwhelming majority of patients in both cohorts experienced pain of this nature suggest these criteria to be consistent among IC/PBS cases.

## Conclusions

Non-directive questions about effects upon pain of dietary substances, bladder filling and urination captured 151/156 (97%) of EPIC cases. These criteria were then applied to another well-studied cohort, the ICDB, and captured the same proportion, 262/270 (97%). These three criteria may describe the pain of IC/PBS and may contribute to a sensitive case definition, i.e., one that identifies most IC/PBS patients. Estimating its specificity, however, requires studying patients with other diseases that have similar symptoms.

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**Table 1**

Characteristics of EPIC respondents (N=158)

Age (SD)	43.7 years (12.8)
Symptoms at worst, baseline	
Pain (0 – 10), mean (SD)	8.5 (1.5)
Urgency (0 – 10), mean (SD)	7.4 (2.5)
Frequency $\geq$ 11/24 hours	86%
Nocturia $\geq$ 3/night	66%
Urologic Procedures, baseline	
Hunner's/hydrodistention	7/67 (11%)
Glomerulations/hydrodistention	60/66 (91%)*
Ongoing interviews	Symptomatic*
Baseline	154/156 (99%)
6 months	117/124 (94%)
12 months	98/102 (96%)
18 months	67/71 (94%)
24 months	37/39 (95%)
Medications, before last followup**	
Standard IC/PBS medications	145/156 (93%)
Narcotics	87/156 (56%)

\* pain  $\geq$ 1/10, urgency  $\geq$ 1/10, frequency  $\geq$ 11/24 hours and/or nocturia  $\geq$ 2/night

\*\*  $\geq$ 1 of oral pentosanpolysulfate, amitriptyline or hydroxyzine or bladder instillation of dimethylsulfoxide, heparin or lidocaine<sup>3</sup>



**Table 2**

EPIC: experiences affecting pain\*

<b>“When your symptoms are at their worst ....”, at least one pain:</b>	
<u>Gets worse</u>	
With certain food or drink	131/154 (85%)
With bladder filling	130/155 (84%)
Just before your period**	59/75 (79%)
With tight clothing	108/155 (70%)
With emotional stress	105/155 (68%)
While riding in the car	102/156 (65%)
During vaginal intercourse‡	79/121 (65%)
With certain exercises	95/154 (62%)
During your period**	46/74 (62%)
After vaginal intercourse‡	73/120 (61%)
With touching the area	69/153 (45%)
At insertion of tampon	21/78 (27%)
<u>Gets better</u>	
With urination★	130/155 (84%)
After your period**	51/74 (69%)

\* denominators vary as not all women answered all questions

\*\* among premenopausal women

‡ among women sexually active

★ During, immediately after, and/or half hour after urination

**Table 3**  
EPIC and ICDB pain criteria

	EPIC At least one pain ....	ICDB*
Single criterion		
1. Worsens with diet	131/154 (85%)	209/270 (77%)
2. Worsens with bladder filling	130/155 (84%)	244/270 (90%)
3. Improves with urination	130/155 (84%)	220/270 (81%)
Combinations of criteria		
1. and/or 2.	151/154 (98%)	261/270 (97%)
1. and/or 3.	151/155 (97%)	251/270 (93%)
2. and/or 3.	144/154 (94%)	251/270 (93%)
1., 2. and/or 3.	151/156 (97%)	262/270 (97%)

\* "urinary symptoms"(1.) or "pain" (2. & 3.)