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Symptoms of Interstitial Cystitis, Painful Bladder Syndrome and Similar Diseases in Women: A Systematic Review

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Purpose: In women symptoms of interstitial cystitis are difficult to distinguish from those of painful bladder syndrome and they appear to overlap with those of urinary tract infection, chronic urethral syndrome, overactive bladder, vulvodynia and endometriosis. This has led to difficulties in formulating a case definition for interstitial cystitis, and complications in the treatment and evaluation of its impact on the lives of women. We performed a systematic literature review to determine how best to distinguish interstitial cystitis from related conditions.

Materials and Methods: We performed comprehensive literature searches using the terms diagnosis, and each of interstitial cystitis, painful bladder syndrome, urinary tract infection, overactive bladder, chronic urethral syndrome, vulvodynia and endometriosis.

Results: Of 2,680 screened titles 604 articles were read in full. The most commonly reported interstitial cystitis symptoms were bladder/pelvic pain, urgency, frequency and nocturia. Interstitial cystitis and painful bladder syndrome share the same cluster of symptoms. Chronic urethral syndrome is an outdated term. Self-reports regarding symptoms and effective antibiotic use can distinguish recurrent urinary tract infections from interstitial cystitis in some but not all women. Urine cultures may also be necessary. Pain distinguishes interstitial cystitis from overactive bladder and vulvar pain may distinguish vulvodynia from interstitial cystitis. Dysmenorrhea distinguishes endometriosis from interstitial cystitis, although many women have endometriosis plus interstitial cystitis.

Conclusions: In terms of symptoms interstitial cystitis and painful bladder syndrome may be the same entity. Recurrent urinary tract infections may be distinguished from interstitial cystitis and painful bladder syndrome via a combination of self-report and urine culture information. Interstitial cystitis and painful bladder syndrome may be distinguished from overactive bladder, vulvodynia and endometriosis, although identifying interstitial cystitis and painful bladder syndrome in women with more than 1 of these diseases may be difficult.

Key Words: bladder; cystitis, interstitial; pain; symptoms; female

Prior literature indicates a general lack of a consensus on the case definition of IC in women.¹⁻³ Difficulties with advancing a case definition, especially for epidemiological research, arose due to the overlap in symptoms between IC and other conditions. Toward the development of a case definition for use in epidemiological research in women we performed a systematic literature review to 1) determine the differences and similarities in reports by women of the symptoms of 3 seemingly related conditions, including IC, PBS and CUS, and 2) determine how best to distinguish IC based on patient reports of symptoms of diseases with similar symptoms, including UTI, OAB, vulvodynia and endometriosis.

MATERIALS AND METHODS

To determine appropriate search terms for IC and related conditions we consulted experts in IC, urology, gynecology and pelvic pain who served as consultants for the current

study (see Appendix). Based on their input we performed systematic literature searches of the PubMed® database from 1950 to the present using the word diagnosis and synonyms (diagnostic criteria, case definition and terminology) and the name of each disease (IC, PBS, CUS, UTI, OAB, vulvodynia and endometriosis). Our consultants also suggested supplementing these searches with a search on pelvic floor dysfunction and 1 on incontinence. We did not search and review identifiable conditions with symptoms similar to those of IC that are already accepted as NIDDK exclusionary criteria for IC, eg bladder cancer, bladder stones, exposure to cyclophosphamide or pelvic radiation.²

Two types of articles were sought, including 1) systematically developed diagnostic criteria and 2) empirically based reports of the symptom prevalence of each disease in women. Because the initial search for endometriosis and diagnosis yielded 7,514 articles, we refined it before screening, using additional key words suggested by our study consultants, ie endometriosis plus frequency, urgency or bladder.

Two coders selected potentially relevant articles based on an independent title screening. Abstracts of these articles were reviewed and independently coded as relevant or irrelevant and relevant articles were obtained and read in full. The coders independently abstracted the prevalence rates of various symptoms and discrepancies were resolved through

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TABLE 1. Literature search and results

Search Terms	No. Titles Screened	No. Articles Read
Diagnosis AND:		
Interstitial cystitis	804	333
Painful bladder disorder/syndrome	326	16
Vulvodynia	103	77
Pelvic floor dysfunction	96	19
Overactive bladder	199	57
Urethral syndrome	126	66
Urinary tract infection, chronic or persistent, not recurrent, asymptomatic or complicated	339	11
Incontinence (not stress)	70	11
Endometriosis AND:		
Bladder	303	—
Urinary frequency	4	—
Urinary urgency	4	—
Combined terms	306	14
Totals	2,680	604

Searches were de-duplicated and titles from the search using the key word, endometriosis, only were not screened.

collaboration. Studies typically described only a subset of symptoms of interest. Any abstracted studies that included 100 patients or greater and had systematic inclusion criteria, ie consistently used the same criteria to define the disease sample, were used to compare symptoms. However, we included smaller studies when necessary if other information on the topic was not available. When several articles appeared to describe results based on the same data set, we included only the article that reported the largest number of patients.

RESULTS

Table 1 shows the literature searches. The titles of select articles were circulated among our consultants, who suggested additional relevant reports. Article bibliographies were also used to identify additional reports. Of the 2,680 titles screened 604 were obtained and read in full.

IC

Although Skene first used the term interstitial cystitis in 1887,⁴ widely acceptable diagnostic criteria for IC were not developed until a small group of urologists was convened by the NIDDK 100 years later.² These preliminary criteria, which were modified at a 1988 meeting,³ required mucosal ulcers, as first identified by Hunner.⁵ Pain on bladder filling

that was relieved by emptying as well as suprapubic, pelvic, urethral, vaginal or perineal pain and/or glomerulations (epithelial hemorrhages elicited by bladder hydrodistention) were deemed positive factors for IC, of which 2 were required for diagnosis. Urgency was not included in the consensus criteria at the meeting because it was assumed that virtually all patients would present with urgency.

Pain was a prominent part of the case definition discussion at the 1987 NIDDK meeting.² Gillenwater et al introduced IC by referring to "painful bladder disease."² Holm-Bentzen presented extensive data on "the painful bladder syndrome."² Held et al surveyed 127 board certified urologists about their experiences with patients with IC and pain was ranked as the single most common criterion for diagnosing IC, while "pain on filling and relieved by emptying" was ranked fourth and nonpain symptoms were ranked lower, including urgency as seventh, nocturia as seventeenth and waking frequency as nineteenth.⁶

Symptom prevalence. Of the abstracted studies reporting prevalence rates of IC symptoms we identified 6 studies with 100 patients or greater, of whom almost all were female.^{6–11} Two studies were excluded because inclusion criteria were unclear.^{12,13} In the 6 abstracted studies 63% to 92% of patients reported pain (table 2). Four studies were useful for understanding the locations and character of pain in patients with IC.^{8,11,14,15} Pain in the bladder, urethra and vagina was most commonly reported and most patients reported the character of pain as pressure, aching or burning (table 3). Two studies described activities that relieved or increased pain.^{6,8} Urination decreased pain in 57% to 73% of patients. For pain exacerbation 61% of patients reported stress, 50% reported sexual intercourse and 49% reported constrictive clothing.⁸ Certain foods and drinks were reported to exacerbate IC pain in 1 study, including acidic beverages in 54% of patients, coffee in 51% and spicy foods in 46%.⁸

In addition to pain, symptoms of urgency, frequency and nocturia were commonly reported (table 2). Other types of urinary and pain symptoms have been observed to a lesser extent. Held et al reported that 47% of patients with IC said that they had difficulty starting urine flow and 51% reported difficulty emptying the bladder.⁶ Dyspareunia was reported by about half of patients with IC (table 2).^{6,8,11} Although 2 articles mentioned incontinence symptoms in women with IC,^{14,16} it is not considered part of the diagnosis.¹⁷

The literature search also revealed 3 symptom indexes developed for IC clinical trials.^{18–20} These indexes have been successfully used to assess symptom severity and response to therapy. However, to our knowledge no question-

TABLE 2. Reports of symptoms by disease

Condition	% Pts (No. studies)					
	Pain	Urgency	Frequency	Nocturia	Dyspareunia	Incontinence
IC	63–92 (6) ^{6–11}	84–98 (5) ^{6–9,11}	80–92 (5) ^{6–9,11}	61–89 (5) ^{6,7,9–11}	45–57 (3) ^{6,8,11}	26 (1) ⁶
PBS	95 (1) ²²	69 (1) ²²	97 (1) ²²	97 (1) ²²	Not reported	Not reported
OAB	Not reported	Recruiting criterion (5) ^{33–37}	Recruiting criterion (3), ^{35–37} 85 (1) ³⁴	Not reported	Not reported	55–74 (5) ^{33–37}
Vulvodynia	57–91 Vulvar (2) ^{45,63}	46 (1) ⁶³	45 (1) ⁶³	Not reported	71–81 (2) ^{45,63}	Not reported
Endometriosis	80–90 Dysmenorrhea (2), ^{51,52} 62 CPP (1) ⁵²	Not reported	Not reported	Not reported	43–62 (2) ^{51,52}	Not reported

Only symptoms reported in the referenced studies are included and each symptom was defined differently in the articles summarized.

TABLE 3. Pain location, prevalence and character in IC studies

Location	Prevalence (%) ^{8,11,14}	Character (%) ¹⁵
Bladder, suprapubic, lower abdomen	55–71	Pressure (75), aching (55), bloating (51)
Urethra	50–74	Pressure (68), burning (63)
Vagina	51–61	Burning (55), aching (52), pressure (50)
Perineum	47	Aching (62), dull (50)
Groin	19–34	Not mentioned
Low back	10–65	Aching (88), dull (50)
Rectum	24	Pressure (59)

naire has been developed as a screening tool to distinguish IC from other diseases with similar symptoms.

PBS

Use of the phrase painful bladder goes back at least to 1951.²¹ In 1987 in a clinical trial of “interstitial cystitis and painful bladder disease” Holm-Bentzen et al described PBS in terms similar to those for IC.²² They and others used the phrase painful bladder syndrome with various definitions, of which most included IC in some way (table 4).

Since 1976, the ICS has standardized the terminology of lower urinary tract diseases. Although the 1976²³ and 1988²⁴ reports did not use the term painful bladder syndrome, the 2002 report did for the first time. “Painful bladder syndrome is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as daytime and nighttime frequency, in the absence of proven urinary infections or other obvious pathology.”²⁵

The report also included a footnote recommending that IC should be defined as a condition that is symptomatically the same as PBS in terms of pain and other symptoms, such as frequency, but must be confirmed clinically. “The ICS believes this to be a preferable term to ‘interstitial cystitis.’ Interstitial cystitis is a specific diagnosis and requires confirmation by typical cystoscopic and histological features.”²⁵

These features typically include ulcers or glomerulations observable on the bladder wall. Other committees recently came to similar conclusions about IC and PBS, and several suggested that the names should be combined into 1 term.^{26–28}

CUS

CUS is a poorly defined condition that is no longer alluded to in the modern medical literature.²⁹ Most of the literature on CUS was published in the 1980s and earlier. A recent review suggested that the term “urethral syndrome” has become outdated and it “should be abandoned.”³⁰ Moreover, we found no consensus definition for CUS and case definitions

vary across research. Thus, CUS was not considered further as a possible overlapping condition of IC.

UTI

A few groups have examined the accuracy of patient reported symptoms for predicting UTI. A recent meta-analysis showed that 4 symptoms (dysuria, frequency, hematuria and back pain) were significantly associated with a higher likelihood of UTI and presentation with at least 1 of these symptoms led to about a 50% probability of infection.³¹ The meta-analysis also indicated that the likelihood of UTI decreased with an absence of dysuria and back pain, a history of vaginal discharge and a history of vaginal irritation. An epidemiological study of women presenting with urinary symptoms in primary care found that painful voiding, urgency, frequency and tenesmus increased the probability of UTI.³² In addition, self-reports regarding the patient response to antibiotics have been used to identify UTIs. For example, previous studies, including the Interstitial Cystitis Database Study, have included a self-report question assessing whether patient urinary symptoms were eliminated with antibiotics to distinguish UTI from IC.⁹ However, self-report questions regarding antibiotic use would not be able to identify UTIs in those who never visited a provider for symptoms and, therefore, never received antibiotics.

OAB

The words overactive bladder did not appear in the 1976²³ or 1988²⁴ ICS terminology reports. The 2002 ICS report defined overactive bladder as “Urgency with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome, urge syndrome or urgency-frequency syndrome.”²⁵ We identified 5 studies of OAB with 100 patients or greater that described symptom prevalence (table 2).^{33–37} Consistent with ICS criteria, all required urgency as a recruitment criterion, while frequency was sometimes an inclusion criterion and sometimes reported as a symptom. The majority of patients experienced incontinence.

No study has yet determined the degree of bladder pain in patients with OAB, most likely because in many OAB studies bladder pain and/or IC are exclusionary criteria and pain has rarely been measured.^{33–35,38–40} Moreover, the contemporary interpretation of these 2 conditions is that pain is a defining feature of PBS but not of OAB.⁴¹ Thus, the literature seems to be consistent in defining OAB as a condition with a primary complaint of sudden urgency without warning, usually in the absence of bladder pain.

TABLE 4. Painful bladder disease/syndrome definitions

References	Terminology	Description
Bourque ²¹	Painful bladder	IC, bladder tuberculosis, recurrent bacterial infections, bladder Ca
Holm-Bentzen et al ²²	Painful bladder disease	IC (detrusor mastocytosis), detrusor myopathy, chronic unspecific cystitis, eosinophilic cystitis
Witherow et al ⁶⁴	PBS	Nonulcer IC
Ramahi and Richardson ⁶⁵	PBS	IC
Stone ⁶⁶	PBS	Any painful bladder condition for which no specific etiology can be determined
Thilagarajah et al ⁶⁷	PBS	Nonulcer IC
Thilagarajah et al ⁶⁸	Painful bladder disease	IC, PBS, abacterial cystitis, urethral syndrome
Abrams et al ²⁵	PBS	Suprapubic pain related to bladder filling with other symptoms (daytime + nighttime frequency), absent proven UTI or other obvious pathological condition

Vulvodynia

Although it was described more than a century ago, the tender vulva was not widely commented on in the literature until 1984, when the International Society for the Study of Vulvovaginal Diseases described the “burning vulva syndrome.”⁴² The most recent definition by the International Society for the Study of Vulvovaginal Diseases was that vulvodynia is “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant and visible findings or specific, clinically identifiable, neurological disorder.”⁴³

Harlow and Stewart studied the prevalence of chronic vulvar pain in 4,915 women randomly selected in the Boston area.⁴⁴ They defined it as 3 months or longer of vulvar burning, knife-like or sharp pain, or excessive vulvar pain on contact. Results indicated that 16% of women at some time in life had such a syndrome and 7% were experiencing symptoms at the time of the survey.

We found 2 studies of 100 cases or greater that described the prevalence of vulvodynia symptoms (table 2).^{45,46} Each mentioned that most patients had vulvar burning and dyspareunia, while neither mentioned urinary urgency, frequency or nocturia. None of the reports mentioned vulvar pain in relation to or exacerbated by urinary symptoms. However, research suggests that vulvodynia and IC may be comorbid in some women. For example, a Web based survey of 428 women reporting vulvar pain with unconfirmed vulvodynia diagnoses showed that 11% had been diagnosed with IC.⁴⁷ Additional systematic research with clinician diagnosed participants is needed to understand the level of comorbidity in the population.

Endometriosis

Although there is a general lack of large-scale research on symptom prevalence for endometriosis, research suggests that most women with endometriosis report CPP, dysmenorrhea and/or dyspareunia. At laparoscopy endometriosis is found in 32% to 50% or higher of women with CPP^{48,49} and in 15% to 45% without CPP who are undergoing laparoscopy for other reasons.^{48,50} In 2 research studies of patient symptoms, including 1 with 90 consecutive patients⁵¹ and 1 with 7,200 women in a North American endometriosis research registry,⁵² 80% to 90% of patients reported dysmenorrhea (table 2).

We found 3 studies of urinary symptom reports in women with CPP, of whom many presented with endometriosis plus IC.^{20,53–55} Because of the high overlap between the 2 diseases, these reports could neither distinguish whether the observed urinary symptoms were due to endometriosis or IC nor provide estimates regarding the prevalence of urinary symptoms in patients with endometriosis. For example, Chung et al performed a retrospective review of 60 women presenting with dyspareunia and dysmenorrhea who underwent laparoscopy and cystoscopy.⁵⁴ Of the patients 45 (75%) were characterized as having “irritable urinary symptoms.”⁵⁴ Endometriosis was diagnosed at laparoscopy or by history in 56 patients (93%) and IC was diagnosed by glomerulations and terminal hematuria at hydrodistention in 58 (93%).

In women with endometriosis bladder implants are uncommon,⁵⁶ although 1 report suggests that 4% to 15% have endometriosis located on the bladder.⁴⁹ Symptoms experi-

enced by these women can be similar to those of IC.^{57,58} Diagnosis can often be made by cystoscopy because most lesions are transmural.⁵⁶

DISCUSSION

This review indicates that a substantial majority of women with IC show at least 1 of the 4 symptoms of pain, urgency, frequency and nocturia (table 2). Symptoms of PBS appear to be almost identical to those of IC. Therefore, we accept the conclusion at several recent international meetings that the symptoms of IC and PBS are the same. In addition, prior groups suggested that IC is a subgroup of PBS that requires specific cystoscopic and histological features, in addition to symptoms.^{2,25} Thus, a subset of women who show PBS symptoms also have IC. However, in epidemiological studies focused on symptoms the 2 conditions can be treated in the same way.

Although pain has historically been accepted as a primary characteristic of IC, some patients did not report pain in the reviewed empirical research (table 2). In part the discrepancy between prior case definitions and empirical research may be due to methodological reasons related to cross-sectional assessments and the wording of survey items. For example, a small study of initial symptom reports of IC suggests that the onset of particular symptoms varies in patients with early disease and many patients with IC do not initially experience pain.⁵⁹ Findings indicated that 41% of patients originally presented with urgency, frequency and/or nocturia without pain but all subsequently also reported pain as the condition worsened with time. Furthermore, patient endorsement of pain on self-reported questionnaires may differ according to the wording of the questions. For example, pain is described as “burning, discomfort, pain or pressure” on the IC problem index, which measures the bother of pain, and as “burning or pain” in the IC symptom index, which measures the presence of pain.¹⁹ A recent study showed that reports of pain bother on the IC problem index and the presence of pain on the IC symptom index correlated at only 0.70, possibly because patients who experience pain as discomfort or pressure did not respond affirmatively to the question assessing only pain and burning.⁶⁰ Future research is essential to develop valid assessments of IC pain that include the types of words that patients use to describe pain.

We suggest that UTI may be distinguished from IC and PBS by a combination of self-reports regarding symptoms and the ineffectiveness of antibiotics as well as by the presence or absence of bacteriuria in urine cultures collected by patients. Although certain UTI symptoms (frequency and urgency) may overlap with those of IC, other UTI symptoms (dysuria and hematuria) and medical history information (vaginal discharge and irritation) appear to be unique to UTIs and, therefore, they can be used to distinguish the 2 diseases. Self-reported data on these symptoms and the antibiotic response could be used in conjunction with urine culture information in epidemiological studies to provide upper and lower boundaries for prevalence estimates for IC and PBS in women, that is a more conservative estimate, ruling out those with positive urine cultures, and a less conservative estimate, using self-report information only for determining prevalence.

OAB can be distinguished from IC because pelvic or bladder pain, which is a hallmark symptom of IC, is rare in patients with OAB.⁴¹ Furthermore, unlike the urgency of OAB, which is linked to incontinence or fear of incontinence, the urgency of IC is associated with bladder pain.⁴¹ For example, the ICS described urgency as “the complaint of a sudden compelling desire to pass urine which is difficult to defer.”²³ However, the urgency of IC may differ from the urgency of OAB, in that it may develop with time, not suddenly, may occur with pain and rarely results in incontinence.

Thus, in most cases focusing on the bladder pain component of IC and PBS may help to distinguish between OAB and IC.^{61,62} Nevertheless, because pain is not assessed or it is an exclusion criterion in many OAB studies, no research to date allows us to determine the percent of patients with OAB who have pain. In addition, some patients with IC with early disease have urgency but no pain.⁵⁹ Such patients may be difficult to distinguish from those with OAB, especially in a cross-sectional epidemiological survey that does not capture symptom progression with time. Future epidemiological research identifying the proportion of patients with IC and PBS who do not report pain as well as the proportion with OAB who report pain is necessary to refine prevalence estimates of IC and OAB.

Women with vulvodynia can probably be distinguished from those with IC by self-reported vulvar pain but not self-reported frequency or nocturia. However, dual diagnoses of IC and vulvodynia are possible. Although the overlap between diagnoses of endometriosis and IC may lead to difficulties with diagnosis, research suggests that the symptom of dysmenorrhea may distinguish IC from endometriosis. In prior research a high proportion of women with endometriosis reported pain with menstruation (dysmenorrhea).⁵² We did not observe corresponding empirical reports in women with IC (table 2).

CONCLUSIONS

This systematic literature review suggests that IC and PBS can be studied together as the same entity symptomatologically in women, and IC may be considered at this time to be a subgroup of PBS. CUS is an outdated term and a poorly defined condition that should no longer be considered in the study of IC and PBS. IC and PBS in women may be distinguished from UTI, OAB, endometriosis and vulvodynia, although comorbidity between IC and PBS and other diseases as well as the need to collect urine cultures to test for recurrent UTIs may pose difficulties in epidemiological studies.

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APPENDIX

Study consultants: Drs. Phillip M. Hanno, University of Pennsylvania; Fred M. Howard, University of Rochester; Edward M. Messing, University of Rochester; Vicki Ratner, Interstitial Cystitis Association; and Ursula Wessellmann, Johns Hopkins University.

Abbreviations and Acronyms

CPP	=	chronic pelvic pain
CUS	=	chronic urethral syndrome
IC	=	interstitial cystitis
ICS	=	International Continence Society
NIDDK	=	National Institute of Diabetes and Digestive and Kidney Diseases
OAB	=	overactive bladder
PBS	=	painful bladder syndrome
UTI	=	urinary tract infection

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