BJUI BJU INTERNATIONAL

Prognostic factors for recent-onset interstitial cystitis/painful bladder syndrome

John W. Warren*†, Daniel J. Clauw‡ and Patricia Langenberg†

**Department of Medicine, †Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, and ‡Departments of Anesthesiology and Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA*

Accepted for publication 10 May 2012

Study Type – Prognosis (case series)
Level of Evidence 4

What's known on the subject? and What does the study add?
Interstitial cystitis/painful bladder syndrome (IC/PBS) comprises pain perceived to be from the bladder, urinary urgency and frequency, and nocturia. As diagnosed at present, it is primarily identified in adult women. It is a chronic disease yet its natural history has not been well studied.

In a prospective study of 304 incident female IC/PBS cases followed for a median of 33 months after onset, women with baseline chronic fatigue syndrome had a worse prognosis for IC/PBS. Mild IC/PBS at baseline was the only variable that was directly associated with a good prognosis.

OBJECTIVE

- To identify baseline variables that predict the prognosis of interstitial cystitis/painful bladder syndrome (IC/PBS) in women seeking medical care for recent onset of this syndrome.

SUBJECTS AND METHODS

- In a prospective study of women with incident IC/PBS (≤12 months of symptoms), we contacted patients at intervals and asked standardized questions about IC/PBS symptoms in the previous week.
- Logistic regression analyses assessed baseline variables as predictors of mild vs more severe IC/PBS at the last follow-up.

RESULTS

- Median length of follow-up was 33 months after onset of IC/PBS; 304 (97%) patients had at least one follow-up assessment.
- Mild IC/PBS at baseline was the only variable that was directly associated with a mild IC/PBS endpoint.
- Conversely, a history of chronic fatigue syndrome (CFS) was inversely associated with a mild endpoint of IC/PBS (i.e. individuals with CFS had a worse prognosis for their IC/PBS symptoms).

CONCLUSIONS

- At a median of nearly 3 years after onset, baseline mild IC/PBS was directly associated with a milder disease severity.
- Baseline co-morbid CFS was associated with more severe disease.
- Whether CFS was uniquely associated or represented several co-morbid non-bladder syndromes (NBSs) could not be determined.

KEYWORDS

interstitial cystitis, painful bladder syndrome, prognostic factors, chronic fatigue syndrome

INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS) comprises pain perceived to be from the bladder, urinary urgency and frequency and nocturia. As diagnosed at present, it is primarily identified in adult women. Its aetiology is unknown [1].

Interstitial cystitis/painful bladder syndrome is a chronic disease [1]. In a prospective study of 304 incident female IC/PBS patients followed for a median of 33 months after onset, we reported that complete disappearance of IC/PBS symptoms was rare, but that improvement occurred in a substantial minority of patients [2]. To provide data for discussions about prognosis with patients with recent-onset IC/PBS, we report here baseline factors that predicted differential clinical status at a median of nearly 3 years after onset of symptoms.

SUBJECTS AND METHODS

Events Preceding Interstitial Cystitis (EPIC) was a case–control study seeking risk factors for IC/PBS in women; methodological details are presented elsewhere [2–5]. Briefly, 312 women aged ≥ 18 years with a syndrome beginning within the previous 12 months and lasting ≥ 4 weeks that comprised pain that they perceived to be from the bladder (≥3 on a scale of 10) plus at least two of the symptoms of urgency (≥3/10), frequency (≥eight times/24 h) or nocturia (≥once per night). Cases were recruited nationally through patient support groups and urologist and gynaecologist associations by letters, posters and the internet.

  doi:10.1111/j.1464-410X.2012.11422.x

This syndrome had to have been evaluated by at least one physician and patients were required to give permission to review medical records from 1 year before the onset of symptoms to the present. Of 1088 medical records sought, 1062 (98%; 3.4/patient) were obtained and reviewed to exclude mimicking diseases, confirm the onset date of IC/PBS symptoms and record IC/PBS diagnostic and therapeutic initiatives [6]. Respondents were excluded by self-report or medical record evidence of 12 possibly mimicking diseases as listed in the 1990 definition of interstitial cystitis of the National Institute of Diabetes, Digestive and Kidney Diseases [7]. Because of the possibility of a neurogenic bladder, exclusions also included stroke, spinal cord injury, Parkinson's disease, multiple sclerosis and spina bifida. The index date for cases was the onset date of the first IC/PBS symptom and was identified by a five-step process: (i) estimate by the participant; (ii) probing questions about earlier symptoms; (iii) probing questions about similar episodes lasting ≥ 4 weeks in the previous 5 years; (iv) medical record review; and (v) final concurrence with the case. For enrolment, cases required medical record diagnosis of interstitial cystitis by a urologist or gynaecologist and/or treatment with IC/PBS-specific medications.

The characteristics of these patients [6] were similar to those of previously reported patient series [8,9]. The mean score of worst IC/PBS pain was 8.4/10. In all, 86% of cases reported this pain to worsen with bladder filling, 81% reported it to improve with voiding, and 83% reported it to worsen with certain dietary products; 97% reported one or more of these. The mean urgency was 7.5/10, 87% had frequency of ≥11/24 h and 71% reported nocturia of ≥three times per night. The mean Interstitial Cystitis Symptom Score [9] was 14.8. These cases met the definitions of IC/PBS of the Fourth International Consultation on Incontinence [10], the European Society for the Study of Interstitial Cystitis [11], and the AUA [12].

Controls were recruited by national random digit dialling, matched to cases by gender, age, region of the country and index date, and compared with cases on antecedent characteristics.

The baseline interview took place a mean of 9 months after IC/PBS onset. Follow-up interviews took place at 6, 12, 18, 24, 36 and 48 months after the baseline interview [2]. Trained female interviewers performed all interviews by telephone; to the extent possible, the same interviewer contacted each patient over the course of the study. At the baseline interview and at each follow-up, the interviewer asked standardized questions about IC/PBS symptoms in the previous week. Pain and urgency were scored as 0–10 (10 being the worst imaginable), frequency as number of times/24 h. Composite IC/PBS symptom scores [13] of none, mild, moderate or severe were constructed from scores of the individual symptoms of pain, urgency and frequency [2]. At the baseline interview, five (2%) patients had a composite score of none, 82 (26%) had a composite score of mild, 155 (50%) had a composite score of moderate and 70 (22%) had a composite score of severe IC/PBS.

At follow-up we defined remission as the absence of IC/PBS symptoms but found that few patients achieved remission and, for most of those who did, it was temporary [2]. Because of the low incidence and instability of remissions, for the present study we defined the endpoint as a composite symptom score of mild or no IC/PBS symptoms at the last follow-up ('mild endpoint') [13]; those who did not achieve this endpoint had either moderate or severe IC/PBS at the last follow-up ('moderate/severe endpoint').

Three sets of baseline variables were assessed as potential prognostic factors. Two sets were of variables before the index date. The first comprised the following demographics: age, race, religion, education and presence or absence of health insurance. The second set was of queried variables before the index date that distinguished cases from controls on bivariable analyses. These included pre-index date histories of: ever pregnant; use of birth control pills, female hormone therapy, douches and condoms; surgeries and abortions; sexual activity, dyspareunia and genital warts [5,14,15]; and 11 non-bladder syndromes (NBSs) [4,15]. These NBSs included eight diagnosed by symptom-based expert consensus: chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel syndrome (IBS), sicca syndrome, migraine, chronic pelvic pain (CPP), panic disorder and vulvodynia. The other three NBSs were allergy, diagnosed by self-report, and asthma and depression, scored if both physician diagnosis and medical therapy were reported.

The third set of variables described baseline IC/PBS: from medical records, the presence of Hunner's ulcer or glomerulations; and from self-reports, sites of IC/PBS pain [3], severity of IC/PBS symptoms (see earlier), and IC/PBS therapy that had been prescribed between the index date and the baseline interview (baseline therapy). Therapies queried were bladder distension; bladder instillations with dimethylsulphoxide, heparin, hyaluronic acid, lidocaine or other; and systemic therapies including pentosanpolysulphate, amitriptylene, hydroxyzine, non-narcotic pain medications, narcotics, antispasmodics or other.

To assess confounding by IC/PBS treatment, the use of these therapies was also assessed between the previous and last follow-up (interval therapy).

Chi-squared and *t*-tests screened each baseline variable for association with a mild endpoint. Associations with P values ≤0.10 were entered into logistic regression analyses adjusted for demographics, duration of follow-up, and interval IC/PBS therapies. The present study was approved by the University of Maryland Institutional Review Board.

RESULTS

In all, 304 patients (97%) participated in at least one follow-up interview. The median duration of follow-up was 33 months after the index date. At their last follow-up, 20 (7%) patients had no IC/PBS symptoms and 109 (36%) had mild symptoms, i.e. 129/304 (42%) had a mild endpoint. Of the remainder, 123 (40%) had moderate and 52 (17%) severe IC/PBS symptoms, i.e. 175 (58%) had a moderate/severe endpoint.

In bivariable analyses, only mild IC/PBS at baseline was directly associated with a mild IC/PBS endpoint, but several baseline variables were inversely associated. All variables associated directly or inversely with a mild endpoint with $P \leq 0.10$ are shown in Table 1. Each of these variables was entered into logistic regression analyses

adjusted for age, race, religion, education, medical insurance and duration of follow-up (Table 2). Logistic analysis 1 included the five NBSs that were inversely associated with a mild endpoint by bivariable analyses: CFS, CPP, migraine, panic disorder and FM. This logistic regression analysis revealed that three baseline variables remained associated: mild IC/PBS at baseline was directly associated, and CFS and history of condom use were inversely associated with a mild endpoint of IC/PBS.

We repeated the logistic regression analysis but for the individual NBSs, we substituted the number of NBSs (0–1, 2–5, and ≥6 NBSs) (Table 2, analysis 2). Baseline mild IC/PBS was still directly associated with a mild endpoint, ≥6 NBSs was inversely associated, and condom use became non-significant.

In logistic regression analyses 3–4 in Table 2, we sought to adjust for possible confounding. Because condoms are used to prevent pregnancies and sexually transmitted infections (STIs), number of pregnancies was substituted for 'ever pregnant' and a new variable was added: lifetime history of STI, defined as self-report of ≥1 of gonorrhoea, syphilis, HIV, genital chlamydia, warts or herpes. Interval therapies were integrated to adjust for possible confounding. The odds ratios (ORs) found in analyses 1 and 2 did not change substantively. Interval narcotic use was inversely associated with a mild endpoint.

In analysis 5 in Table 2, all variables in analyses 1–4 were included, specifically NBSs both as individual syndromes and as number of NBSs per patient. Only one variable substantively changed: ≥6 NBSs was no longer significantly associated. A history of CFS remained inversely associated with a mild endpoint.

Because of the inverse association with CFS, we hypothesized that fatigue alone at baseline might be predictive of a poor outcome of IC/PBS. The stem question that led to the series of queries about CFS symptoms was: 'At any time in your life before your index date, did you experience, for 6 months or longer, persistent fatigue that was not relieved with rest and that limited your activities?' Of the 85 patients who answered 'yes', 61 reported the other criteria for CFS (≥4 of impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, or post-exertion malaise) and 24 did not. Significantly fewer of the 61 patients who met the criteria for CFS had a mild

TABLE 1 Baseline variables associated with a mild IC/PBS endpoint (P ≤ 0.10)

	Proportions with mild IC/PBS endpoint (*n*/*N* [%])		
Baseline variable	Baseline variable present	Baseline variable absent	*P* value
Mild IC/PBS	56/85 (66%)	73/219 (33%)*	<0.001
Non-bladder syndromes			
CFS	12/61 (20%)	117/243 (48%)	<0.001
CPP	38/110 (35%)	91/194 (47%)	0.036
Migraine	35/102 (34%)	94/202 (47%)	0.042
Panic disorder	29/86 (34%)	100/218 (46%)	0.054
FM	22/68 (32%)	107/236 (45%)	0.056
Number			0.001
0–1	37/69 (54%)	–	
2–5	86/199 (43%)	–	
6–9	6/36 (17%)	–	
Reproductive			
Ever pregnant	86/222 (39%)	43/82 (52%)	0.032
Lifetime ≥ one/week douche	8/30 (27%)	121/274 (44%)	0.066
Lifetime, always + usually use condoms	20/61 (33%)	109/134 (45%)	0.088
IC/PBS therapy			
Bladder distension	71/187 (38%)	58/117 (50%)	0.046
Narcotics	57/153 (37%)	72/151 (48%)	0.066

**Absence of mild IC/PBS = IC/PBS symptom score of moderate/severe.*

TABLE 2 Logistic regression analyses for a mild IC/PBS endpoint (OR [95% CI])

	Analysis*				
Variable	1	2	3	4	5
Baseline variables					
Mild IC/PBS	3.7 (2.0–6.7)	3.6 (2.0–6.4)	3.6 (2.0–6.6)	3.5 (1.9–6.3)	3.6 (1.9–6.5)
CFS	0.32 (0.14–0.75)	ND	0.26 (0.11–0.61)	ND	0.29 (0.11–0.71)
6–9 non-bladder syndromes	ND	0.29 (0.10–0.86)	ND	0.27 (0.09–0.81)	0.64 (0.14–3.0)
History of condom use	0.46 (0.23–0.94)	0.51 (0.26–1.0)	0.43 (0.21–0.88)	0.50 (0.25–1.0)	0.42 (0.21–0.87)
Interval IC/PBS therapy					
Narcotics	ND	ND	0.32 (0.15–0.71)	0.39 (0.18–0.85)	0.33 (0.15–0.73)

**See text for details. ND, not done. Adjusted for age, race, religion, education, medical insurance and duration of follow-up. Variables listed are those significant in at least one of these analyses.*

TABLE 3 Mild IC/PBS endpoint ranked by frequency of condom use before the onset of IC/PBS

Condom use	Mild IC/PBS endpoint (*n*/*N* [%])
Always	14/36 (39%)
Usually	6/25 (24%)
Sometimes	29/58 (50%)
Rarely	33/82 (40%)
Never	47/103 (46%)

P = *0.23*.

endpoint (12, 20%) than did the 24 patients with ≥6 months of fatigue but not the other criteria for CFS (12/24, 50%). Indeed the latter group was not significantly different from patients who answered 'no', i.e. who did not have chronic fatigue before onset of IC/PBS (105/219, 48%). When fatigue as a symptom (i.e. in the 85 patients) was substituted for CFS in analysis 5 in Table 2, it was not associated with a mild IC/PBS endpoint (OR = 0.68, 0.33–1.4).

A history of condom use was initially analysed as (always + usually) vs (sometimes + rarely + never). In Table 3, we expanded this variable into these five frequency-of-use categories and observed no monotonic association with IC/PBS outcome.

DISCUSSION

In this prospective longitudinal study of 304 incident IC/PBS patients, logistic regression analyses revealed two variables that predicted a mild IC/PBS endpoint: mild IC/PBS at baseline and absence of a history of CFS.

The association with mild IC/PBS at baseline with a mild endpoint was anticipated. Earlier we reported that most women with mild IC/PBS at baseline had mild IC/PBS at each follow-up [2]. This is consistent with the observations of others that symptoms of IC/PBS generally reach a plateau rapidly after onset and then wax and wane about this level for years [8,16,17].

The association of CFS with a poor outcome of IC/PBS is perhaps the more interesting finding. It might be worth emphasizing that the observation is that CFS preceded the onset of IC/PBS; in other words, this association cannot be explained by symptoms of IC/PBS causing poor sleep and subsequent chronic fatigue. It should also be noted that full recovery from CFS is uncommon [18]. CFS present before IC/PBS probably persisted after the onset of IC/PBS in most patients, but we did not query the continued presence of its symptoms.

The association of prior CFS with a poor outcome of subsequent IC/PBS suggests either that CFS was uniquely associated with a more severe outcome of IC/PBS or that it was a representative of several, co-morbid, NBSs.

If CFS itself is the important link to a poor outcome of IC/PBS, two hypotheses are generated: (i) that a preceding process is responsible for the presence of CFS and the outcome of IC/PBS; or (ii) that CFS initiates a process that affects the prognosis of IC/PBS. Either type of process could be physiological, behavioural, structural, environmental or another type and could be affected by genetics. Many credible investigators believe that CFS patients, or perhaps a subset of them, exhibit a pathophysiology that differs from the other syndromes studied here. These include infection, immune dysfunction [19] and a different neuroendocrine profile. The evidence is perhaps strongest for the latter, i.e. that hypothalamic–pituitary–adrenal (HPA) axis dysfunction might be differentially present in individuals with CFS. A recent meta-analysis of HPA studies in CFS, FM and IBS patients showed that only for CFS was there a consistent finding of HPA hypoactivity [20]. Whether this precedes or follows the onset of CFS has not been determined.

The second possibility is that CFS is a representative of several syndromes. This would be the case if other syndromes were associated with CFS and also with a poor outcome of IC/PBS, but the latter associations were weaker than that with CFS. Numerous studies [21–26], including of these patients [4], have shown these syndromes to be associated with CFS; the data in Tables 1 and 2 are consistent with but do not prove the existence of the rest of this scenario.

How might several syndromes be associated with each other and with the outcome of IC/PBS? One can begin with the two hypotheses outlined earlier. The first could be expanded to this: (1) that a preceding process is responsible for the presence of each of the syndromes and the outcome of IC/PBS. The second is more complicated: (2a) that each syndrome initiates the same process that affects the prognosis of IC/PBS; or (2b) that each syndrome initiates a different process that affects the prognosis of IC/PBS. Several pathophysiologies have been identified in these syndromes and include abnormalities in supraspinal sensory processing, in autonomic function, and, again, in the HPA axis [27]. Whether any of these precedes or follows a given syndrome has never been determined.

These syndromes have many similarities: symptom-based diagnoses, prominence of pain and fatigue, over-represention among women, normal or incidental local histology, non-diagnostic laboratory tests, exacerbation by stress, co-morbidity, chronicity and unknown aetiology [28]. Indeed, several of the syndromes, FM, CFS and IBS, are commonly discussed together as functional somatic syndromes (FSSs). Others, CPP and migraine, are sometimes included as FSSs; and still others, depression and panic disorder, are often associated with FSSs [28]. Whether these similarities suggest a commonality in their associations with the onset of IC/PBS, i.e. hypothesis 1 or 2a, is unknown.

We believe that the association of history of condom use with IC/PBS outcome is spurious, for several reasons: in bivariable analysis, the association was not significant; in logistic regression analyses, significance varied with entry of other variables; there was no stepwise increase with frequency of use; and there appears to be no literature support for a potential mechanism.

Because interval therapies might affect the endpoint, we integrated them into our analyses as possible confounders. Although the present study design is inappropriate to measure efficacy of an intervention, the finding that no interval therapy was directly associated with a mild IC/PBS endpoint is consistent with the known dearth of successful treatments for IC/PBS [1]. The most likely interpretation for the association of interval narcotic use with a poor outcome

of IC/PBS is that narcotic use was simply a marker for more severe IC/PBS symptoms. An interesting alternative is that some individuals given opioids might actually have been made worse because of the development of opioid-induced hyperalgesia, a phenomenon described in animals that is only beginning to be explored in humans [29].

Of the 61 variables studied, very few were revealed as prognostic factors for IC/PBS. This replicates studies of other chronic pain conditions in which only a handful of factors have been shown to predict outcome. Those identified are similar to ours: symptoms and pain elsewhere, depression and anxiety, and baseline severity of the pain [18,30–34]. In these other studies, syndrome duration was often associated with a poor prognosis. Although duration was included in our analyses, it was not associated with the endpoint, possibly because our participants were incident cases with similar, and short, durations of IC/PBS.

It is intriguing to contemplate that identification of the process linking CFS with IC/PBS outcome might lead to an intervention that would improve the prognosis of the latter syndrome.

The strengths of the present study are exclusion of conditions that could mimic IC/PBS, standardized collection of baseline and follow-up data, and, in particular, the prospective design. Its limitations are that only women were studied, patients unable to identify an onset date were not enrolled, and follow-up was only for the first few years of IC/PBS. Additionally, prognosis could vary by the recruitment methods of IC/PBS patients, e.g. population-based vs primary physician practices vs gynaecology practices vs urology practices.

In conclusion, mild IC/PBS at baseline was associated with a mild IC/PBS endpoint. CFS, however, predicted a moderate/severe IC/PBS endpoint. Whether CFS was uniquely associated or represented several co-morbid NBSs could not be determined.

CONFLICT OF INTEREST

None declared. Source of Funding: National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health (R01 DK 064880 and U01 DK 066136) and the Interstitial Cystitis Association.

REFERENCES

1 **Hanno P, Lin A, Nordling J *et al*.** Bladder pain syndrome committee of the international consultation on incontinence. *Neurourol Urodyn* 2010; **29**: 191–8

2 **Warren JW, Greenberg P, Diggs C, Horne L, Langenberg P.** A prospective early history of incident interstitial cystitis/painful bladder syndrome. *J Urol* 2010; **184**: 2333–8

3 **Warren JW, Langenberg P, Greenberg P, Diggs C, Jacobs S, Wesselmann U.** Sites of pain from interstitial cystitis/painful bladder syndrome. *J Urol* 2008; **180**: 1373–7

4 **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

5 **Warren JW, Clauw DJ, Wesselmann U, Langenberg PW, Howard FM, Morozov V.** Sexuality and reproductive risk factors for interstitial Cystitis/Painful bladder syndrome in women. *Urology* 2011; **77**: 570–5

6 **Warren JW, Brown V, Jacobs S, Horne L, Langenberg P, Greenberg P.** Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. *Urology* 2008; **71**: 1085–90

7 **Wein AJ, Hanno PM, Gillenwater JY.** Interstitial cystitis: an introduction to the problem. In Hanno PM, Staskin DR, Krane RJ, Wein AJ eds, *Interstitial Cystitis*, New York: Springer-Verlagp, 1990: 3–15

8 **Simon LJ, Landis JR, Erickson DR, Nyberg LM, the ICDB Study Group.** The interstitial cystitis data base study: concepts and preliminary baseline descriptive statistics. *Urology* 1997; **49** (Suppl. 5A): 64–75

9 **O'Leary MP, Sant GR, Fowler FJ Jr, Whitmore KE, Spolarich-Kroll J.** The interstitial cystitis symptom index and problem index. *Urology* 1997; **49** (Suppl.): 58–63

10 **Abrams P, Andersson KE, Birder L *et al*.** Fourth international consultation on incontinence recommendations of the international scientific committee: evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn* 2010; **29**: 213–40

11 **van de Merwe JP, Nordling J, Bouchelouche P *et al*.** Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol* 2008; **53**: 60–7

12 **Hanno PM, Burks DA, Clemens JQ *et al*.** AUA guideline for the diagnosis and treatment of interstitial Cystitis/Bladder pain syndrome. *J Urol* 2011; **185**: 2162–70

13 **Propert KJ, Schaeffer AJ, Brensinger CM, Kusek JW, Nyberg LM, Landis JR.** A prospective study of interstitial cystitis: results of longitudinal followup of the interstitial cystitis data base cohort. the interstitial cystitis data base study group. *J Urol* 2000; **163**: 1434–9

14 **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. e1,286.e6

15 **Warren JW, Wesselmann U, Morozov V, Langenberg PW.** Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. *Urology* 2011; **77**: 313–9

16 **Held PJ, Hanno PM, Wein AJ, Pauly MV, Cahn MA.** Epidemiology of interstitial cystitis: 2. In Hanno PM, Staskin DR, Krane RF, Wein AJ eds, *Interstitial Cystitis*, London: Springer-Verlag, 1990: 29–48

17 **Hand JR.** Interstitial cystitis: report of 223 cases (204 women and 19 men). *J Urol* 1949; **61**: 291–310

18 **Cairns R, Hotopf M.** A systematic review describing the prognosis of chronic fatigue syndrome. *Occup Med (Lond)* 2005; **55**: 20–31

19 **Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG.** Plasma cytokines in women with chronic fatigue syndrome. *J Transl Med* 2009; **7**: 96

20 **Tak LM, Cleare AJ, Ormel J *et al*.** Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. *Biol Psychol* 2011; **87**: 183–94

21 **Deary IJ.** A taxonomy of medically unexplained symptoms. *J Psychosom Res* 1999; **47**: 51–9

22 **Aaron LA, Buchwald D.** A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001; **134**: 868–81
23 **Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ.** The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? *Int J Epidemiol* 2006; **35**: 468–76
24 **Schur EA, Afari N, Furberg H *et al*.** Feeling bad in more ways than one: comorbidity patterns of medically unexplained and psychiatric conditions. *J Gen Intern Med* 2007; **22**: 818–21
25 **Kato K, Sullivan PF, Pedersen NL.** Latent class analysis of functional somatic symptoms in a population-based sample of twins. *J Psychosom Res* 2010; **68**: 447–53
26 **White PD.** Chronic fatigue syndrome: is it one discrete syndrome or many? Implications for the 'one vs. many' functional somatic syndromes debate. *J Psychosom Res* 2010; **68**: 455–9
27 **Williams DA, Clauw DJ.** Understanding fibromyalgia: lessons from the broader pain research community. *J Pain* 2009; **10**: 777–91
28 **Henningsen P, Zipfel S, Herzog W.** Management of functional somatic syndromes. *Lancet* 2007; **369**: 946–55
29 **Bannister K, Dickenson AH.** Opioid hyperalgesia. *Curr Opin Support Palliat Care* 2010; **4**: 1–5
30 **Croft PR, Dunn KM, Raspe H.** Course and prognosis of back pain in primary care: the epidemiological perspective. *Pain* 2006; **122**: 1–3
31 **Von Korff M, Miglioretti DL.** A prognostic approach to defining chronic pain. *Pain* 2005; **117**: 304–13
32 **McBeth J, Macfarlane GJ, Hunt IM, Silman AJ.** Risk factors for persistent chronic widespread pain: a community-based study. *Rheumatology (Oxford)* 2001; **40**: 95–101
33 **Janssen HA, Muris JW, Knotterus JA.** The clinical course and prognostic determinants of the irritable bowel syndrome: a literature review. *Scand J Gastroenterol* 1998; **33**: 561–7
34 **Clark MR, Katon W, Russo J, Kith P, Sintay M, Buchwald D.** Chronic fatigue: risk factors for symptom persistence in a 2 1/2-year follow-up study. *Am J Med* 1995; **98**: 187–95

Correspondence: John W. Warren, Department of Medicine, University of Maryland School of Medicine, 10 South Pine Street, #900, Baltimore MD 21201, USA.
e-mail: jwarren@medicine.umaryland.edu

Abbreviations: **CFS**, chronic fatigue syndrome; **CPP**, chronic pelvic pain; **FM**, fibromyalgia; **FSSs**, functional somatic syndromes; **HPA**, hypothalamic–pituitary–adrenal; **IBS**, irritable bowel syndrome; **NBSs**, non-bladder syndromes; **OR**, odds ratio.