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## Disease activity and disease damage scoring systems for BPS/IC

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aspects of effect of a disease on a patient <sup>1,2</sup> 

- disease activity  
*potentially reversible with treatment*
- disease damage  
*irreversible*
- the patient's own perception  
*symptom scores*  
*different from the physician's perception*

1. Sultan SM. The assessment and importance of disease activity versus disease damage in patients with inflammatory myopathy. *Curr Rheumatol Rep* 2003;5:445-50.2.  
2. Sultan SM. Clinical assessment in adult onset idiopathic inflammatory myopathy. *Curr Opin Rheumatol* 2004;16:668-72.

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### symptoms scores for IC

- O'Leary-Sant scores
  - IC Symptom Index (ICSI)
  - IC Problem Index (ICPI)
- Wisconsin IC Inventory (WICI)
- Pain, Urgency, Frequency score (PUF)

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### O'Leary-Sant score

Interstitial Cystitis Symptoms Index (ICSI)	Interstitial Cystitis Problem Index (ICPI)
<i>During the past month:</i>	<i>During the past month:</i>
<i>How often have you felt the strong need to urinate with little or no warning?</i>	<i>How much has each of the following been a problem for you.</i>
0 ___ Not at all	<i>Frequent urination during the day?</i>
1 ___ Less than 1 time in 5	0 ___ No problem
2 ___ Less than half the time	1 ___ Very small problem
3 ___ About half the time	2 ___ Small problem
4 ___ More than half the time	3 ___ Medium problem
5 ___ Almost always	4 ___ Big problem
<i>Have you had to urinate less than 2 hours after you finished urinating?</i>	<i>Getting up at night to urinate?</i>
0 ___ Not at all	0 ___ No problem
1 ___ Less than 1 time in 5	1 ___ Very small problem
2 ___ Less than half the time	2 ___ Small problem
3 ___ About half the time	3 ___ Medium problem
4 ___ More than half the time	4 ___ Big problem
5 ___ Almost always	
<i>How often did you most typically get up at night to urinate?</i>	<i>Need to urinate with little warning?</i>

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### Wisconsin Symptom Instrument (WUI)

KELLER UNIVERSITY OF WISCONSIN SYMPTOM INSTRUMENT

Please circle the one number answer that comes closest to the way you feel, whether or not you have the following symptoms.

Symptom	Not At All	(Circle one number on each line)	A Lot
1. Bladder Discomfort	0	1 2 3 4 5 6	
2. Bladder Pain			4 5 6
3. Other Pelvic C			4 5 6
4. Headache			4 5 6
5. Backache			4 5 6
6. Dizziness			4 5 6
7. Feelings of Gu			4 5 6
8. Chest Pain			4 5 6
9. Ringing in Ears	0	1 2 3 4 5 6	
10. Getting Up at Night to Go to the Bathroom	0	1 2 3 4 5 6	
11. Aches in Joints	0	1 2 3 4 5 6	
12. Swollen Ankles	0	1 2 3 4 5 6	
13. Nasal Congestion	0	1 2 3 4 5 6	
14. Flu	0	1 2 3 4 5 6	
15. Abdominal Cramps	0	1 2 3 4 5 6	

0..6 rating scale  
- 7 IC symptoms  
- 18 reference items

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### Wisconsin IC Symptom Score (WICI)

- bladder discomfort
- bladder pain
- nocturia
- daytime frequency
- sleeping difficulty due to bladder symptoms
- urge to urinate
- burning sensation in bladder

Goin JE et al. Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. *J Urol* 1998;159:1085-90.

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### Pain, Urgency, Frequency score (PUF)

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PELVIC PAIN AND URGENCY/FREQUENCY PATIENT SYMPTOM SCALE

Please circle the answer that best describes how you feel for each question.

	0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1. How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2. a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
b. If you get up at night to go to the bathroom does it bother you?	Never	Mildly	Moderate	Severe			
3. Are you currently sexually active?	YES NO						
4. a. IF YOU ARE SEXUALLY ACTIVE, do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5. Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, testicles, penis, or scrotum)?	Never	Occasionally	Usually	Always			
6. Do you have urgency after going to the bathroom?	Never	Occasionally	Usually	Always			
7. a. If you have pain, is it usually?		Mild	Moderate	Severe			
b. Does your pain bother you?	Never	Occasionally	Usually	Always			
8. a. If you have urgency, is it usually?		Mild	Moderate	Severe			
b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
SYMPTOM SCORE = (1, 2a, 4a, 5, 6, 7a, 8a)							
BOTHER SCORE = (2b, 4b, 7b, 8b)							
TOTAL SCORE (Symptom Score + Bother Score) =							

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### symptom scores

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Neurology and Urodynamics 28:179-182 (2009)

#### Is There a Discrepancy Between Patient and Physician Quality of Life Assessment?

Sushma Srikrishna,<sup>1\*</sup> Dudley Robinson,<sup>3,4\*</sup> Linda Cardozo,<sup>3†</sup> and Juan Gonzalez<sup>2‡</sup>  
<sup>1</sup>Department of Urogynaecology, King's College Hospital, Denmark Hill, London, UK  
<sup>2</sup>King's College Hospital, Denmark Hill, London, UK

symptoms as perceived by:  
 - the patient } may be very different!  
 - the doctor }

Kings Health Questionnaire (KHQ) : to assess symptom severity and QoL in women with lower urinary tract dysfunction

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### Kings Health Questionnaire (KHQ)

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Below are some daily activities that can be affected by bladder problems. How much does your bladder problem affect you?

We would like you to answer every question. Simply tick the box that applies to you.

**3. ROLE LIMITATIONS**

A. Does your bladder problem affect your household tasks? (cleaning, shopping etc)

B. Does your bladder problem affect your job, or your normal daily activities outside the house?

**4. PHYSICAL SOCIAL LIMITATION**

A. Does your bladder problem affect your physical activities (e.g. going for a walk, running, sport, gym etc)?

B. Does your bladder problem affect your ability to travel?

C. Does your bladder problem limit your social life?

We would like to know what your bladder problems are and how much they affect you? From the list below choose only those problems that you **have at present**. Leave out those that don't apply to you.

How much do they affect you?  
 1. A little 2. Moderately 3. A lot

**FREQUENCY:** going to the toilet very often  
 1. A little 2. Moderately 3. A lot

**NOCTURIA:** getting up at night to pass urine  
 1. A little 2. Moderately 3. A lot

**URGENCY:** a strong and difficult to control desire to pass urine  
 1. A little 2. Moderately 3. A lot

**URGE INCONTINENCE:** urinary leakage associated with a strong desire to pass urine  
 1. A little 2. Moderately 3. A lot

**STRESS INCONTINENCE:** urinary leakage with physical activity eg. coughing, running  
 1. A little 2. Moderately 3. A lot

**NOCTURNAL ENURESIS:** wetting the bed at night  
 1. A little 2. Moderately 3. A lot

**INTERCOURSE INCONTINENCE:** urinary leakage with sexual intercourse  
 1. A little 2. Moderately 3. A lot

### Kings Health Questionnaire (KHQ)

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TABLE II. Mean Kappa Scores

KHQ domain	Mean weighted kappa	Patient-physician agreement
General health perception (GHP)		
Incontinence impact (II)		
Role limitation (RL)		
Physical/social limitation (PL/SL)		
Physical relationships (PR)		
Emotions (E)		
Sleep/energy (SE)		
Severity measures (SM)		

kappa=1 : complete agreement  
 kappa=0 : no agreement other than would be expected by chance

weighted kappa: greater emphasis to large differences between ratings

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### Kings Health Questionnaire (KHQ)

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TABLE II. Mean Kappa Scores

KHQ domain	Mean weighted kappa	Patient-physician agreement
General health perception (GHP)	0.47	Moderate
Incontinence impact (II)	0.50	Moderate
Role limitation (RL)	0.34	Fair
Physical/social limitation (PL/SL)	0.26	Fair
Physical relationships (PR)	0.40	Moderate
Emotions (E)	0.18	Poor
Sleep/energy (SE)	0.36	Fair
Severity measures (SM)	0.36	Fair

patient-physician agreement is "not good"

weighting emphasis to large differences between ratings

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### what can we expect from symptom scores?

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symptom scores from patients depend at least on:

- activity of the disease
- damage caused by the disease
- psychological coping capacity of the patient
- the patient's ability to translate the perception of the severity of the symptoms into an answer to the question of the scoring system

→ symptom scores measure a complex mixture of various aspects of a disease, and the patient's or doctor's perception

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## disease activity and disease damage

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### disease activity

actual changes in anatomy, physiology, or function ...

causing symptoms and/or future damage ...

that are reversible with treatment

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### disease damage

irreversible changes in anatomy, physiology, or function

accumulated since the onset of the disease ....

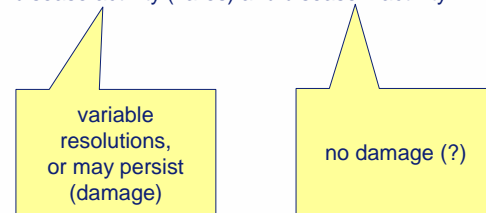
- from the disease itself
- from comorbid conditions, or
- as a result of therapy

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### disease damage

many chronic diseases, including BPS/IC, show periods of disease activity (flares) and disease inactivity



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### damage = irreversible change

suppose: a Hunner's lesion is an irreversible change

1. surgical resection: is the removed Hunner's lesion still damage?

*yes, because damage can only remain the same or increase*

2. suppose that imatinib can heal a Hunner's lesion: is a Hunner's lesion still damage?

*no, it is disease activity (active disease) as it is reversible in this example*

**an irreversible change (damage) to day may be reversible (activity) tomorrow!!**

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### inactive subclinical disease may cause organ damage

#### examples

rheumatoid arthritis  
systemic lupus erythematosus  
Sjögren's syndrome  
inflammatory myositis  
chronic liver disease  
- autoimmune hepatitis  
systemic sclerosis  
sarcoidosis

Crohn's disease

#### organ damage

joint destruction  
premature atherosclerosis  
sensory polyneuropathy  
myopathy

cirrhosis  
pulmonary fibrosis  
pulmonary fibrosis  
uveitis anterior (iridocyclitis)  
fibrotic strictures  
fistulae

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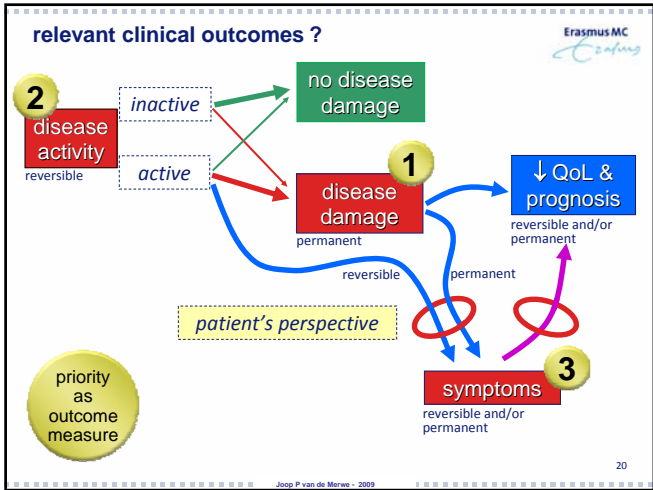
**active clinical disease may NOT cause organ damage**

*examples*

systemic lupus erythematosus	joints
Sjögren's syndrome	joints
sarcoidosis	erythema nodosum
	granulomatous hepatitis
	lymphadenopathy
subacute cutaneous lupus erythematosus	skin
hepatitis A	liver

*usually no damage despite local active disease*

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**no scoring system exists for disease activity or disease damage in BPS/IC**

**aspects of effect of a disease on a patient**<sup>1,2</sup>

- disease activity: potentially reversible with treatment
- disease damage: irreversible
- the patient's own perception: different from the physician's perception

**symptom scores**

1. Sultan SA. The assessment and importance of disease activity versus disease damage in patients with inflammatory myopathy. *Curr Rheumatol Rep* 2003;4(4):30-2.  
 2. Sultan SA. Clinical assessment in adult onset idiopathic inflammatory myopathy. *Curr Opin Rheumatol* 2004;14:658-72.

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**1. correlation between disease damage and symptoms**

*as an example of damage: Hunner's lesion*

**2. what can we learn from urinary markers**

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**Hunner's lesion: Peeker & Fall 2002**

130 patients with classic IC (with Hunner's lesions; BPS type 3)  
 101 patients with nonulcer IC (no Hunner's lesions)

	classic IC	nonulcer IC	p
age at diagnosis (yrs)	62	39	<0.0001
age at onset symptoms (yrs)	57	31	<0.0001
bladder capacity (ml) functional	199	248	<0.01
bladder capacity (ml) under general anaesthesia	468	747	<0.0001

- median pain scores at diagnosis were the same  
 - no detectable difference in symptom pattern

Peeker R, Fall M. Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. *J Urol* 2002;167:2470-2.

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**Hunner's lesion: Braunstein et al 2008**

86 patients with classic IC (with Hunner's lesions; BPS type 3)  
 137 patients with nonulcer IC (no Hunner's lesions)

	classic IC	nonulcer IC	p
mean age (yrs)	60	47	<0.0001
microscopic hematuria (%)	31	21	N.S.

- symptom duration  
 - history gross hematuria  
 - degree of microscopic hematuria  
 - history of irritable bowel syndrome  
 - pain scores

} no significant differences

Braunstein R, Shapiro E, Kaye J, Moldwin R. The role of cystoscopy in the diagnosis of Hunner's ulcer disease. *J Urol* 2008;180:1383-6.

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**Hunner's lesion: Logadottir et al 2004**

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classic IC    nonulcer IC    controls

mean age (yrs)

intravesical nitric oxid

classic IC = with Hunner's lesions

Specification of the relevant subtype of 17 patients with IC

Pt	Age - Sex	Measurement 1		Measurement 2	
		Ppb NO	Symptoms	Ppb NO	Symptoms
<b>Classic IC</b>					
77-F		275	Yes	1,000	Yes
73-M		255	Yes		
63-F		1,313	Yes		
65-F		1,604	Yes		
62-F		1,679	No	1,058	Yes
61-F		3,253	No		
60-F		967	Yes		
54-F		2,596	No	2,175	No
47-M		307	Yes	316	Yes
35-F		297	Yes		
<b>Nonulcer IC</b>					
60-F		1	Yes		
50-M		1	Yes	1	Yes
53-F		1	Yes		
46-F		1	Yes	3	No
44-F		1	Yes		
35-F		1	Yes	1	Yes
20-F		1	Yes		
<b>Control</b>					
66-F		5			
50-F		1			
54-F		1			
36-F		1			
35-M		1			
30-F		2		1	

Logadottir YR, Ehren I, Fall M, Wiklund NP, P. discriminates between classic and nonulcer

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**urinary markers: Erickson et al 2002**

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36 patients with IC according to NIDDK criteria  
36 healthy female controls

Table 1. Urine marker levels in patients with interstitial cystitis and healthy controls

Marker	Patients (n=36)	Controls (n=36)	P Value
IL-6 (pg/ml)	1.26 (1.72)	0.63 (0.26)	0.0005
Methylhistamine (µg/g creatinine)	131.10 (40.58)	95.17 (29.99)	0.0630
Histamine (µg/g creatinine)	67.57 (55.52)	37.02 (21.76)	0.0390

Erickson DR, Xie SX, Bhavanandan VP, et al. A comparison of multiple urine markers for interstitial cystitis. J Urol 2002;167:2461-9.

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**urinary markers: BPS/IC versus healthy controls**

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**increased in IC**  
anti-proliferative factor (APF)  
epidermal growth factor (EGF)  
insulin-like growth factor (IGF)  
binding protein-3  
IL-6

**decreased in IC**  
heparin-binding EGF-like growth factor  
cyclic guanosine monophosphate  
methylhistamine

**not different**  
total glycosaminoglycans  
epitectin  
hyaluronic acid  
IL-8  
IL-1  
nitrates plus nitrites.

Erickson DR, Xie SX, Bhavanandan VP, et al. A comparison of multiple urine markers for interstitial cystitis. J Urol 2002;167:2461-9.

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**urinary markers in BPS/IC and symptoms**

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total University of Wisconsin IC symptom score (WICI)

- no marker levels correlated with the total WICI score
- the only significant association of marker with individual symptom score was a positive correlation of IL-6 with nocturia

IL-6 normalized to creatinine : r=0.30; p=0.013  
IL-6 normalized to 24 hr : r=0.27; p=0.024

> correlation is very weak (r<sup>2</sup>= 0.09 and 0.07)  
> no corrections for multiple testing

Erickson DR, Xie SX, Bhavanandan VP, et al. A comparison of multiple urine markers for interstitial cystitis. J Urol 2002;167:2461-9.

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**urinary markers: Lamale et al 2006**

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40 female patients with IC  
fulfilling the Interstitial Cystitis Data Base study eligibility criteria  
29 healthy controls

methylhistamine, histamine and IL-6

TABLE V. Inflammatory markers in patients with interstitial cystitis and healthy controls

Marker	Patients (n = 40)	Healthy Controls (n = 29)	95% CI		P Value
			Patients	Healthy Controls	
IL-6 (pg/ml)	2.26 (1.72)	0.63 (0.26)	1.36-5.76	0.45-0.89	0.0005
Methylhistamine (µg/g creatinine)	131.10 (40.58)	95.17 (29.99)	105.10-165.55	72.95-124.19	0.0630
Histamine (µg/g creatinine)	67.57 (55.52)	37.02 (21.76)	47.39-94.30	22.42-58.19	0.0390

Abbreviations as in Table 1.  
Data presented as mean values, with SD in parentheses.

IL-6 and histamine: in IC > healthy controls

Lamale LM, Lutgendorf SK, Zimmerman MB, Kreder KJ. Interleukin-6, histamine, and methylhistamine as diagnostic markers for interstitial cystitis. Urology 2006;68:702-6.

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**urinary markers: overview**

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urinary marker	ref. 1	ref. 2	ref. 3	ref. 4	ref. 5
APF	↑				
IL-6	↑	↑			
histamine		↑			↑
methylhistamine	↓	↔			↑↑
tryptase (spot)			↔	↑	
tryptase (24-h)			↑↑		

- Erickson DR, Xie SX, Bhavanandan VP, et al. A comparison of multiple urine markers for interstitial cystitis. J Urol 2002;167:2461-9.
- Lamale LM, Lutgendorf SK, Zimmerman MB, Kreder KJ. Interleukin-6, histamine, and methylhistamine as diagnostic markers for interstitial cystitis. Urology 2006;68:702-6.
- Boucher W, el-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. Br J Urol 1995;76:94-100.
- Okragly AJ, Niles AL, Saban R, et al. Elevated tryptase, nerve growth factor, neurotrophin-3 and glial cell line-derived neurotrophic factor levels in the urine of interstitial cystitis and bladder cancer patients. J Urol 1999;161:438-41.
- el-Mansoury M, Boucher W, Sant GR, Theoharides TC. Increased urine histamine and methylhistamine in interstitial cystitis. J Urol 1994;152:350-3.

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### urinary markers: Erickson *et al* 2004



Erickson *et al*\* did not find significant associations between urine methylhistamine and

- symptom scores
- response to bladder distension
- cystoscopic findings
- bladder biopsy features, including mast cell count by tryptase staining

studies comparing urinary markers between BPS/IC patients and healthy controls:

- failed to show that urinary markers are useful for discrimination between these groups, with the possible exception of APF; the APF test, however, is not widely available.

\* Erickson DR, Kunselman AR, Bentley CM, *et al*. Is urine methylhistamine a useful marker for interstitial cystitis? *J Urol* 2004;172:2256-60.

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### urinary markers



- parameters that distinguish BPS/IC patients from healthy subjects are not of much interest as this is never a relevant clinical question in patient care
- more interesting is the question whether urinary markers correlate with disease activity, disease damage or long-term prognosis in individual patients when measured longitudinally
- no such markers have been found to date

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### cluster analysis using bladder biopsies: Leiby 2007

three clusters were recognized:

cluster C2 (n=7):

multiple pathological features of parenchymal damage

- mastocytosis of >50 cells/mm<sup>2</sup> in the lamina propria (LP);
- complete denudation of the urothelium;
- granulation tissue;
- mucosal edema;
- lymphocytosis involving >10% of the LP;
- small nerve proliferation involving >10% of the LP

cluster C1 (n=17): limited features of complete denudation of the urothelium and variable LP edema

cluster C0 (n=179): none of these pathological features

Leiby BE, Landis JR, Probert KJ, Tomaszewski JE. Discovery of morphological subgroups that correlate with severity of symptoms in interstitial cystitis: a proposed biopsy classification system. *J Urol* 2007;177:142-8.

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### clusters and symptoms



cluster C2 - the most severe biopsy findings

→ the most severe night time frequency, 24-hour frequency and urgency.

cluster C1 - intermediate biopsy group

→ intermediate frequency and urgency values

cluster C0 - normal biopsy findings

→ the lowest frequency and urgency values

*pain did not correlate to any biopsy data*

Leiby BE, Landis JR, Probert KJ, Tomaszewski JE. Discovery of morphological subgroups that correlate with severity of symptoms in interstitial cystitis: a proposed biopsy classification system. *J Urol* 2007;177:142-8.

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### clusters and symptoms



- the authors realized that the clusters may represent a severity index relating the primary symptoms urgency and frequency but not pain to biopsy findings

- unfortunately, the clustering is based on a mixture of expressions of disease activity and disease damage, as well as on symptoms, making it not very useful for practical applications such as parameters in therapy trials

Leiby BE, Landis JR, Probert KJ, Tomaszewski JE. Discovery of morphological subgroups that correlate with severity of symptoms in interstitial cystitis: a proposed biopsy classification system. *J Urol* 2007;177:142-8.

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### steps (1)



1. list all possible detectable effects of BPS/IC  
*this list includes all possible symptoms and signs that can be attributed to BPS/IC in any stage of the disease*

2. indicate on the basis of consensus whether each item in the list can be considered to be a measure of:  
disease activity (reversible),  
disease damage (irreversible),  
a combination of both, or  
neither of them

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## steps (2)

3. test the feasibility of the scoring system in a small patient group
4. evaluate the performance (validation) of the disease activity and disease damage scores in intervention trials as an addition to the current symptom scores

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## conclusions (1)

the assessment of disease activity and disease damage is fundamental for the care of patients with chronic diseases to optimize therapy and long-term prognosis

the characteristic symptoms such as bladder pain, discomfort, pressure, frequency, nocturia and persistent urge to urinate are unlikely to be useful parameters to measure disease activity and disease damage separately

findings at cystoscopy with hydrodistension and histological findings are probably better measures for disease activity and damage as they reveal the inflammatory process and its consequence (Hunner's lesions, fibrosis) but do not provide useful information on bladder function

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## conclusions (2)

cystoscopy with hydrodistension and biopsies is unfriendly to the patient and therefore, less suitable to be used as outcome measures in therapy trials

however, as proper assessment of disease activity and damage, in addition to the patient's own perception of the disease, has the highest priority, further studies are needed to find parameters that can be obtained in a patient-friendly way and correlate with disease activity, damage, and long-term prognosis

the design, definition and validation of disease activity and disease damage scoring systems seem to be the first necessary steps in this process

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the end

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