Disease activity and disease damage scoring systems for BPS/IC

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1. disease activity
   potentially reversible with treatment
2. disease damage
   irreversible
3. the patient’s own perception
   symptom scores
different from the physician’s perception

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)

O’Leary-Sant score

Interstitial Cystitis Symptoms Index (ICSI)
During the past month:
How often have you felt the strong need to urinate with little or no warning?
0. never
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

Have you had to urinate less than 2 hours after you finished urinating?
0. never
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

How often did you usually get up at night to urinate?
0. never
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

Wisconsin Symptom Instrument (UWI)

KELLER UNIVERSITY OF WISCONSIN SYMPTOM INSTRUMENT
Please circle one number on each line to indicate how much of a problem you have had over the past 4 weeks.

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

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
symptom scores

symptoms as perceived by:
- the patient
- the doctor

May be very different!

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

what can we expect from symptom scores?

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

patient-physician agreement is "not good"
**Disease Activity and Disease Damage Scoring Systems for BPS/IC**

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**Disease Activity**
- Actual changes in anatomy, physiology, or function ...
- Causing symptoms and/or future damage ...
- That are reversible with treatment

**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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**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) today 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 (iritis keratitis)
- Fibrotic strictures
- Fistulae
active clinical disease may NOT cause organ damage

examples

- systemic lupus erythematosus
- Sjögren's syndrome
- sarcoidosis
- subacute cutaneous lupus erythematosus
- hepatitis A

usually no damage despite local active disease

joints
joints
erthema nodosum
granulomatous hepatitis
skin
lymphadenopathy

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

1. correlation between disease damage and symptoms

as an example of damage: Hunner's lesion

2. what can we learn from urinary markers

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)

<table>
<thead>
<tr>
<th></th>
<th>classic IC</th>
<th>nonulcer IC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at diagnosis (yrs)</td>
<td>62</td>
<td>39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>age at onset symptoms (yrs)</td>
<td>57</td>
<td>31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>bladder capacity (ml) functional</td>
<td>199</td>
<td>248</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>bladder capacity (ml) under general anesthesia</td>
<td>468</td>
<td>747</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

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)

<table>
<thead>
<tr>
<th></th>
<th>classic IC</th>
<th>nonulcer IC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age (yrs)</td>
<td>60</td>
<td>47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>microscopic hematuria (%)</td>
<td>31</td>
<td>21</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

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

no significant differences
Hunner’s lesion: Logadottir et al 2004

- mean age (yrs)
- intravesical nitric oxide
- classic IC = with Hunner’s lesions


urinary markers: Erickson et al 2002

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


urinary markers: BPS/IC versus healthy controls

- 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, epilid, hyaluronic acid, IL-8, IL-1, nitrates plus nitrates.


urinary markers in BPS/IC and symptoms

- 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 (\( r^2=0.09 \) and 0.07)
  - No corrections for multiple testing


urinary markers: Lamale et al 2006

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


urinary markers: overview

- IL-6 and histamine: in IC > healthy controls

- TABLE V. Lactation indices in patients with interstitial cystitis and healthy controls


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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.


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

clusters and symptoms

three clusters were recognized:

cluster C2 (n=7):
multiple pathological features of parenchymal damage
- mastocytosis of >50 cells/mm² 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

- 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

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
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

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

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

the end