Stratification of Patients With Interstitial Cystitis/Bladder Pain Syndrome According to the Anatomical Bladder Capacity

Charles Mazeaud, Jérôme Rigaud, Amélie Levesque, François-Xavier Madec, Quentin-Come Le Clerc, Maxime Wack, Loïc Le Normand, Thibault Riant, and Marie-Aimée Perrouin-Verbe

OBJECTIVE To compare the data of score symptoms (Interstitial Cystitis Problem Index, Interstitial Cystitis Symptom Index, Pelvic Pain and Urgency/Frequency Patient Symptom Scale and SF-36 quality of life), voiding diaries, urodynamic studies, and cystoscopy under general anesthesia according to the anatomical bladder capacity for patients with interstitial cystitis/bladder pain syndrome (IC/BPS).

MATERIAL AND METHOD Single-centre descriptive observational epidemiological study based on retrospective review of 134 patients managed for IC/BPS between January 2010 and December 2016. Patients were stratified into 2 groups according to anatomical bladder capacity measured under general anesthesia: ≤ 400 mL (n = 40) and >400 mL (n = 94).

RESULTS Patients with an anatomical bladder capacity less than 400 mL presented significantly different results for voiding diary data: higher total frequency (P = .0023) especially at night (P = .0008), lower functional bladder capacity (P = .0082) and lower maximum bladder capacity (P = .0001); urodynamic data: earlier onset of painful urge during bladder filling (P = .0002), lower maximum bladder filling capacity (P = .0001) and lower compliance (P = .0067); and the findings of cystoscopy under general anesthesia: more Hunner's lesions (P = .00013). These patients presented poorer Pelvic Pain and Urgency/Frequency Patient Symptom Scale symptom scores (P = .0176) but associated with better overall quality of life as assessed by SF-36 (P = .0295).

CONCLUSION The anatomical bladder capacity, measured under general anesthesia, can be used objectively to define 2 distinct groups of patients with symptoms of IC/BPS.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complex disease with an estimated prevalence between 45 and 500 cases per 100,000 women and 8 and 40 cases per 100,000 men depending on the definition used, but this prevalence probably remains underestimated and the etiopathogenesis of IC/BPS remains poorly defined.

The initial definition of IC was established by the National Institute of Gastrointestinal and Kidney Diseases in 1988, which created the first prospective patient cohort, and was essentially based on inclusion criteria used in clinical trial protocols. These excessively restrictive criteria were subsequently extended and a new definition was proposed by the International Continence Society in 2002. This definition was again modified in 2008 by the European Society for the Study of IC/BPS (ESSIC) as chronic (≥6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency; with or without cystoscopic abnormalities. Finally, the International Continence Society has very recently revised the ESSIC definition and proposes 3 distinct entities: pelvic hypersensitivity, IC/BPS, and IC/BPS with Hunner's lesions.

The variability of definitions over time and between different learned societies highlights the fact that this disease remains poorly defined and sometimes corresponds to
several subgroups of patients experiencing similar symptoms but not presenting the same disease.

Clinical interview and physical examination must identify comorbidities, the presence of other painful syndromes, urological, gastrointestinal, gynecological, genital and sexual, neuropathic, and myofascial functional disorders. The voiding diary is essential, as it provides objective values concerning voiding frequency and functional bladder capacity to guide the diagnosis. Patients can then be stratified into various subgroups essentially on the basis of clinical symptoms. There are 2 main groups of patients with IC/BPS: those with organic disease of the bladder wall and those with painful hypersensitivity with pain experienced in the bladder and other organs. However, the current definitions do not propose objective values for complementary investigations to more reliably distinguish these 2 groups of patients.

It is recommended to perform a minimum complementary urological assessment as part of the initial work-up of IC/BPS, with at least a voiding diary and cystoscopy under general anesthesia, while urodynamic studies remain optional but can be informative.

The objective of this study was to compare symptom scores, data of voiding diaries, urodynamic studies and cystoscopy under general anesthesia according to the anatomical bladder capacity determined under general anesthesia for patients with symptoms of IC/BPS.

MATERIAL AND METHODS

Design
A single-centre descriptive observational epidemiological study was conducted on the basis of retrospective review of the charts of all patients managed for IC/BPS, as defined by ESSIC, between January 2010 and December 2016.

All patients with diagnosis of IC/BPS and who had a cystoscopy under general anesthesia were included in the study. Data from symptom scores (Interstitial Cystitis Problem Index [ICPI], Interstitial Cystitis Symptom Index [ICSI], Pelvic Pain and Urgency/Frequency Patient Symptom Scale [PUF] and SF-36 quality of life), voiding diary and urodynamic studies were collected.

Cystoscopy Under General Anesthesia
Cystoscopy under general anesthesia was performed in every case according to the following protocol:

- Cystoscopy using a rigid cystoscope.
- Bladder filling with physiological saline by a bag placed at a height of 80 cm above the patient to achieve a pressure equilibrium between the bag and the bladder.
- The cystoscopic appearance of the mucosa was recorded during filling and progressive emptying of the bladder, particularly looking for the presence of Hunner’s lesions, glomerulation or inflammatory mucosa.
- Brief hydrodistension was performed after obtaining pressure equilibrium to obtain a pressure of 80 cmH2O at the end of bladder filling.
- We did not stop infusion during the distension.
- We realized only one distension for 5 minutes.
- Measurement of the volume of distension by emptying the bladder at the end of filling, corresponding to the “anatomical bladder capacity.”

Voiding Diary
The voiding diary was filled in for 3 days before cystoscopy under general anesthesia. It comprised 4 columns: voiding times, voiding volume (mL), prevoiding pain numerical rating scale (prevoiding NRS) and postvoiding numerical rating scale (postvoiding NRS). The pain NRS was scored between 0 (no pain) and 10 (intolerable pain).

This voiding diary provided objective values for daytime frequency, night-time frequency, total frequency, minimum voiding volume, maximum voiding volume, mean prevoiding NRS scores and mean postvoiding NRS scores. “Functional bladder capacity” was defined as the mean voided volume ± standard deviation.

Urodynamic Studies
Urodynamic testing was performed before cystoscopy and comprised uroflowmetry (mL/s), determination of residual urine (mL), cystometry, and urethral pressure profile.

The volume corresponding to the onset of pain during filling (mL), maximum bladder filling capacity (mL), baseline bladder pressure and bladder pressure at the end of filling (cmH2O), and maximum urethral closure pressure (cmH2O) were recorded and compliance at maximum cystomanometric capacity was calculated by dividing the volume change (ΔV) by the change in detrusor pressure (Δpdet) (C = ΔV/Δpdet, expressed in mL/cmH2O).

Statistical Analysis
Patients were stratified into 2 groups according to anatomical bladder capacity determined under general anesthesia with a cutoff of 400 mL.

The 2 groups were compared by means of a Mann-Whitney test for quantitative variables and Fisher’s exact test for ordinal variables. Data were considered statistically significant with an alpha risk of 0.05.

RESULTS

Study Population
One hundred thirty-four patients were included in the study. All patients had undergone cystoscopy under general anesthesia. The mean anatomical bladder capacity under general anesthesia in this population was 573 ± 255 mL. Patients were stratified into 2 groups according to anatomical bladder capacity: ≤400 mL (n = 40) and >400 mL (n = 94).

Symptom scores (ICPI, ICSI, PUF and SF-36) were collected in 57 patients (20 for the ≤400 mL group and 37 for the >400 mL group). Voiding diaries were recorded in 87 patients (30 for the ≤400 mL group and 57 for the >400 mL group) and urodynamic studies were...
performed in 76 patients (25 for the ≤ 400 mL group and 51 for the >400 mL group).

The sex ratio was identical in the 2 groups, with a marked female predominance of 71% (96 of 134). The population of the ≤ 400 mL group was significantly older than the population of the >400 mL group (69 years versus 52 years, \( P = .00005 \)).

Cystoscopy Under General Anesthesia

The finding of comparison of cystoscopy under general anesthesia between the 2 groups is represented in Table 1. Patients with an anatomical bladder capacity ≤ 400 mL presented significantly more Hunner’s lesions \( (P = .00013) \), significantly more inflammatory mucosa \( (P = .00014) \), and significantly more bleeding during bladder filling \( (P = .0017) \) and emptying \( (P = .0043) \). In contrast, no significant difference in terms of glomerulations was observed between the 2 groups \( (P = .053) \).

Symptom Scores

Comparison of symptom scores between the 2 groups is represented in Table 2. Patients with an anatomical bladder capacity ≤ 400 mL presented poorer PUF scores \( (P = .0176) \), particularly for the symptom subscore \( (P = .0080) \), but with no significant difference for the ICPI and ICSI scores. Inversely, this group of patients presented a better quality of life as assessed by SF-36 \( (P = .0295) \).

Voiding Diary

Comparison of voiding diary data between the 2 groups is represented in Table 3. Patients with an anatomical bladder capacity ≤ 400 mL presented higher total frequency \( (P = .0023) \), especially at night \( (P = .0008) \). Functional bladder capacity (or mean voiding volume) was lower \( (P = .0082) \), with a more limited standard deviation \( (P < .000001) \) and a lower maximum bladder capacity \( (P = .0001) \).

Urodynamic Studies

Comparison of urodynamic parameters between the 2 groups is represented in Table 4. Patients with an anatomical bladder capacity ≤ 400 mL presented an early painful urge to void during filling \( (P = .0002) \), a lower maximum bladder filling capacity \( (P = .0001) \) and lower compliance \( (P = .0067) \).

<table>
<thead>
<tr>
<th>Table 1. Cystoscopy under general anesthesia findings according to anatomical bladder capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystoscopy</strong></td>
</tr>
<tr>
<td>Hunner’s lesions (presence)</td>
</tr>
<tr>
<td>Glomerulation (presence)</td>
</tr>
<tr>
<td>Inflammatory mucosa</td>
</tr>
<tr>
<td>Bleeding during filling</td>
</tr>
<tr>
<td>Bleeding during emptying</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Symptom scores (ICPI (Interstitial Cystitis Problem Index), ICSI (Interstitial Cystitis Symptom Index), PUF (Pelvic Pain and Urgency/Frequency Patient Symptom Scale) and SF-36 quality of life) according to anatomical bladder capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Score</strong></td>
</tr>
<tr>
<td>ICPI</td>
</tr>
<tr>
<td>ICSI</td>
</tr>
<tr>
<td>Total PUF</td>
</tr>
<tr>
<td>PUF Symptom subscore</td>
</tr>
<tr>
<td>PUF Discomfort subscore</td>
</tr>
<tr>
<td>SF-36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Voiding diary data according to anatomical bladder capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voiding Diary</strong></td>
</tr>
<tr>
<td>Mean total frequency</td>
</tr>
<tr>
<td>Mean daytime frequency</td>
</tr>
<tr>
<td>Mean night time frequency</td>
</tr>
<tr>
<td>Mean minimum voiding volume</td>
</tr>
<tr>
<td>Mean maximum voiding volume</td>
</tr>
<tr>
<td>Mean voiding volume</td>
</tr>
<tr>
<td>Standard deviation of mean voiding volume</td>
</tr>
<tr>
<td>Mean prevoiding NRS</td>
</tr>
<tr>
<td>Mean postvoiding NRS</td>
</tr>
</tbody>
</table>
DISCUSSION

his study demonstrated statistically significant differences in terms of voiding diary data, symptom scores, urodynamic parameters, and cystoscopy under general anesthesia according to the anatomical bladder capacity under general anesthesia.

Patients with an anatomical bladder capacity under general anesthesia less than 400 mL presented significantly different results in terms of voiding diary data: higher total frequency especially at night, lower functional bladder capacity with a more limited standard deviation and lower maximum bladder capacity; urodynamic parameters: earlier onset of painful urge during filling, lower maximum bladder filling capacity and lower compliance; and cystoscopy under general anesthesia findings: more Hunner’s lesions, more inflammatory mucosa, more bleeding during bladder filling and emptying. These patients presented poorer PUF scores, particularly for symptom items, but associated with globally better quality of life, as assessed by SF-36.

Since the first description of bladder inflammation in 1809,13 followed by the description of Hunner’s ulcer in 191414 in patients complaining of bladder pain, learned societies have tried to more clearly characterize the specific population affected by IC/BPS. The variability of definitions and the abundance of nonspecific symptoms, comorbidities and associated diagnoses complicate the diagnosis and management of these patients.15-17 IC/BPS is used to describe various types of patients who are not present with all the same disease, as no objective criteria are available for the definition or stratification of these patients. Nevertheless, 2 distinct patient groups can be identified, corresponding to patients with organic disease of the bladder wall and patients with painful hypersensitivity, experiencing pain in the bladder as well as other organs.18 The problem raised by these definitions is that they do not include any objective criteria to differentiate these 2 groups of patients. In the present study, we therefore propose an objective parameter: anatomical bladder capacity measured under general anesthesia with an intravesical pressure of 80 cmH2O.

Cystoscopy, with measurement of anatomical bladder capacity, must be systematically performed as part of the initial assessment of IC/BPS, as proposed by ESSIC,10 particularly in patients with a maximum functional capacity less than 200 mL or major night-time frequency. A cut-off of 400 mL has been proposed as a biomarker associated with the specific expression of a group of patients who differ from the rest of the IC/BPS population.19,20 The presence of mucosal glomerulations on cystoscopy has been demonstrated to be not specific of IC/BPS.21 Inversely, Hunner’s lesions were significantly correlated with lower anatomical bladder capacity as in the present study.10

Although the natural history of IC/BPS remains poorly elucidated, inflammatory mechanisms have been demonstrated, especially between bladder fibrosis and frequency and impaired compliance, which could explain the various bladder phenotypes.3,22,23 Furthermore, in patients with decreased anatomical bladder capacity, the genetic expression of molecular phenotype acting on mechanisms of inflammation appears to be significantly different from that of the rest of the IC/BPS population.19 Similarly, it has been shown that patients with IC/BPS and presenting cystoscopic abnormalities, but with no reduction of bladder capacity, presented a statistically significant reduction of urodynamic parameters.24 A recent study also demonstrated an association between anatomical bladder capacity ≤400 mL and frequency, and the O’Leary/Sant Voiding & Pain Indices (ICPI& ICSI), as well as the PUF score,25 suggesting the existence of a clinical phenotype specifically centered on the bladder.

Patients with an anatomical bladder capacity ≤400 mL present a poorer voiding diary data and urodynamic parameters, and more cystoscopic abnormalities. Inversely, it also appears possible to predict the bladder phenotype by exclusively analyzing all voiding diary data and urodynamic parameters.

CONCLUSION

IC/BPS remains a complex and very heterogeneous disease according to the definition proposed by the ESSIC. In practice, these patients complain of painful frequency and various combinations of symptoms and comorbidities. It appears important to differentiate these patients on the basis of objective criteria, and not exclusively on a clinical

---

### Table 4. Urodynamic parameters according to anatomical bladder capacity

<table>
<thead>
<tr>
<th>Urodynamic Studies</th>
<th>Population (n = 76)</th>
<th>Capacity ≤ 400 mL (n = 25)</th>
<th>Capacity &gt; 400 mL (n = 51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline pressure (cmH2O)</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>.97</td>
</tr>
<tr>
<td>Pressure at the end of filling (cmH2O)</td>
<td>22</td>
<td>23</td>
<td>21</td>
<td>.52</td>
</tr>
<tr>
<td>Volume of onset of painful urge (mL)</td>
<td>165</td>
<td>99</td>
<td>196</td>
<td>.00022</td>
</tr>
<tr>
<td>Maximum bladder capacity (mL)</td>
<td>203</td>
<td>124</td>
<td>241</td>
<td>.0001</td>
</tr>
<tr>
<td>Compliance (mL/ cmH2O)</td>
<td>57</td>
<td>39</td>
<td>65</td>
<td>.0067</td>
</tr>
<tr>
<td>Maximum flow rate (mL/s)</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td>.61</td>
</tr>
<tr>
<td>Urethral closure pressure (cmH2O)</td>
<td>86</td>
<td>84</td>
<td>86</td>
<td>.83</td>
</tr>
<tr>
<td>Residual urine (mL)</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>.77</td>
</tr>
</tbody>
</table>
body of evidence in order to define a “bladder phenotype.” This bladder phenotype can be simply and objectively defined by the anatomical bladder capacity measured under general anesthesia. In the present study, we demonstrated a statistically significant difference between these 2 groups of patients in terms of voiding diary, urodynamic parameters, and finding of cystoscopy under general anesthesia.

Finally, this phenotype stratification based on anatomical bladder capacity also appears to be interesting to predict the efficiency of treatments, but this must be analyzed with other prospective studies.

References

EDITORIAL COMMENT

The authors report bladder capacity (BC) under anesthesia (anatomic) in 134 patients with interstitial cystitis/bladder pain syndrome (IC/BPS). After dividing the cohort based on a cutoff of 400 mL, they found that patients with a lower capacity had increased urinary frequency and nocturia, lower urodynamic (functional) BC, and were more likely to have Hunner’s lesions on cystoscopy. It is quite obvious that lower anatomic capacity is associated with worse frequency, urgency, nocturia, and functional capacity. However, the finding of a higher likelihood of harboring Hunner’s lesions is of clinical significance because fulguration of ulcers typically results in dramatic symptomatic improvement.

There is little agreement regarding initial management for patients with IC/BPS. The European Society for the Study of Interstitial Cystitis and European Association of Urology recommend cystoscopy under anesthesia with hydrodistention (HD) and biopsy for the diagnosis of IC/BPS.2,4 Similarly, the Japanese Urologic Association and the Society of Interstitial Cystitis of Japan suggest establishing the presence of Hunner’s lesions or mucosal bleeding after HD.3 On the other hand, the American Urological Association guidelines focus more on a clinical diagnosis, relegating cystoscopy and HD as third-line therapy.1 However, there is nearly universal agreement that fulguration, vaporization or other treatment of ulcers nearly always leads to symptomatic improvement, that can last up to 3 years in half the patients.5

And while Hunner’s lesions are relatively easy to identify either before or after HD, as “circumscript, reddened mucosal area with small vessels radiating toward a central scar, with a fibrin deposit or coagulum,”4 currently they can only be identified and treated cystoscopically, which is often too painful to perform in the awake patient with IC/BPS. It can be frustrating, however, that in patients without ulcers, cystoscopic HD alone has shown inconsistent therapeutic results.5
Hence, the search for ways to predict the patients who are most likely to have bladder ulcers, and thereby benefit from cystoscopic HD and fulguration. Unfortunately, there are several studies that show a general lack of clinical differences between those with and without bladder ulcers with regard to urinary symptoms and pain. While current trends in managing patients with IC/BPS have focused more on phenotyping patients based on bladder centric versus more systemic symptoms, such symptomatic grouping has not led to substantial improvements in treatment outcome. In contrast, there is a well-known substantial improvement in patients’ symptoms following fulguration of bladder ulcers. It is clinically relevant, therefore, that the authors demonstrated that patients with <400 mL BC were 4 times more likely to have Hunner’s lesions than those with BC > 400 mL, confirming results of a similar trial previously reported by Peters’ group. Perhaps future studies may use continuous modeling based on BC in those with versus those without Hunner’s lesions. This type of work may yield an even stronger ability to predict the presence or absence of ulcers than that based on a predetermined BC cutoff, with the goal of establishing for which patients’ cystoscopy and fulguration are indicated.

Craig V. Comiter, Departments of Urology and Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA

References

https://doi.org/10.1016/j.urology.2018.07.066