A review of the
4th INTERNATIONAL CONSULTATION ON INCONTINENCE

5-8 July, 2008, Palais des Congrès, Paris, France

The 4th International Consultation on Incontinence was held 5-8 July 2008 in Paris and attended by a total of 750 people.

Aspects covered in this review:
- Task of the 23 ICI Committees
- Committee 19: Painful Bladder Syndrome
- Poster abstract on IC from France
- Successful IPBF info stand raises question: is sufficient attention being paid to this topic in medical education?

Task of the 23 ICI Committees

The purpose of this 4th International Consultation on Incontinence (ICI), attended by medical professionals with a special interest in all aspects of incontinence including Interstitial Cystitis/Painful Bladder Syndrome, was to:

- Review the current state of knowledge on incontinence
- Propose a widely accepted strategy for the practical diagnostic and therapeutic management of incontinence following the Evidence-Based Medicine principles
- Propose validated standard international instruments (i.e. Symptom Scores) to evaluate incontinence in collaboration with the major associations involved in the field of incontinence
- Help standardize response criteria and recommendations for clinical research on incontinence.

In addition to their presentation in Paris, each of the 23 committees dealing with a specific topic will contribute a chapter to a book to be published hopefully by the end of this year, or early 2009.

Each committee was asked to assess:

- What we know
- What we think we know
- What we don’t know
- What we need to know.

The consultation’s methodology follows Evidence Based Principles defined in collaboration with the Oxford and Cochrane groups.
Committee 19: Painful Bladder Syndrome
A summary

Since committee chairman Professor Philip Hanno from the USA was unable to attend the ICI meeting in Paris, the report on Painful Bladder Syndrome was instead presented by Professor Jørgen Nordling from Denmark. He opened with a brief history of the name and proposed changing the name to Bladder Pain Syndrome, in accordance with the name change proposal (2006) by the European Society for the Study of IC/PBS (ESSIC) of which he is chairman. This proved to be a controversial issue since it is only 4 years since the last ICI meeting in Monaco in 2004 when this committee proposed using the name ‘Painful Bladder Syndrome including Interstitial Cystitis’.

Professor Nordling reviewed definitions and criteria used over the years, including the NIDDK criteria, the ICS definition and most recently the ESSIC definition, with an explanation of the ESSIC classification system based on findings at cystoscopy, hydrodistension and biopsy and whether or not these investigations have been performed.

On the topic of IC epidemiology, he quoted from the 2004 Consultation with its description of epidemiology as being: “....confounded by the lack of a uniform definition, lack of any readily available validated diagnostic marker than can be reproducibly utilized in the general population, and an unknown etiology and pathophysiology”. Professor Nordling then added that today in 2008 there has been no significant improvement in those confounding factors.

This committee emphasized that disorders associated with IC are being inadequately investigated. These associated disorders did not form part of the classic NIDDK diagnostic criteria and have not been considered to be part of the routine history or physical examination for IC. They have not been reported on in published clinical studies of IC and updated literature is not discussed in major urology textbooks. These associated disorders should be explored because:

- there is no agreed-upon pathognomonic bladder pathology to suggest that it is solely an end-organ disorder;
- the outcome of well-designed, multi-centre, placebo-controlled trials directed at the bladder have been disappointing;
- if asked, patients frequently complain of diverse concomitant symptoms which are also chronic and bothersome.

While there has been increasing interest in IC and associated disorders, they have largely been investigated by specialists in the associated diseases. The committee concluded that when properly investigated, it can be demonstrated that there are many symptom-based chronic pain disorders significantly associated with IC. Professor Nordling also mentioned genetic links that have been studied.

Professor Nordling presented a diagram with an etiological hypothesis: it may commence with a bladder insult which hypothetically could be caused by pelvic floor dysfunction, an autoimmune disorder, bacterial cystitis, primary neurogenic inflammation, bladder trauma or bladder overdistension, leading to damage to the bladder epithelium. The bladder then fails to repair the damage (possibly due to antiproliferative factor secreted by epithelial cells), causing leakage of toxic urine constituents (potassium) into the interstitium. This could result in a number of events
such as mast cell activation and histamine release, C-fiber activation, substance P release as well as immunogenic and allergic responses, leading to progressive bladder injury. Consequent chronic pain could perhaps lead to change in neurotransmission in the spinal cord or brain, with the possibility of causing persistent chronic neuropathic pain even when the original bladder insult has ceased.

Moving on to diagnosis and evaluation, Professor Nordling emphasized that confusable diseases must be excluded as the cause of the symptoms. The long list of confusable diseases can be excluded in stages by a detailed medical history and focused physical examination, urinalysis and culture, flow, pressure-flow and ultrasound, cystoscopy and biopsy.

On the subject of clinical symptom scores: no questionnaire has either the specificity or sensitivity to be used in clinical diagnosis. A variety of questionnaires can be used for following the course of the disease, assessing the severity of the disease or as primary endpoint in clinical treatment studies to measure overall improvement.

Treatment: Grades of recommendation go from A (highest) to D (lowest), and levels of evidence from 1 (highest) to 4 (lowest). Please note that grading is based on evidence from published studies. This may differ from unpublished clinical practice.

In the field of conservative treatment: behavioural modification (evidence level 3), physical therapy (level 2 evidence), stress reduction (level 4 evidence) and dietary manipulation (level 4 evidence) all received a grade C recommendation.

Pharmacotherapy: Oral medications discussed were:
- Antidepressants
- Antihistamines
- Immunosuppressants
- Pentosan Polysulfate Sodium
- Analgesics.

Antidepressants: 
**Amitriptyline**: Level 2 evidence, grade B recommendation. There has been 1 randomized controlled trial and a number of non-controlled studies. The theoretical mechanisms of amitriptyline include: central and peripheral anticholinergic action, sedative action, blocking H1-histaminergic receptors, analgesic action (inhibiting re-uptake of serotonin and noradrenaline). Desipramine and doxepin received level 3 evidence and grade C recommendation.

Antihistamines: 
**Hydroxyzine**: Level 1b evidence, grade D recommendation. Blocks neuronal activation of mast cells, is anticholinergic, angiolytic and analgesic. It has been shown to have good therapeutic effects by several non-controlled studies, but an NIDDK study in 2003 showed no significant benefit.

Immunosuppressants: 
**Cyclosporine**: Level 3 evidence, grade C recommendation. 3 uncontrolled studies, 1 study comparing cyclosporine with PPS. Cyclosporine appears to improve pain and
frequency, but has potentially serious side effects and should only be considered in severe, intractable patients.

IPD-1151T: Suppresses helper T-cells producing IL-4 and 5. There has only been one uncontrolled study reported, but a large-scale placebo-controlled study is underway.

**Pentosan Polysulfate Sodium (PPS):**
There have been 5 randomized controlled trials with mixed results. Unfavourable results came from Holm-Bentzen et al in 1997 and Sant et al (NIDDK study) in 2003; favourable results from Parsons & Mulholland (1987), Mulholland et al (1990), Parsons et al (1993). The committee awarded PPS level 1 evidence but grade D recommendation due to conflicting level 1 evidence.

**Intravesical treatment**

The committee’s grading for intravesical treatment was as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO (Dimethyl sulfoxide)</td>
<td>2</td>
</tr>
<tr>
<td>Heparin</td>
<td>3</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>4</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>4</td>
</tr>
<tr>
<td>Pentosan polysulfate sodium</td>
<td>4</td>
</tr>
<tr>
<td>Capsaicin, Resiniferatoxin</td>
<td>1</td>
</tr>
<tr>
<td>Bacillus Calmette-Guerin (BCG)</td>
<td>1</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>4</td>
</tr>
</tbody>
</table>

**Sacral Neuromodulation**

Sacral Neuromodulation for IC patients is still an investigational procedure. Its therapeutic effects have not yet been fully confirmed. The committee emphasized that strict patient selection and detailed discussion with the patient, including providing the patient with reported long-term results are all essential before embarking on this procedure.

**Bladder distension**

Bladder distension has been used for many years not only as a diagnostic tool but also for the treatment of IC patients. However most studies are retrospective and uncontrolled and evidence is conflicting. Level of evidence 3, grade C recommendation.

**Hunner’s lesion (ulcer)**

**Transurethral resection**: results with this method of treatment were first reported in 1974 by Greenberg et al. Peeker et al reported in 2000 that 92 of 116 patients experienced an improvement in their symptoms. The average duration was 23 months, ranging from 0-180 months. Up to 16 re-resections were performed.

**Laser fulguration**: in 1994 Malloy & Shanberg reported improvement but a need for further therapy in some patients. Small bowel perforation was seen in 2 patients by Shanberg & Malloy in 1987.
In 2001 Rofeim et al reported on Nd:YAG laser ablation in 24 IC patients with Hunner’s lesion. Within days all experienced symptom improvement without complications. Pain, urgency, nocturia and frequency were improved after 23 months, but relapse in 11 patients necessitated up to four further treatments.

Transurethral resection, coagulation or laser ablation of Hunner’s lesion (ulcer) were given level 3 evidence and grade C recommendation.

Cystoplasty
According to the committee, there is some evidence that cystoplasty with supratrigonal resection may benefit selected patients with end stage classic IC (with Hunner’s lesion). There is no evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy but is associated with more complications and poorer functional bladder rehabilitation.

Surgery
The committee gave the following evidence levels and recommendation grades in the field of surgery:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Evidence Level</th>
<th>Recommendation Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrodistension</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Hunner’s lesion resection/fulgeration</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Bladder augmentation/cystoplasty - end stage disease</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Diversion with or without cystectomy</td>
<td>3</td>
<td>C</td>
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</tbody>
</table>

Principles of Management
Recommendations by the committee included the following: treatment decisions should be based as far as possible on placebo-controlled RCTs; treatment should be guided by patient-driven outcomes; start with the least invasive treatments; approach surgical therapies with caution; add or subtract treatments on the basis of results in individual patients; consider more extensive evaluation and more invasive therapies in patients who have failed oral and intravesical treatments; unproven therapies should be given within the framework of clinical trials; irreversible surgery should be a last resort, with rare exceptions.

The treatment algorithm presented by Professor Nordling and which will be published in the chapter included:

Symptoms: in accordance with the Essic definition – pain, pressure or discomfort perceived to be related to the bladder with at least one other urinary symptoms (eg frequency, nocturia, urgency);

Basic assessment: history, frequency/volume chart, focused physical examination, urinalysis, culture, cytology;

1st line treatment: conservative therapy, patient education, dietary modification, non-prescription analgesics, pelvic floor relaxation, address treatment of pain;

2nd line treatment: consider: oral therapies, intravesical therapies, physical therapy, address treatment of pain;

3rd line treatment: consider: cystoscopy under anaesthesia with bladder distension, fulgeration of Hunner’s lesion, address treatment of pain;
4\textsuperscript{th} line treatment: consider in context of clinical trial: neuromodulation, botulinum toxin intramural, pharmacologic management, address treatment of pain. Consider: diversion with or without cystectomy, substitution cystoplasty.

Future directions of research

- Epidemiological study
The committee suggested that a screening tool with adequate sensitivity and specificity should be developed and that epidemiological studies should be conducted in the population aimed at detecting incidence and prevalence and at identifying risk factors.
A patient database should be established in different regions with long-term follow-up for the purpose of understanding the natural history of the disease and to examine differences in the natural history of the disease between regions.

- Phenotyping/sub-grouping patients
Patients who also have pain syndromes or autoimmune diseases may have different pathophysiology, natural history and treatment responses from patients who do not have associated disorders.

Sub-grouping patients would allow better treatment strategies to be developed but may also answer the question as to whether this is an end-organ disease of the bladder or a systemic condition.

A simple tool should be developed for non-specialists to pick out patients with concomitant disorders.

Researchers should test the concept that categorizes all types of pelvic pain into one ‘chronic urological pelvic pain syndrome’, bearing in mind that some patients have symptoms involving multiple pelvic organs, concurrently or sequentially.

- Development of a simple diagnostic test
The committee is of the opinion that this is most likely to involve urinary markers. It may help to phenotype patients and may differentiate this condition from other conditions.

- Development of a practical multi-disciplinary care model
According to the committee, a practical, multi-disciplinary care model, which includes physicians in charge, dieticians, physiotherapists, pain specialists, psychologists, psychiatrists and patient support groups should be developed and evaluated in various settings.

This is merely a brief summary of the committee’s presentation. The chapter on Painful Bladder Syndrome that will ultimately be contributed to the Incontinence book by committee 19 will of course be much more detailed and include all references.

The ICI 2008 committee 19 for Painful Bladder Syndrome comprised the following 6 members:

Philip Hanno, MD (Chairman), Jorgen Nordling, MD, Arndt van Ophoven, MD, Alex Lin, MD, Tomohiro Ueda, MD, Leroy Nyberg, MD.
Poster Abstract on interstitial cystitis

114 abstracts covering a broad scope of topics in the field of incontinence were presented as posters during ICI in Paris. All the ICI poster abstracts can be read exclusively in the new online UroToday International Journal (UIJ):
http://www.urotoday.com/component/option.com_uij/Itemid,3353/view.current/sectionid,27/

There was one study on interstitial cystitis presented from France:

**Using the Interstitial Cystitis New Diagnostic Criteria in Daily Practice: About 156 Patients.**


The aim of this study was to describe the characteristics of patients with IC and to determine what percentage of a group of 156 patients diagnosed with IC met the ESSIC (European Society for the Study of IC/PBS) 2005 definition of IC and to see how those who met the definition differed from those who did not. The authors concluded that the ESSIC 2005 definition may not be sufficiently sensitive since it appears to exclude over 26% of patients diagnosed as having IC. Minor modifications in the definition (pain type and location) appeared to increase its sensitivity.

Read the complete abstract online:

**Explanatory note:**

The definition referred to here is an International Continence Society (ICS) definition modified by ESSIC in 2005 and subsequently published in European Urology Today in March 2006 in an article entitled: “Interstitial Cystitis: definitions and confusable diseases” by Dr Joop P van de Merwe and Professor Jørgen Nordling. This definition was also cited by Professor Nordling in 2006 in his review article: J. Nordling. Sensory Bladder Disorders. Int J Clin Pract Suppl 2006 December;(151): 38–42:

‘IC is a disease of unknown origin consisting of the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime (1 8·) and night-time (1 1·) frequency, and with cystoscopic (glomerulations and/or Hunner’s lesions) and/or histological features (mononuclear inflammatory cells including mast cell infiltration and granulation tissue) in the absence of infection or other pathology’.

This differs from the current ESSIC definition published in 2008 (Van de Merwe JP, Nordling J et al. Diagnostic criteria, classification and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008 Jan;53(1):60-7. Epub 2007 Sep 20) which is as follows:

‘Chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency.’
Successful IPBF info stand raises question: is sufficient attention being paid to this topic in medical education?

We would like to thank the ICI organizers for so kindly providing us with complimentary stand space in the most perfect location possible. We were overwhelmed by requests for information about IC! Clinicians are also increasingly seeking information about associated disorders. The upcoming NIH/NIDDK MAPP project has already triggered much interest in this aspect. There is still clearly a huge need for information on IC which seems to indicate that insufficient attention may be being paid to this topic in medical education and/or educational courses. It is indeed possible that the information being provided in education and courses is insufficiently practical for clinicians and particularly those working at grass roots level in countries where the treatment options are limited.

With the name issue being an exceedingly controversial topic in Paris, we had every opportunity for feedback on our stand and it was becoming increasingly clear that doctors outside Europe (and indeed many IC experts in Europe) do not think that another change in nomenclature is advisable right now and that it should only be done on the basis of scientific evidence. A typical comment was that repeated name changes will result in the disease itself losing credibility in the eyes of both the doctors and the patients. This is a very worrying prospect. For the sake of the patients, internationally acceptable solutions need to be sought.

Jane Meijlink

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