ESSIC 2015

17-19 September

ABSTRACT BOOK

ROME
Catholic University

Meeting Chair
Mauro Cervigni

ESSIC

International Society for the Study of Interstitial Cystitis/Bladder Pain Syndrome

ESSIC PRESIDENT MESSAGE

Dear Friends and Colleagues,
It is a real pleasure to meet all of you during this ESSIC Annual Meeting 2015 in Rome.
As many of you know, ESSIC was founded in 2004 and since then has promoted and developed the knowledge of the BPS/IC with researchers, clinicians and patient groupsfrom around the world.
We can count now on an important network what creates better communication, increasing knowledge and first of all bears the possibility to get better understanding of underlying causes and their treatment for the benefit of patients.
This year the ESSIC annual meeting is a pivotal event for our Society: scientifically because it will draw up a first draft of a global proposal for guidelines on the main topics of BPS; administratively as new structures will be discussed for the next step in the functioning of our organisation; socially because it will bring us all together reinforcing friendship and mutual support to attain our goals.
Time has come to make a next evolution taking into account the wonderful work that has been done so far by ESSIC with its outstanding scientific meetings, its work in several international committees, its collaboration with industry and its wonderful textbook.
We count on all to step forward and engage to support this evolution.
Rome, as city, represents many different things but is known overall by its charm, friendly hosts and "sweet life".
Nice to have you here!

Jean Jacques Wyndaele
ESSIC President

MEETING CHAIR MESSAGE

Dear Friends and Colleagues,
It gives me great pleasure and honour as Meeting Chair to invite you to the ESSIC Annual Meeting which will be taking place in Rome this year in September.
It will be an extraordinary opportunity to introduce so many renowned experts from all over the world, invited to focus on the hot topics of Bladder Pain Syndrome and to contribute to one of our Society's main missions. The change in the nomenclature, as well as the creation of an important network involving international scientific associations, also outside Europe (US, Asia), are just an example of some of the important goals reached by the ESSIC group.
AUA, ICI and EAU proposed some Guidelines for Bladder Pain Syndrome to the scientific international community; however, this year ESSIC annual meeting has the ambitious goal to formulate an important delineation of international shared guidelines on BPS, which will be implemented by the specific algorithms in the near future.
I'm convinced that our Faculty will actively contribute to this mission and Rome will surely do its part.
Charm and pleasant atmosphere will not be missing!

Mauro Cervigni
ESSIC Meeting Chair

Where are we today?

Authors: Philip Hanno[1], Jørgen Nordling[2]
University of Pennsylvania, School of Medicine, Philadelphia, PA[1]; University of Copenhagen, School of Medicine, Denmark[2]

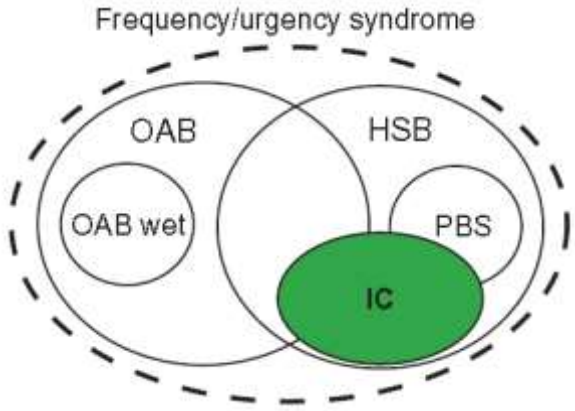
Nomenclature: USA AUA Guideline

- Interstitial Cystitis/Bladder Pain Syndrome
- IC/BPS
- No distinguishing between the two names; to be used in tandem

Definitions: Asian Guideline

Frequency/urgency syndrome (FUS): frequency (frequent voiding) and urgency (strong desire to void).
It is an inclusive term incorporating overactive bladder syndrome (OAB), hypersensitive bladder syndrome (HSB), and other conditions that are associated with frequency and urgency.
Hypersensitive bladder syndrome (HBS): FUS in which urgency is persistent and due to fear of pain
Painful Bladder Syndrome: HBS with pain
IC: frequency, hypersensitivity, and/or bladder pain AND abnormal cystoscopy AND no confusable disease

Nomenclature: Japan/Korea/Taiwan



Definition: ESSIC

Chronic (6 months or more) 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 urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.
Based on symptoms
Diagnosis of exclusion

Definition EAU

BPS or PBS indicates at least 6 months of pain perceived to be related to the bladder.

Interstitial Cystitis to be reserved for a subset of patients with verified signs of chronic inflammation extending submucosally.

Diagnosis International Journal of Urology

Table 2 Recommended tests for diagnosis of interstitial cystitis

Mandatory	Recommended	Optional
Clinical history	Urine culture	Ultrasonography
Physical examinations	Urine cytology	Urodynamic study
Urinalysis	Symptom scores	X-ray examination
	QOL scores	Potassium test
	Frequency-volume chart	Biopsy
	Residual urine measurement	
	Prostate-specific antigen	
	Cystoscopy and/or hydrodistension	

Diagnosis ESSIC

PATIENT SELECTION
patient with 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

↓

EXCLUSION OF CONFUSABLE DISEASES
medical history, physical examination, urinanalysis, urine cultures, PSA in males >40 yrs, uroflowmetry, post-void residual urine volume by ultrasound scanning, cystoscopy and biopsy

↓

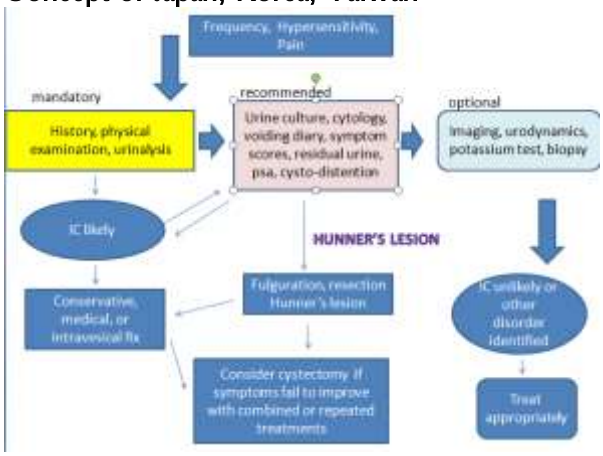
CLASSIFICATION OF BPS
cystoscopy with hydrodistension[1] and biopsy if indicated

symbol 1: cystoscopy findings	symbol 2: biopsy findings
X: not done	X: not done

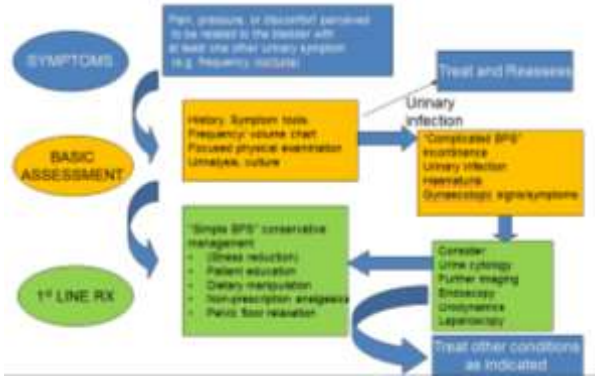
ESSIC CLASSIFICATION OF BLADDER PAIN SYNDROME TYPES

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

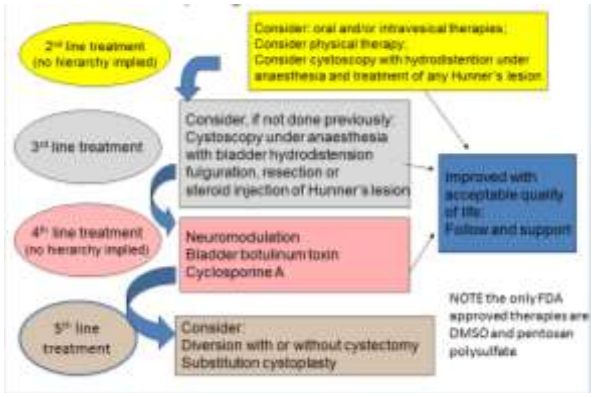
Concept of Japan, Korea, Taiwan

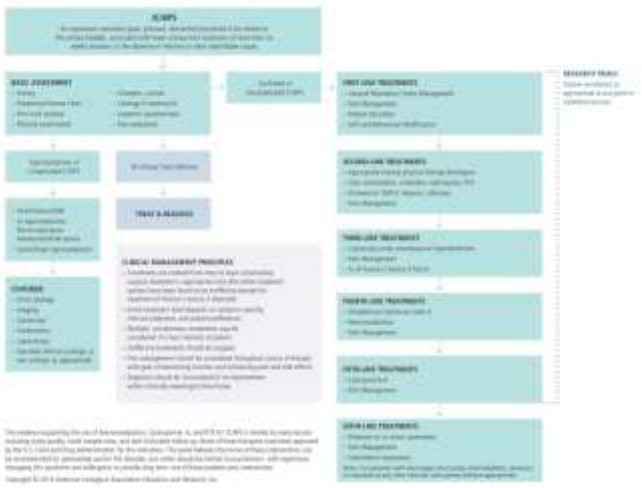


Bladder Pain Syndrome

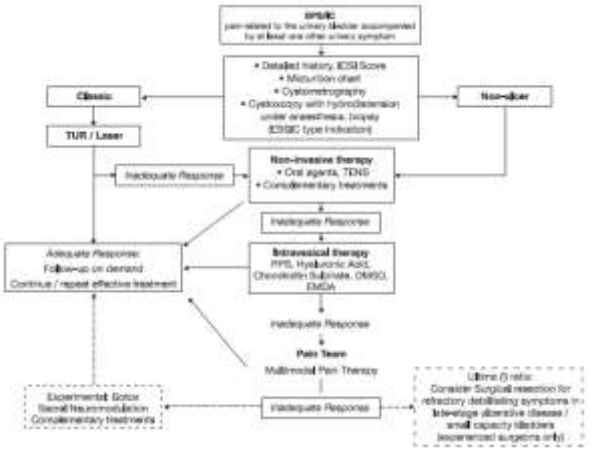


BPS requiring more active intervention





EAU



Harmonization: Name

- Bladder Pain Syndrome (BPS) is understood to identify the syndrome in the United States and in Europe.
- Interstitial Cystitis remains a part of the American nomenclature for political and historical reasons (IC/BPS) and is synonymous with BPS.
- East Asian nomenclature uses the term interstitial cystitis, painful bladder syndrome, and hypersensitive bladder syndrome. The use of the terms can lead to major discrepancies when comparing findings, depending upon exact definitions in individual publications.

Harmonization: Definition

- ESSIC and EAU and AUA are aligned
- Symptom duration 6 months for ESSIC/EAU
- Symptom duration 6 weeks for AUA to avoid diagnosis/treatment delay
- Future studies may further harmonize duration if symptoms at 6 weeks can be shown to be chronic the majority of the time.
- East Asian definitions allow for diagnosis in absence of "pain"
- "IC" basically need to meet NIDDK criteria
- Urgency maintained as key concept in Asia

Harmonization: Diagnosis

- "Where the rubber meets the road", a success story.
- Surprisingly similar after years of conferences.
- History, physical examination, urinalysis and exclusion of confusable diseases adequate around the world.
- Further testing not mandatory for making diagnosis.
- Has this information been communicated to others?

Harmonization: Management

- ESSIC has yet to publish an updated management algorithm.
- Generally empiric, from less invasive to more invasive.
- Standardization awaits results of long term phenotyping trials and more effective forms of therapy.

The complexity of Chronic Pelvic Pain

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The International Association for the Study of Pain (IASP) 2008 working definition for pain is "an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage" (1). There are two different categories of pain; nociceptive, associated with tissue damage or inflammation, sometimes also called 'inflammatory pain', and neuropathic resulting from a lesion or dysregulation of the peripheral and/or central nervous systems. Many painful conditions have a mixed etiology. Chronic pain involves negative cognitive, behavioral, sexual or emotional consequences with an impact on quality of life.

Chronic pelvic pain (CPP) illustrates the complexity about the diagnostics and treatment. Possible causes of symptoms range from well-defined inflammatory processes to centralized pain lacking distinctive peripheral organ signs. Alteration of CNS mechanisms can magnify perception with involvement of muscles, including multiple trigger points and at the same time other organs may be sensitive like the bowel and the urogenital system.

Depending on complex interactions in CPP, it has been proposed to put more focus on pain mechanisms, integrating psychological, social and sexual dimensions of the problem - to go beyond the organ-centered origin of symptoms (2). When it comes to clinical practice, it is recommended to use a very thorough assessment already from the beginning. Ideally, a four step plan like the one suggested by Quaghebeur and Wyndaele (3) can be used. Step 1 is a very careful history, step 2 an as complete as possible evaluation of previous assessments, step 3 a thorough clinical examination including a close search for confusable diseases, and also neurologic assessment of the lumbosacral plexus, rather detailed mechano-sensitivity testing, sometimes supplemented by electro-diagnostic evaluation. Step 4 implies an extensive clinical assessment of the musculoskeletal system in different postures, not restricted to the pelvis only. Such systematic investigations are time-consuming and call for a multidisciplinary approach, to be performed at specialized units. So far, such an approach is offered to just a minority of CPP patients. For the time being, the way to go is mostly trial and error using various treatment regimes, at the best following a systematic algorithm. It is worth remembering, though, that local treatment, like ablation of lesions in classic IC, might be the adequate measure when there is a well-defined process, no need for an extended

treatment plan then. However, as mentioned above, absence of treatable organ manifestations calls for a comprehensive approach.

We need a different outlook in the management of CPP. There are some very interesting current projects, like the UPOINT classification to phenotype CPP (4) and the MAPP research project (5) identifying and combining the various facets of CPP, efforts that will provide building blocks when designing a clinically relevant and generally useful phenotype system for the variety of syndromes under the CPP umbrella. Without relevant phenotyping we will continue to grope in the dark when we try to help sufferers of CPP.

1. Loeser J, Treede R. The Kyoto protocol of IASP Basic Pain Terminology. Pain 2008;31;137(137):473-7. .
2. Engeler D, Baranowski A, Dinis-Oliveira P, Elneil S, Hughes J, Messelink E, et al. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol. 2013;64(3):431-9.
3. Quaghebeur J, Wyndaele J. Chronic pelvic pain syndrome: Role of a thorough clinical assessment. Scand J Urol 2014; Sep 25:1-9. [Epub ahead of print].
4. Shoskes D, Nickel J, Rackley R, MA. P. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. Prostate Cancer Prostatic Dis 2009;12 (2):177-83.
5. Landis J, Williams D, Lucia M, Clauw D, Naliboff B, Robinson N, et al. The MAPP research network: design, patient characterization and operations. BMC Urol. 2014;1 (14):58.

Why ESSIC Uses The Name BPS

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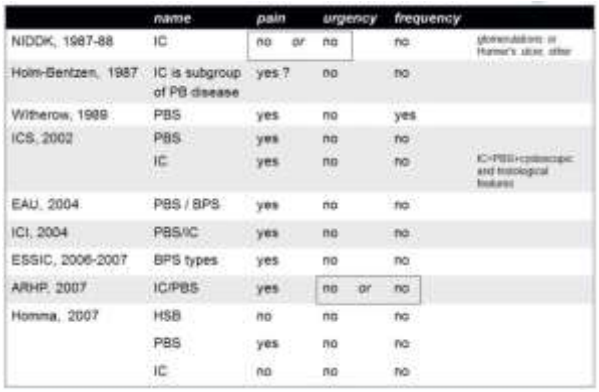
Much work has been going on in international organizations to create a logical and workable terminology for chronic (persistent) pain conditions. For background information we refer to the 2007 Guidelines on Chronic Pelvic Pain issued by the European Association of Urology (EAU).1 The EAU definitions were in line with recommendations for terminology from the ICS and use the axial structure of the IASP classification2,3. This implies a taxonomy-like approach under the umbrella term of chronic pelvic pain syndrome (Figure 1).

Figure 1. Selected part of the axial structure of the IASP classification of chronic pelvic pain.

Further identification is based on the primary organ that appears to be affected on clinical grounds. Urologic pelvic pain syndromes are divided into bladder pain syndrome, urethral pain syndrome, penile pain syndrome, prostate pain syndrome, and others. More specific terminology is based on the identification of, for example, inflammation or infection.

The classification system of chronic pelvic pain syndromes aimed to draw together the expertise of many specialist groups. The impact of the classification of chronic pelvic pain syndromes thus goes far beyond the scope of IC.

Looking at the features of IC/PBS that were considered to be mandatory for a diagnosis by various research groups (Figure 2), it can be concluded that there was strong international support (ICS, EAU, IASP, ICI, ARHP, ESSIC) to consider pain as a key feature of interstitial cystitis/painful bladder syndrome (IC/PBS) while urgency and frequency were common but not considered to be a prerequisite for a diagnosis.



	name	pain	urgency	frequency	
NIDDK, 1987-88	IC	no or	no	no	
Holm-Bentzen, 1987	IC is subgroup of PB disease	yes ?	no	no	
Witherow, 1989	PBS	yes	no	yes	
ICS, 2002	PBS	yes	no	no	
	IC	yes	no	no	
EAU, 2004	PBS / BPS	yes	no	no	
ICI, 2004	PBS/IC	yes	no	no	
ESSIC, 2006-2007	BPS types	yes	no	no	
ARHP, 2007	IC/PBS	yes	no or	no	
Homma, 2007	HSB	no	no	no	
	PBS	yes	no	no	
	IC	no	no	no	

Figure 2. Mandatory features for the diagnosis of IC/PBS by various research groups.

ESSIC considered it to be essential that the nomenclature and knowledge of pathophysiologic mechanisms did not conflict with each other.4 In this context, the name bladder pain syndrome was considered to be the most appropriate name for IC/PBS to date, because the name is in line with the other chronic pelvic pain syndromes and is in balance with the clinical presentation of the syndrome and the level of knowledge of its pathophysiology.

ESSIC realized that changing the name of IC into BPS could have emotional implications, understandably for patients, but also for patient organizations with a scope limited to IC/PBS and for insurance and reimbursement in different health systems around the world.

Considering these consequences, although BPS is the name of choice, ESSIC agreed that including IC in the overall term (BPS/IC) could be used in parallel to BPS during a transition period.

In this context, it is worth remembering that a subgroup of BPS patients with Hunner lesions (BPS type 3C) presents interstitial inflammation and is thus fulfilling the requirements of the original term of IC.

Literature

1. Fall M, Baranowski AP, Fowler CJ, et al. EAU guidelines on chronic pelvic pain. Eur Urol 2004, 46:681-9.
2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002, 21:167-78.
3. Merskey H, Bogduk N. Classification of chronic pain, descriptions of chronic pain syndromes and definitions of pain terms. IASP Press; 2002.
4. 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.

MAPP Research Network

Author: Robert Moldwin
Hofstra North Shore-LIJ School of Medicine, The Arthur Smith Institute for Urology, North Shore-LIJ Healthcare System, New Hyde Park, NY

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP), sponsored by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), is a multi-institutional, multidisciplinary collaborative network dedicated to the study of interstitial cystitis/ bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. The principal justifications for funding this effort were the lack of clinical advancement in the field of chronic pelvic pain coupled with new literature (and clinical experience) suggesting that these urinary chronic pelvic pain syndromes (UCPPS) likely represent a heterogeneous group of patients, many of whom suffer from pain that reaches far beyond the urogenital system. The network's objective is to better understand the etiology and treated natural history of these chronic pain syndromes, and to identify clinical factors and research measurements that will define clinically relevant sub-groups of these patients for future clinical trials. The primary clinical studies are conducted across "discovery sites" (Trans-MAPP); with each site also contributing to additional, targeted investigations, i.e., biomarker, microbiome, neuroimaging, genetics, animal modeling studies, etc.

The MAPP I Trans-MAPP Epidemiology Phenotyping Study was conducted from 2009 through 2012. 1,039 men and women were enrolled, including persons with UCPPS (n=424); persons with other comorbid illnesses, including fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome (n=200 for all conditions); and healthy controls (n=415).

The diversity of MAPP Network-related studies is demonstrated with some recently published/ presented findings:

*Evaluation of UCPPS patients using 6 commonly employed symptom measures showed regression to the mean significantly influencing the proportion of patients clinically improving or worsening. A run in period of 2-4 weeks was suggested for future outcomes research. Stephens A, et al. Regression to the mean in a prospective study of urological chronic pelvic pain syndrome (UCPPS). J. Urol. 2014; 191: e882–e883.

*Analysis of responses of the complete MAPP Network UCPPS patient cohort (n=424) to multiple frequently employed instruments for patient assessment demonstrated urinary symptoms and pain as the two most meaningful factors to characterize and clinically follow UCPPS. These parameters have the added value of independently correlating to comorbid conditions. Griffith J, et. al. A psychometric analysis of pain and urinary symptoms in patients with interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome: findings from MAPP research network. J. Urol. 2015; 193: e303.

*Patient's who characterize symptoms as "painful filling" or "painful urgency" tended to have more severe urologic symptoms, more generalized symptoms, and worse quality of life than participants who reported neither characteristic.

Lai HH, et al. Painful Bladder Filling and Painful Urgency Are Distinct Characteristics in Men and Women with Urologic Chronic Pelvic Pain Syndromes – A MAPP Research Network Study. J. Urol. 2015: 1–26.

*Of RICE high sensitivity UCPPS participants, 47% had non-urological pelvic pain syndromes such as irritable bowel syndrome, fibromyalgia, or chronic fatigue syndrome. A high prevalence of these syndromes was identified in both sexes (but higher in females) and associated with more severe symptoms, longer duration, and higher rates of depression and anxiety.

Krieger JN, et al. Relationship between chronic non-urological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: Baseline evaluation of the MAPP study. J. Urol. 2015; 193: 1254–1262.

*White matter abnormalities, many of which correlated to pelvic pain severity and urinary symptoms, were detected in female IC/BPS patients using diffusion tensor imaging or fractional anisotropy. Farmer MA et al. Brain white matter abnormalities in female interstitial cystitis/bladder pain syndrome: a MAPP network neuroimaging study. J. Urol. 2015; 194: 118–126.

Functional MRI studies demonstrated alterations in resting state oscillations and enhanced connectivity in sensory and motor networks in IC/BPS patients compared to controls. Increased connectivity was greatest in patients reporting pain during bladder filling. Also identified was altered activity and connectivity of pelvic floor sensorimotor cortical control regions IC/BPS patients. Kilpatrick LA, et al. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with Interstitial Cystitis/Painful Bladder Syndrome. J. Urol. 2014; 192: 947–955.

Structural MRI demonstrated that IC/BPS patients when compared to controls have increased grey matter volume in multiple brain regions. Increased grey matter volume in the right primary somatosensory cortex was associated with greater pain, mood (anxiety) and urological symptoms. Kairys AE, et. al. Increased brain gray matter in the primary somatosensory cortex is associated with increased pain and mood disturbance in patients with Interstitial Cystitis/Painful Bladder Syndrome. J. Urol. 2015; 193: 131–137.

Collectively, these studies suggest that, similar to other forms of chronic pain, central nervous system changes likely play a significant role in UCPPS pathophysiology in some patients.

*Using next-generation molecular diagnostic Ibis T-5000 Universal Biosensor technology, microbiome analysis of VB 2 and 3 samples in UCPPS men and a control population showed no clear differences. The gram negative bacterium, Burkholderia cenocepacia, was more frequently identified in UCPPS than controls (14.5 vs. 4.3 %, respectively). Nickel JC, et al. Search for microorganisms in men with urologic chronic pelvic pain syndrome: A culture-independent analysis in the MAPP research network. J. Urol. 2015; 194: 127–135.

MAPP II is now underway. MAPP II's primary protocol is the "Trans-MAPP Symptom Patterns Study (SPS) in which participants will be followed for 3 years. One of its highlight sub-studies is the Analysis of Therapies during the Longitudinal Assessment of Symptoms (ATLAS) protocol during which, we will focus efforts to identify correlations that may exist between specific UCPPS phenotypes and responses to an array of predefined therapies.

Phenotyping: how can we prove the value?

Author: Daniel Shoskes
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BPS/IC is a syndrome rather than a specific disease and patients have a heterogeneity of complaints and physical findings. Much as we classify cancers according to stage and grade to diagnose patients and rationally and effectively direct therapy, so too can we classify BPS/IC patients according to their clinical phenotype. We have developed the UPOINT phenotype system which classifies patients according to 6 clinical domains (urinary, psychosocial, organ specific, infection, neurologic/systemic, tenderness of pelvic muscles). Multimodal therapy is then directed only at the positive domains. We have found this approach highly successful in chronic prostatitis/chronic pelvic pain syndrome as well as BPS/IC. This is contrary to the approach suggested in the AUA IC

guidelines in which tiers of therapies are used successively.

How can we prove the value of a phenotyping system? First the components must be discriminative. There is no point in having a domain or component of the system that is present in 0.1% or 99% of the patients. This is a weakness of UPOINT for BPS/IC since close to 100% of the patients do have urinary symptoms and evidence for bladder involvement by definition (domains U and O). Second, the phenotypic domains must make a difference to treatment selection. If all patients improve with drug X regardless of the phenotype, then the phenotype has no practical value. This is a strength of UPOINT since patients without true infections don't improve with antibiotics and those without pelvic floor spasm won't be helped by pelvic floor physical therapy. Third, the phenotype must be flexible, able to adjust as new biomarkers and therapies are discovered. Finally, treatment directed by the phenotype needs to have a better outcome than blanket treatment recommendations. This can be difficult to prove for multimodal therapy using traditional placebo/sham controlled trials given the complexity and large sample size needed for multiple arms studies. Single center studies such as we have done are subject to multiple selection biases. Nevertheless, clinical phenotyping holds the promise for improving patient outcomes today, while a better understanding of the pathophysiology of BPS/IC is still sought. Any new phenotyping system will need to be assessed using these same benchmarks.

1

1. Bladder Pain Syndrome as a peripheral sensory disorder

Authors: Ifeoma Offiah[1] - Elaine Dilloughery[1] - Stephen McMahon[2] - Barry O'Reilly`[1]
Urogynaecology Department, University College Cork, Cork, Ireland[1] - Wolfson CARD, King's College London, London, United Kingdom [2]

Introduction and aim of the study

Bladder Pain Syndrome (BPS) is a disease of unidentified aetiology and poorly understood pathophysiological mechanisms. Precise pain perception in this disease is not understood. Is this a peripheral pathology with pain of peripheral origin or has the pain become centralized? We hypothesise pain centralization with severe and chronic cases.

To study the effect of alkalinized lidocaine on pain perception using urodynamics in BPS patients.

Materials and Methods

21 female patients referred to the Urodynamic Department of the Cork University Maternity Hospital (CUMH), with histories indicative of BPS. Written consent was given and the King's Health Questionnaire completed. Urodynamic assessment was completed as per normal CUMH protocol. Participants completed a Visual Analogue Scale (VAS) at maximum cystometric capacity and cystometric capacity. The bladder was emptied and a pain score recorded. Participants were randomly assigned to 'lidocaine' or 'control' groups; 'lidocaine' participants received 20mls of 2% alkalinized lidocaine into the bladder, while the 'control' participants received 20mls normal saline. These solutions were allowed to remain in-situ for 10 minutes and saline urodynamic protocol repeated.

Results

Lidocaine administration resulted in a decrease in pain perception, leading to an improvement in the second urodynamic recording. This was evidenced by an increase in urodynamic parameters and volumes. In addition, these patients reported significantly lower pain post void after lidocaine treatment. However, there was a lack of analgesic effect (VAS score post lidocaine > 2) in 4 of the 16 patients who received lidocaine, with a corresponding deterioration in their urodynamic parameters, similar to the saline controls.

Interpretation of results

We failed to see an analgesic effect in 4 patients. This suggests pain centralisation may be a contributing factor in BPS, thus making exclusive peripheral treatment strategies ineffective in this small group.

Conclusions

By using urodynamics, we have demonstrated an objective assessment of lidocaine treatment on BPS.

2

2. Bladder instillations with a combination of hyaluronic acid and chondroitin sulfate in Bladder Pain Syndrome patients: preliminary results of a 12 weeks administration schedule

Authors: Leopoldo Marzullo Zucchet[1] - Laura Lorenzo Soriano[1] - Miguel Angel Bonillo Garcia[1] - Esther Martinez Cuenca[1] - Salvador Arlandis Guzman[1] - Enrique Broseta Rico[1] - Francisco Boronat Tormo[1]
Hospital Universitari i politècnic La Fe, Hospital Universitari i politècnic La Fe, Valencia, Spain [1]

Introduction and aim of the study

Glicosaminglycans replenishment therapy has been seen to improve pain, urinary symptoms and quality of life of patients with BPS. The objective of this study is to evaluate the efficacy and safety of a 12 weeks bladder instillations schedule of a combination of hyaluronic acid and chondroitin sulfate (Ialuril®) in patients with BPS.

Materials and methods

Retrospective, no randomized study, evaluating efficacy and safety before and after treatment. 25 Patients with diagnosis of BPS/IC were included. Physical exploration, Visual Analogue Scale, and

Bladder Pain Interstitial Cystitis Symptom Score (BPIC-SS) were performed. Weekly Ialuril® bladder instillations were administered for 12 weeks. Complications and adverse events were registered. Differences pre and post treatment were determined using Rank Wilcoxon test ($p<0.05$). Primary and rescue treatments (patients previously treated with DMSO, Hyaluronic acid or onabotulinumtoxinA) were compared.

Results

Table 1. Changes in VAS pain and BPIC-SS in the primary treatment group

	VAS pre	VAS post	BPIC-SS pre	BPIC-SS post
Score	6,9 ± 2,2	4,5 ± 3,2	24,8 ± 5,8	18,1 ± 9,7
Reduction (%)	34%		27%	
p value	0,002		0,012	

Interpretation of results

There was a significant improvement in both VAS pain and BPIC-SS in the primary treatment group with no adverse events. Improvement was also recorded in the rescue treatment group but it does not reach statistical significance probably due to small sample (10 patients).

Conclusions

GAGs replenishment therapy with weekly bladder instillations of Ialuril® for 12 weeks, reduces pain VAS and BPIC-SS in BPS patients, more obvious in those not previously treated with other intravesical treatments, and with a good safety profile.

3. Intravesical instillation therapy in IC/BPS patients: a challenging new way with remarkable advantages

Author: Sandor Lovasz[1]
Urological Department, Semmelweis University, Budapest, Hungary [1]

Introduction and aim of the study

Intravesical instillation of bladder cocktails via catheter is a widely spread, effective way of local medical treatment of IC/BPS patients. Catheterization of the bladder in women is a simple and quick procedure with a low complication rate. Yet in IC/BPS patients the illness very often affects the urethra causing its tenderness or even expressed urethral pain. Therefore catheterization with the minimal superficial mucosal lesions trigger unproportionally strong and long lasting pain and sometimes even bleeding.

Materials and methods

We invented a special adapter for Luer-lock syringes which let us directly inject "bladder cocktails" into the bladder through the urethral orifice in a retrograde way. Its special conical tip and isolating neck-piece, let us perform a drop-free instillation without catheterization of the urethra.

In the last 6 months we used this method in instillation therapy of 62 patients. In 7 of 62 patients (11%) the instillation using the conical adapter was unsuccessful due to deep located urethral orifice or urethral kinking. In these patients we had to use conventional catheterization. 55 of 62 patients (89%) were easily treatable by using the new catheter free method.

Results

All the patients who were treatable with the catheter free method preferred it over the conventional catheterization. They did not report on any pain, neither on long lasting burning sensation nor on any other complications.

The new non-invasive instillation method prevents superficial lesions of the urethra and treats its mucosa with a highly concentrated, non-diluted drug solution.

It also enables a reduction of time, costs and inconvenience of bladder instillation.

Conclusions

By using the small adapter for bladder instillation, 89% of IC/BPS patients can enjoy the advantages of reduced inconvenience, pain and complications of conventional catheterization in a simple

procedure of reduced time and costs at the same time.

4. Hydrodistension plus botulinum toxin in bladder pain syndrome refractory to conservative treatments.

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Introduction and aim of the study

Bladder pain syndrome (BPS) is a disease with a complex and multidisciplinary treatment. When conservative management fails, European guidelines suggest carrying out hydrodistension plus botulinum toxin, as an effective option. The aim of this study is to assess our experience with this procedure.

Materials and methods

We performed a retrospective study of 25 patients with refractory BPS, who underwent bladder hydrodistension plus 100 U of botulinum toxin in trigone, between September 2011 and May 2015. 38 procedures (25 first procedures and 13 relapses) were performed. In order to assess the pain improvement we used: TBS and PGIC, visual analogue scale (VAS) and BPICC-SS questionnaire. Moreover, we evaluated the degree of change in micturition frequency with a three day bladder diary. We used Wilcoxon test for the data analysis. Finally, we assessed how long the improvement lasted by means of a Kaplan-Meier curve and Log-Rank test.

Results

In 34 of 38 procedures (89,5%), the patients described that their pain had improved (16 strongly, 14 mildly and 4 slightly). VAS decreased strongly one month after the procedure, with a statistically significant difference (p:0.001). We also observed a decrease in diurnal and nocturnal micturition frequency, both of them with statistically significant difference (p:0.015 and p:0.004 respectively). On the other hand, the improvement was seen as in first procedures as in successive ones. These results were independent of age and previous cystoscopic findings. The median duration of pain relief was 6 months (IC95%: 3,95-8,03).

Interpretation of results and conclusions

Bladder hydrodistension under general anesthesia plus botulinum toxin injection is a suitable treatment in refractory BPS. Moreover, this procedure can be performed every six months since the effectiveness in relapses cases is similar to that obtained in primary cases.

1.Kuo H-C, Jiang Y-H, Tsai Y-C, Kuo Y-C. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment - A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. Neurourol Urodyn. 2015 Apr 24
2.Kuo H-C. Repeated onabotulinumtoxin-a injections provide better results than single injection in treatment of painful bladder syndrome. Pain Physician. 2013 Jan;16(1):E15–23.

5. BPS and histamine intolerance - a link?

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Introduction and aim of the study

The cause of Painful Bladder Syndrome / Interstitial Cystitis is currently unknown.Histamine seems to play a major role in IC.Within this retrospective case collection the role of histamine overload in the gut and vagina is highlighted.

Materials and methods

Between September 2012 and May 2015 a total of 52 women (mean age 50) were surveyed.Histamine in fecal samples was measured with a commercially available ELISA kit (LDN Labor Diagnostika Nord GmbH &Co. KG, Nordhorn, Germany).Additionally, vaginal swabs were analysed for histamine producing bacteria of the Enterococcus and Enterobacteriaceae family.

Results

Stool and Serum results:In 39 of the 52 analysed women elevated histamine levels were found in fecal samples.Vaginal swab results:In 22 out of these 39 women the presence of Enterococcus and/or Enterobacteriaceae in vaginal swabs was also detected. In 9 women only the presence of histamine producing bacteria in the vagina was found.

Interpretation of results

There are paralleles between IC and histamine intolerance: prevalence of 1%, 80% female and middle aged, symptom improvement in pregnancy (diamine oxidase level 500 fold higher); histamine intolerance can present with a variety of symptoms like e.g.migraine, irritable bowel syndrome, urticaria, tachykardia, nasal congestion and perhaps also IC?Histamine can increase intestinal permeability causing a leaky gut which prompts the body to initiate immune reactions causing autoimmune diseases, also comorbidities of IC.In irritable bowel syndrome it has been demonstrated that abdominal pain correlates with activated mast cells in proximity to colonic nerve.Moreover histamine alone as shown in mice can also cause pelvic pain.

Conclusions

A neural-mediated crosstalk between pelvic organs could be the answer to the histamine overload in the gut and vagina.

Barbara et al, Gastroenterology 2004;126:693-702
Rosa et al, British Journal of Pharmacology 2013;170: 38-45
Rudick et al, J Urol 2012;187: 715-724

6. Repetitive Transcranial Magnetic Stimulation As Treatment Of Neuropathic Pain In Bladder Pain Syndrome: Preliminary Data

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Introduction and aim of the study

Chronic pelvic pain associated to the Bladder Pain Syndrome (BPS) is a typical example of neuropathic pain, involving peripheral and central mechanisms of sensitization. Although neuropathic pain responds to antidepressants, anticonvulsants and opioid agonists, these drugs are often ineffective or can induce severe adverse effects. Hence, to manage this disturbance other safe and effective therapeutic options are need. In these settings, cortical stimulation has emerged as a novel approaches for pain relief. Specifically, a non-surgical technique modulating cortical excitability and inhibiting pain perception is repetitive transcranial magnetic stimulation (rTMS) applied to the motor cortical areas. Standard TMS coils (such as the figure-of-8 coil) permit to stimulate only superficial cortical regions of the human brain. A newer cooled coil, the Hesed (H)-coil allows deep brain stimulation without significantly increasing fields induced in superficial cortical regions. The H-coil can therefore be used to stimulate the motor cortex concerning the pelvic area, a region that lied deep in medial motor area sections folding into the brain medial longitudinal fissure. To date, no studies have used rTMS with an H-coil to stimulate the motor cortex as therapy for resistant neuropathic pain in BPS patients.

Materials and methods

In the present pilot study, we investigated whether modulation of excitability of the motor cortex with rTMS in patients with BPS could result in modifications of neuropathic pain and urinary disturbances. Until now, eight patients with BPS were enrolled. Diagnosis of neuropathic pain was confirmed with the Douleur Neuropathique en 4 questions (DN4) questionnaire. All patients were resistant to standard therapies for neuropathic pain taken for at least six months. The patients received two weeks of rTMS sessions, with three week-break between the two weeks of treatment.

In each patient, the rTMS sessions were delivered with a H-coil for 5 consecutive days, lasting 20

minutes and consisting of 30 consecutive trains of 50 stimuli delivered at 20 Hz, at 100% of resting motor threshold, separated by intertrain intervals lasting 30 s. The patient's clinical condition was evaluated before treatment began, immediately after it ended, 3 weeks later, and every 3 weeks in a follow up lasting 126 days (18 weeks). At baseline patients was submitted to DN4 and sensitization scale. At various time-points, all patients underwent to the following assessments: Visual Analogue Scale (VAS) for pain and Neuropathic Pain Symptom Inventory (NPSI) to assess changes in *pain*; Overactive Bladder Questionnaire (OABq), O'Leary Sant questionnaire and post-voiding bladder ultrasound to assess changes in *urinary disturbances*; Short Form-36 Health Survey (SF-36) and Beck depression inventory (BDI) to evaluate changes in the *quality of life*. The *Minnesota Multiphasic Personality Inventory (*MMPI) and a urodynamic examination with cystoscopy were performed at baseline, at the end of the two rTMS sessions and three months later. Data were analyzed using the one way ANOVA and Fisher post hoc test.

Results

Eight women were enrolled (mean±SD: 55.5±10 years). The delay between the onset of symptoms and the inclusion in the study was 18±9.5 years. At the enrollment, the DN4 was 5.28±1.38 and the sensitization scale score was 66.4±20. The bladder residue significantly improved after the rTMS ($F=2.43$; $p=0.02$). The OABq score reduced significantly after the rTMS ($F=1.36$; $p=0.05$). Also the NPSI score reduced after the rTMS ($F=1.62$; $p=0.05$). The VAS, the O'Leary Sant questionnaire, the SF-36, and the MMPI did not

changed after the rTMS. The BDI score reduced but not significantly. The effect on the OABq and the NPSI tests persisted at least for 3 weeks.

Interpretation of results and conclusions

The preliminary results of this pilot study show that the rTMS of the brain motor cortex related to the pelvic area changes both the subjective perception of the pain and the objective measurement of bladder voiding. In a previous study the efficacy of rTMS on chronic drug-resistant neuropathic pain associated to other syndromes was already demonstrated (*Onesti E et al, 2013*). Our results are consistent with the recent characterization of brain white matter micro structural abnormalities in women with BPS, suggesting a brain neuropathological contribution to chronic pelvic pain (*Farmer MA et al, 2015*). In our research, a placebo effect could be ruled out because a long latency between the treatment and the effects was demonstrated, such as previously evidenced (*Onesti E et al, 2013*). Also the frequency, urgency and incontinence symptoms, such as reported in OABq, improved. Moreover, the depression did not improved before the changes in painful and urinary parameters, meaning that the change of psychic disease did not cause the clinical improvement reported.

Conclusion

Deep H-coil rTMS applied to the motor cortex could be provide pain and urinary disturbances relief in patients with BPS. The interpretation of this results is limited by the small sample size, and more data are certainly need to confirm this preliminary report and to better understand the mechanisms by which rTMS may modulate pain and urinary disturbances in BPS patients.

References

Farmer MA, et al. Brain white matter abnormalities in female Interstitial Cystitis/Bladder Pain Syndrome: A MAPP network neuroimaging study. J Urol 2015;194:118-26. doi: 10.1016/j.juro.2015.02.082.

Onesti E, et al. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. Eur J Pain 2013;17:1347-56. doi: 10.1002/j.1532-2149.2013.00320.x.

The "coating": a passive or an active element?

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Bladder Wall Structure

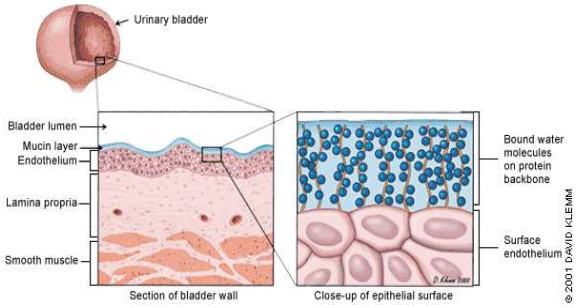

Figure.1 Small blue circles represent bound water molecules, and wavy lines represent the protein Backbone (core proteins). (Julius F. Metts, 2001)

GAGs in BPS/IC

- GAGs in urine significantly reduced vs. controls
- GAGs/ChS in urothelium not different vs. Controls
- TGF-β (growth factors) increased in urothelium
- HA staining intensified in BPS/IC urothelium, but CD44 (major membrane receptor of HA) not, suggesting a disorder of HA internalisation, digestion and reuse for synthesis – interstitial accumulation (model: bleomycin lung fibrosis)

Instillation Therapie

- Hyaluronan / Cystistat®
- Chondroitinsulphate
- Combination HA/ChS
- Pentosanpolysulfate
- Heparin
- DMSO

Hyaluronan

- Different molecular weights (4k to 10MDa) – the higher the better the barrier function (viscosity)
- High molecular (HMW) HA: GAG-Layer restitution
  › Longer half-life
- Low molecular (LMW) HA: receptor activation
  › reduction of leukocytic/immunologic effects inside the bladder wall via specific receptors: CD44, I-CAM, RHAMM, CD 168, TLR 2/4 – β Defensin 2
  › Better penetration into tissue, shorter half-life
- Manufactured from bacterial cultures (Class IIb Medical Device)

Biological Effects of HA

In vitro biological activity	LMW (<500kD)	MMW (500-1000)	HMW (1000-4000)
Inhibition of leukocyte chemotaxis	-/+	+/++	++
Inhibition of phagocytosis	-/+	++	+++
Inhibition of lymphocyte proliferation	-	+++	Not tested
Free radical scavenging	+	++	+++
Inhibition of apoptosis	-	++	+
Stimulation of HA production	-	+++	+++
Inhibition of prostaglandin E2	+	+	+++
Analgesia (in vivo animal studies)	-/+	Not tested	+++

HA & Cytokines & Permeability

- Urothelial cell cultures
- HA decreases TNFα-mediated expression of inflammatory cytokines IL6 and IL8
- Sulphated GAG production is increased by HA (via stimulation of key enzymes for ChS synthesis)
- HA decreases urothelial permeability for big molecules (Dextran 150 kDa), with no increase in tight junction expression

Efficacy of Instillation Regimes

Study	Instillate	No.Instillations	Response Rate	NNT
Nickel 2010	ChS	6	41 %	5.5
Nickel 2008	ChS	10	60 %	2.7
Porru 2008/2011	LMW HA/ChS	12/10	46 %/57%	4.1/3.9
Morales 1996	HMW HA	6	71 %	2.1
Kallestrup 2005	HMW HA	6	65 %	2.4
Riedl 2008	HMW HA	12	85 %	1.6
Engelhardt 2010	HMW HA	10	85 %	1.6
Kim 2014	HMW HA	4-6	61 %	?

The neurogenic component of BPS/IC

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Physical sensation is a perception made by an individual related to a stimulus that occurs in the body. Sensation is by definition always subjective which does not mean that reporting of pathologic sensations would have little health related meaning, on the contrary.

Nociceptive pain, through direct stimulation of nociceptor sites, is different from neuropathic pain, which results from a direct lesion of the peripheral or central nervous system. Both can be present in chronic pelvic pain.

Nociceptive pain: there is an elaborate nervous structure involved in sensory/pain transmission. Through nerves in this network pathologic afferent information will be conducted. This gets a central interpretation by coding of stimulus type, stimulus intensity and stimulus location. Afferents from the bladder show plasticity: the total number of active primary afferents is not static but critically depends on the state of the tissue as in BPS. Cytokines from damaged urothelial cells can lead to mast cell proliferation, phenomenon demonstrated in BPS. Pelvic organ cross talk is now generally accepted and works through complex integrative pathways that may converge peripherally and/or centrally.

One can conclude that neurophysiological mechanisms play an important role in BPS/IC both peripheral and central.

Pudendal neuralgia: is a painful neuropathic condition that involves the Pudendal nerve. As it travels from its end branches in pelvic floor, sphincter, pelvic organs it can get damaged during surgery, physical stress of extrinsic movements and postures, compression in the pudendal canal entrapment by disorders or defection of the obturator internus muscle. Neurophysiological tests is very useful for diagnosis. It gives a good indication of what treatment should be given therapeutic-rehabilitative.

BPS and Associated Rheumatic Conditions

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Associated diseases for BPS are diseases with a higher prevalence among BPS patients than in people without BPS. An association does not imply nor exclude a causal relationship between the associated disease and BPS. The practical consequence is that doctors should know the associations and have a high index of suspicion for the associated diseases in patients with BPS.

	prevalence (%)		
diagnosis	BPS	general population	RR in BPS[a]
allergy	41-47	22.5	2
irritable bowel syndrome	25-43	3-15	2-9
fibromyalgia	9-17.7	2.5-4	4
chronic fatigue syndrome	4-9.5	1-1.7	4-5
Crohn's disease / ulcerative colitis	1-7.3	0.07	14-100
systemic lupus erythematodes	1.7	0.05	34
rheumatoid arthritis	4-13	1.0	10
Sjögren's syndrome	7.2	0.2-1.4[b]	5-36

[a] RR: relative risk; the RR in BPS is the ratio between the prevalence of the disorder in BPS and the prevalence in the general population
[b] population aged 40-44 yr: 0.22%; population aged 71-74: 1.4%

Table 1. Examples of associated systemic disorders diagnosed in 110 BPS patients in comparison with the general population.1

Rheumatic conditions comprise a variety of disorders of mainly the joints and muscles marked by inflammation, degeneration or metabolic derangement, with pain, stiffness or limitation of function. Diseases that can be considered rheumatic diseases mentioned in Table 1 are fibromyalgia (FM), chronic fatigue syndrome (CFS), systemic lupus erythematodes, rheumatoid arthritis and Sjögren's syndrome. Combined data from the literature (Table 1) indicate that the diseases associated with BPS can be grouped in three main groups: allergies, chronic pain syndromes and systemic autoimmune diseases.1

Problems

The interpretation of these data is problematic. The study designs – if any – are very different, often without control subjects, in many studies the diagnosis was based on self-reports by the patients or doctors that were not specialized in the associated diseases. In general, studies were not confirmed by studies from other centers

Recent studies with control subjects, however, have also shown that BPS patients are more likely than persons without BPS to have syndromes manifesting symptoms outside the bladder, and even outside the pelvis (so-called non-bladder syndromes, NBSs). Significantly more BPS cases than controls had each of fibromyalgia, irritable bowel syndrome, chronic pelvic pain, endometriosis, depression, anxiety and vulvodynia.2

Clemens et al. found that IC/BPS cases also significantly exceeded controls in non-specific complaints such as myalgias, gastrointestinal symptoms, gynecologic pain, headache, back disorders, depression, and anxiety.3 Significantly higher prevalence of self-reported FM, CFS, irritable bowel syndrome (IBS), migraine and tension headaches, vulvodynia, temporomandibular disorder and low back pain were found in female IC/PBS cases than in controls.4 Additionally, these IC/PBS patients reported significantly more depression and anxiety than controls. Associated diseases or symptoms of them were found significantly more frequent before the diagnosis of IC/PBS than in matched controls such as FM, CFS, IBS, sicca syndrome, chronic pelvic pain {CPP), migraine, allergies, asthma, depression, panic disorder, and vulvodynia.5

Most of the NBSs associated with BPS appeared in 4 clusters: [FM, CFS, IBS, sicca syndrome], [CPP, migraine], [depression, anxiety] and [allergy, asthma]. In 71-95% of BPS cases, NBSs preceded BPS by ≥12 months. The number of antecedent NBSs was directly correlated with the risk of BPS.5-8

1. van de Merwe JP. Bladder pain syndrome and associated diseases. Unpublished data.
2. Wu EQ, et al. Interstitial cystitis: Cost, treatment and co-morbidities in an employed population. Pharmacoeconomics 2006;24:55-65.
3. Clemens JQ, et al. Case-control study of medical comorbidities in women with interstitial cystitis. J Urol. 2008;179:2222-5.
4. Nickel JC, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J Urol 2010;184:1358-63.
5. Warren JW, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology 2009;73:52-7.
6. Clemens JQ, et al. In: Temporal association between interstitial cystitis/bladder pain syndrome (IC/BPS) and non-bladder conditions. Society for urodynamics and female urology; March 1-5, 2011; Phoenix Arizona; 2011. p. 205.
7. Warren JW, van de Merwe JP, Nickel JC. Interstitial cystitis/bladder pain syndrome and nonbladder syndromes: facts and hypotheses. Urology 2011;78:727-32.
8. 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.

P Pelvic floor - The Posture and Associated Disorders: Treatment

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Background

Bladder Pain Syndrome (BPS) is a debilitating syndrome characterized by urinary urgency, frequency, and pain. Currently multiple therapies are used to decrease BPS symptoms. Unfortunately, these therapies are often suboptimal in alleviating these symptoms, perhaps in part because the true cause of BPS is unknown. Although ruling out other confusable states is crucial in the diagnosis, evaluating the pelvic floor to determine if it is a cause of the symptoms of BPS is frequently not done due to the lack of education on pelvic floor function and dysfunction. Up to 85% of patients labeled with BPS suffer from pelvic floor spasm, which causes

pelvic pain, dyspareunia, urinary frequency and urinary hesitancy. A noxious stimulus may trigger the release of nerve growth factor and substance P in the periphery causing the mast cells in the bladder to release proinflammatory substances, causing neurogenic inflammation of the bladder wall. This can result in painful bladder symptoms (BPS) or vulvar or vaginal pain. There may also be a viscero-muscular reflex resulting in the pelvic floor muscles being in a hypertonic contracted state. This hypertonic state result in decreased muscle function, increased myofascial pain, and myofascial trigger points. The pelvic floor muscles then become a source of pain even if the bladder is treated. In addition, neural cross-talk may explain the interface of many chronic pelvic pain conditions including BPS and irritable bowel syndrome. This session will outline how to evaluate the pelvic floor in patients suffering from BPS (Whitmore) and will focus on treatment of pelvic floor dysfunction.

Key to Successful Treatment of Pelvic Floor Dysfunction (PFD) in the BPS Patient.

Treat the Pelvic Floor First

When evaluating a patient with urinary urgency, frequency, and pelvic pain, it is imperative to not only focus on the bladder as a cause of the syndrome but also the pelvic floor. If palpation of the levator muscles reproduces their pain or "bladder pressure," then it is reasonable to consider pelvic floor treatment as a first-line treatment before any invasive testing or medications are used. If pelvic floor involvement is identified, treatment by a therapist knowledgeable in myofascial release may markedly improve symptoms and often is the only treatment needed. If no levator spasm or tenderness is identified on initial evaluation or if after completing pelvic floor directed therapy the patient continues to have urinary symptoms, then it is reasonable to evaluate and treat them further with standard therapies for BPS.

Multiple modalities used to manage Pelvic Floor Dysfunction

I. Pelvic Floor Physical Therapy
   a. Evaluation of external and internal trigger points and myofascial constrictions
   b. Manual therapy with intravaginal myofacial release
   c. Teaching home stretching using crystal wand or vaginal dilators
II. Intravaginal Valium
   a. Valium can be deposited in the vagina as a pill or cream
   b. Local and some systemic absorption can help reduce the pain associated with PFD
III. Guided Imagery
   a. Focused guided imagery directed to pelvic floor relaxation can help improve the symptoms of pelvic floor dysfunction
IV. Transvaginal Trigger Point Injections
   a. Injecting a local anesthetic and steroid through the vaginal wall into the levator complex can improve the symptoms of PFD
   b. Well tolerated in the office and can be directed at a distinct trigger point or throughout the pelvic floor complex
   c. A series of injections with physical therapy can improve the symptoms of PFD
V. Pudendal Nerve blocks
   a. The pudendal nerve innervates much of the pelvic floor, bladder and urethra
   b. Performing pudendal nerve blocks either trans-vaginal or trans-gluteal can improve the symptoms of PFD and pelvic pain
VI. Denervation of the pelvic floor muscles
   a. Botulinum toxin 200-300 units can be injected into the pelvic floor muscles
   b. 7-10 days until clinical effect
   c. Can markedly reduce pelvic floor spasm
VII. Neuromodulation
   a. Sacral or Pudendal neuromodulation can improve the symptoms of pelvic pain and voiding dysfunction in BPS

Conclusions

BPS has been a difficult disease to recognize and treat for many years. Part of the problem is that there is not an absolute diagnostic test to identify who has BPS, and our treatment has focused solely on the bladder as the cause of symptoms. It is now clear that many patients diagnosed with BPS have significant pelvic floor dysfunction. This levator spasm often is the major contributor to voiding dysfunction and pelvic pain. After ruling out confusable states such as urinary infection, bladder cancer, or urethral diverticulum, the pelvic floor should be evaluated. If the pelvic floor is a source of pain and the muscles are in spasm, treating the pelvic floor first before other invasive testing would be appropriate. Many patients find a marked improvement in symptoms by treating the pelvic floor, and epithelial-based therapy may not be required.

We must look "outside the bladder" when evaluating patients with BPS and be open-minded regarding the underlying cause and potential treatments to improve their quality of life.

Gait and Physical Therapy

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Function of Pelvic Floor
- Maintain bowel and bladder continence
- Support viscera
- Stabilizes the pelvis

Urogenital Diaphragm
- Just deep to genitalia
- Superficial transverse perineal
- Bulbocavernosus/Bulbospongiosus
- Ischiocavernosus

UGD First Layer
- BulboCavernosus
- Ischiocavernosus
- Transverse Perineal
- Vaginal Sphincter
- Impedes drainage from deep dorsal veins from clitoris
- Responsible for erection, orgasm
- Pudendal S2-S4

Deep Layer PF

Levator Ani
- Pubococcygeus
- Puborectalis
- Iliococcygeus
- Tendinous Arch

Role of PF in Sexual Function

Deep Layer Contractions of Levator Ani
- Widen the vaginal introitus
- Elongate the vagina
- Assist in uterine elevation
- Enhance sexual pleasure

Obturator Internus
- Originates on arcuate line of ilium
- Attaches to tendinous arch of levator ani before taking a 90 degree turn to gr trochanter

Coccygeus
- Ischial spine to the anococcygeal ligament and coccyx
- Parallel with the sacrospinous ligament
- Stabilizes the sacrum amd coccyx

High Tone Pelvic Floor

Research links HTPF to:
- Vaginismus
- Dyspareunia
- Vulvar Vestibulitis
- Interstitial Cystitis
- Urgency-Frequency Syndrome
- Proctalgia Neuralgia

Research linking musculoskeletal system to IC

Bassaly et al. (2011)
- 186 patients identified with IC
- 78.3 % at least 1 myofascial trigger point
- 67.9 % had 6 or > trigger points

High Tone Pelvic Floor

Characterics of High Tone
- Pain to palpation
- Trigger points
- Decreased motor control
- Decreased strength
- Resistance to stretch

Internal Assessment

Trigger Point:

A discrete, focal, hypersensitive spots located in a taunt band of skeletal muscle. They produce pain locally and in a referred pattern and often accompany chronic musculoskeletal disorders.

PT Assessment of Pelvic Floor
- Observation of vulva
- Width of introitus
- Palpation for tenderness
- Muscle tone
- Presence of trigger points
- Muscle strength

- Neuromuscular control

Internal Exam

Scoring Muscle Hypertonus:

0. no pressure/pain with exam
1. comfortable pressure with exam
2. uncomfortable pressure with exam
3. moderate pain with exam, intensifies with PF contraction
4. severe pain with exam, unable to contract PF due to pain

Internal massage

Myofascial release Techniques:

- Direct Pressure/compression
- Strumming
- Lateral Stretching
- Contract-relax

What does internal massage accomplish?

- Restores normal muscle tone
- Breaks pain-spasm-pain cycle Restores normal length tension relationship
- Increases blood flow
- Increased elasticity of tissue at vaginal opening
- Increase proprioception
- Decreases nerve impingement
- Decrease fear of vaginal penetration
- Restores sexual function

Does internal massage work?

Weiss et al. (2001)

- 42 patients with urgency-frequency syndrome or IC
- 1-2 visits of PT, 8-12 wks
- 83% of urgency-frequency patients/ 70% of IC pts had marked improvement in symptoms

Oyama et al. (2004)

- Patients with IC and HTPF (n=21)
- Transvaginal massage 2x/wk X 5 wks
- Statistically significant improvement in:
  - Symptom and problem index (O'Leary Sant Questionaire)
  - Pain and urgency VAS
  - Physical and mental component from Quality-of Life Scale

Biofeedback

The patient actively learns to:

- Increase awareness of pelvic floor
- Recruit the correct muscle group
- Identfy faulty muscle patterns
- Restore proper coordination and strength of muscle contraction

PT Treatment

Home Exercise Program:

- Stretching
- Strengthening
- Stabilization exercises
- Self-help techniques
- Self-internal massage

Empower the patient

Dilators

- May add training with dilator insertion
- Decrease anxiety related to vaginal penetration
- Increase flexibility of introitus and PFM
- GOAL: Stabilization of spasm & return of sexual function

Pelvic Floor and Synergists Core Control

- Pelvic Floor
- Transversus Abdominus
- Multifidus
- Diaphtagm

Lack of Form Closure

- Greater potential of mobility
- Increased necessity optimal neural control
- Optimal coordination of muscles
- Need for healthy connective tissue

Janda's Principal

- Muscle resting tone and ability to contract and relax is altered in the presence of metabolic inflammatory properties.
- C fiber facilitation influences muscle properties

Faculty Breathing Patterns

Chronic Pelvic pain

- Upper chest breathing
- Decreased lower lateral rib excursion
- Increased muscle tone abdominals
- Increased intra-abdominal pressure
- Increased stress on pelvic floor

PT Manual treatment

Manual Therapy Techniques

- Soft tissue massage
- Muscle energy techniques
- Joint mobilizations
- Manual stretching
- Internal massage

Physical Therapy Treatment

Goals:

- Normalize pelvic floor resting tone
- Normalize pelvic floor contractile abilities
- Normal ROM of the spine and hips
- Pelvic girdle stability with sustained loads
- Restore sexual function
- Return to recreational exercise.

Vulvodynia: an isolated gynecologic condition or a possible consequence of BPS?

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To understand the relationship between vulvodynia (VD) and Bladder Pain Syndrome (BPS) it is necessary to go through the definition of VD and its position within the recent neurobiological pain classification, which can also help defining the pathogenesis and correlation with other similar pain syndromes.

Definition. According to the 2003 Terminology and Classification of the International Society for the Study of Vulvar Disease (ISSVD), VD is a vulval pain described as a burning sensation, occurring in the absence of relevant visible vulval findings or a specific, clinically identifiable, neurologic disorder. VD is categorized as generalized (involvement of the whole vulva) or localized (involvement of a portion of the vulva: vestibulodynia, clitorodynia, hemivulvodynia, etc.). Both generalized and localized VD are further subdivided into provoked (pain triggered by physical contact), unprovoked (spontaneous pain), or mixed (1).

Neurobiological pain classification. A recent widely accepted classification divides pain, from a neurobiological perspective, into nociceptive, inflammatory, and pathological pain with the latter subdivided into neuropathic and dysfunctional pain. Nociceptive pain is protective, adaptive, high-threshold pain provoked by noxious stimuli. Inflammatory pain is protective, adaptive, low-threshold pain associated with peripheral tissue damage and inflammation. Reversible adaptive changes (functional plasticity) in the sensory nervous system lead to generation of pain hypersensitivity (allodynia, hyperalgesia, spontaneous pain), which has a protective function: the tenderness discourages physical contact and movement thus promoting tissue repair and healing. Pathological pain is non-protective, maladaptive, low-threshold pain caused by structural damage to the nervous system (neuropathic pain) or by its abnormal function (dysfunctional pain) (2). Dysfunctional pain occurs in some pain syndromes, such as fibromyalgia (FM), irritable bowel syndrome (IBS), tension type headache, temporomandibular joint disease, and BPS/ Interstitial Cystitis (IC) in which there is pain hypersensitivity but no noxious stimulus, no inflammation, and no structural damage to the somatosensory nervous system (2). These syndromes are characterized by a similar abnormal and widespread increase in pain sensitivity, which probably reflect a common contribution of central sensitization (3-5).
Abnormal central sensitization can be interpreted as abnormal long-term potentiation, defined as a persistent increase in synaptic strength in central nociceptive pathways, induced by exposure to peripheral precipitating events, specifically peripheral tissue damage and inflammation, in the presence of an individual predisposition to abnormal pain persistence. As a consequence, allodynia, hyperalgesia, and spontaneous pain persist beyond peripheral tissue healing, becoming chronic and maladaptive (6).
Predisposing factors for the developing of abnormal pain persistence include female sex, early life trauma, a personal history of multifocal pain or other central mediated symptoms, such as insomnia, fatigue, memory difficulties and psychological problems, such as anxiety, depression and catastrophizing.
Epidemiological findings suggest that abnormal central sensitization may have a hereditary component, however much remains still to be learned about genetic factors which can increase the risk of producing abnormal pain persistence.

Pathogenesis. A recent review about the nature of the pain in VD has demonstrated that in most of the published data there is no active peripheral tissue inflammation and similarly no neural damage

(7). Therefore, it is reasonable to consider VD as a dysfunctional pain induced by exposure to acute physical or psychological precipitating events in the presence of an individual predisposition to produce or maintain abnormal central sensitization. This central sensitization can be interpreted as an abnormal long-term potentiation initiated by peripheral precipitating events, most frequently an infection e.g recurrent vulvovaginal candidiasis or urinary tract infection, or a dermatosis e.g. lichen planus or contact dermatitis.
Predisposing psychological, sexual and/or social problems can also induce abnormal central pain processing (8). Actually VD is 4-times more likely among women with diagnosed antecedent depression and anxiety disorder, and, moreover, VD increases the risk (hazard ratio 1.7) of both new and recurrent onset of psychopathology (9).

Comorbid pain syndromes. In a recent study it has been calculated that a woman suffering from VD has 2.3-fold to 3.3-fold risk of having any of the following chronic pain conditions: FM, BPS/IC, and IBS. Moreover, as the number of other chronic pain conditions increased from 0 to 3, the odds of having VD increased more than 5-fold (10). This unexpectedly high comorbid rate may account for considering these pain syndromes real separated clinical entities, but shearing a common pathogenetic background represented by an abnormal central sensitization leading to dysfunctional pain.
Therefore VD is not a consequence of BPS, but women affected by VD are at higher risk to develop PBS and vice versa.
Finally, management of these patients must be multidisciplinary and, because dysfunctional pain syndromes result from abnormal central sensitization, the target for treatment in these situations must be the central nervous system not the periphery (4, 11).

References

1. Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. Journal of Reproductive Medicine. 2004; 49:772-777.
2. Woolf CJ. What is this thing called pain? Journal of Clinical Investigation. 2010; 120:3742-3744.
3. Ness TJ, Powell-Boone T, Cannon R, Lloyd LK, Fillingim RB. Psychophisical evidence of hypersensitivity in subjects with interstitial cystitis. J Urol 2005; 173:1983-1987.
4. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152:S2-S15.
5. Lai HH, Gardner V, Ness TJ, Gereau RW. Segmental hyperalgesia to mechanical stimulus in interstitial cystitis/bladder pain syndrome: evidence of central sensitization. J Urol 2014; 191: 1294-1299.
6. Sandkühler J, Gruber-Schoffnegger D. Hyperalgesia by synaptic long-term potentiation (LTP): an update. Current Opinion in Pharmacology. 2012; 12:18–27.
7. Micheletti L, Radici G, Lynch PJ. 2014. Provoked vestibulodynia: inflammatory, neuropathic or dysfunctional pain? A neurobiological perspective. Journal of Obstetrics and Gynaecology 34:285-288.
8. Lynch PJ. Vulvodynia as a somatoform disorder. Journal of Reproductive Medicine. 2008; 53:390-396.
9. Khandker m, Brady SS, Vitonis AF, Maclehose RF, Stewart EG, Harlow BL. Journal of Women's Health . 2011; 20:1445-1451.
10. Reed BD, Harlow SD, Sen A, Edwards RM, Chen D, Haefner HK. Relationship between vulvodynia and chronic comorbid pain conditions. Obstet Gynecol 2012; 120: 145-151.
11. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. The Journal of Pain. 2009; 10:895-926.

P

Pudendal neuralgia and Bladder pain syndrome: confusable diseases

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Pudendal neuralgia is definited as a neuropathic pain in the territory of the 3 branches of the pudendal nerve (Inferior rectal nerve, Perineal nerve and dorsal nerve of the clitoris/penis). Aix en Provence criteria (1)
Pudendal neuralgia is very frequently associated to a visceral pain like the BPS in the pelvi-prerineal hypersensitization syndrome.

But the difference should be done with the bladder symptoms which accompanied the Pudendal nerve entrapment (PNE) syndrome. Indeed, in this particular situation, pain symptoms can be improved or cured with the treatment of the PNE: block nerve injections and especially, the surgical pudendal nerve decompression-liberation (2).

How to recognize bladder pain symptoms of PNE?

- 1 - main symptoms are neuropathic pain, with the DN 4 criteria (3), in the territory of the pudendal branches, with criteria of entrapment as described in the Nantes criteria (4)

- 2 - The bladder symptoms are most often, cystitis sensation and urinary frequency. But in PNE, these symptoms are only occuring during the day. The patients are never woken up at night with the urinary symptoms in PNE and that makes the very big difference with the urinary pain symptoms occuring in the hypersensitization syndromes.

Criteria of pelvi-perineal hypersensitization (5) should be perfectly known. They will help to make the difference between PNE, and the pudendal neuropathic pain with the bladder pain, included in a pelvi-perineal hypersensitization syndrome.

References

1- Mollo M, Bautrant E, Rossi AK, Collet S, Boyer R and Thiers-Bautrant D. Evaluation of diagnostic accuracy of Colour Duplex Scanning, compared to electroneuromyography, diagnostic score and surgical outcomes, in Pudendal Neuralgia by entrapment : A prospective study on 96 patients. Pain. 2009 ; 142 : 159-163.

2- Bautrant E, De Bisschop E, Vaini-Elies V, Massonnat J, Aleman I, Buntix J, De Vlieger J, Di Constanzo M, Habib L, Patroni G, Siboni S, Ceas B, Schiby V, Uglione-Ceas M. La prise en charge moderne des névralgies pudendales. À partir d'une série de 212 patientes et 104 interventions de décompression. J Gynecol Obstet Biol Reprod (Paris) 2003;32:705–12.

3- Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lenteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the neuropathic pain symptom inventory. Pain. 2004 Apr; 108:248-57

4- Labat JJ, Riant T, Robert R, Amarenco G, Lefaucheur JP, Rigaud J. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). Neurourol Urodyn. 2008; 27 (4): 306-10

5- Labat JJ. Consensus on clinical criteria to identify hypersensitization in pelvi-perineal pain syndromes. International federative meeting in pelvi-perineal pain. Convergences PP. 2012; Nîmes, april 26-28.

P Pelvic endometriosis: a confusable disease

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Endometriosis is an estrogen-dependent chronic inflammatory disease affecting 7-10% of women of reproductive age, 60% of women with pelvic pain and up to 50% of women with infertility. It is characterized by the implantation of endometrial glands and stroma outside the uterine cavity in ectopic locations, that include the pelvic peritoneum, ovaries, bowel and urinary tract, causing symptoms of dysmenorrhea, chronic pelvic pain, dyspareunia, dischezia, dysuria and infertility. Sampson's theory of retrograde menstruation, although incomplete in accounting for all the reported clinical manifestations of the disease, is the most widely accepted description of endometriosis pathogenesis. This theory proposes that endometriosis originates from the implantation of sloughed endometrial fragments refluxed into the pelvis via the fallopian tubes during menstruation.

Women with endometriosis suffer from fundamental differences in genetics (the risk of endometriosis is six times higher when the women as a first-degree relative with a severe form of endometriosis), immune systems (impaired immune surveillance) and biochemical factors (increased E2 production and progesterone resistance) compared with women without the disease.

The gold standard for the diagnosis of endometriosis remains direct visualization of lesions at surgery with histologic confirmation of endometrial glands and stroma in biopsies of

suspected lesions, especially in case of lesions with non-classical appearance.

Endometriosis associated pain is as complex as the disease itself and the precise mechanisms leading to nociception remain poorly understood. It is well accepted that no correlation exists between the stage of the disease seen at laparoscopy and the degree of pain symptoms. Pain generation in endometriosis is an intricate interplay of several factors such as the endometriotic lesions themselves that release pain-mediating substances, nerve fibers and cytokine-releasing macrophages. The interaction between these factors seem to induce a neurogenic inflammatory process. Estrogens appear to have an influence on the formation of the peripheral neurogenic inflammation and modulate central sensory impulses.

Establishing the correct diagnosis by laparoscopy before initiating therapy with medication that is associated with significant short-term and long-term side effect is the preferred approach. The use of nonsteroidal anti-inflammatory drugs is a common first line treatment for endometriosis pain because they are safe, easily accessible and inexpensive. The proposed mechanism of action for pain relief is inhibition of endometriotic prostaglandin production thereby causing suppression of inflammation and pain. Despite the lack of high-quality research for endometriosis specifically, they are still common used as initial or adjunct treatment and provide some improvement of pain, especially dysmenorrhea.

Combined hormonal contraceptives have been used in both a cyclic and a continuous fashion in the treatment of symptoms associated with endometriosis. Decidualization followed by atrophy of the endometrial tissue is the proposed mechanism of action.

Progestogens most commonly used for the treatment of endometriosis include medroxyprogesterone acetate and 19-nortestosterone derivatives (e.g. levonorgestrel, norethindrone acetate and dienogest). As with hormonal contraceptives, their proposed mechanism of action involves decidualization and subsequent atrophy of endometrial tissue. Danazol is a derivative of 17 α-ethinyltestosterone. Hyperandrogenic side effect are common and include hirsutism, acne, weight gain and deepening of the voice.

Gonadotropin-releasing hormone agonists induce a down-regolation of the pituitary-ovarian axis and hypoestrogenism. The likely mechanism of action involves the induction of amenorrhea and progressive endometrial atrophy. Side effect relate primarily to the induced hypoestrogenic state. Aromatase inhibitors have been shown to be effective for the treatment of endometriosis pain. However, such treatment is still considered investigational and is not approved by the US Food and Drug Administration for this indication. Laparoscopic treatment of endometriosis does lead to improvement in disease and pain and thus supports the recommendation to treat endometriotic lesions at the time of diagnostic laparoscopy. Pain recurrence after repeat surgery for recurrent disease rages from 20%-40%, similar to primary surgery.

For symptomatic endometriomas, cyst excision is more effective than fenestration and ablation of the cyst wall in terms of reoperation rate and more improvements in symptoms of dysmenorrhea, deep dyspareunia and nonmenstrual pain. However, with cyst excision there is concern about the risk of ovarian damage and impaired ovarian reserve. Laparoscopic uterosacral nerve ablation does not appear to offer any added benefits beyond those that can be achieved with conservative surgery for endometriosis alone. Presacral neurectomy has been proposed for the treatment of midline pain associated with menses because its effects on other components of pelvic pain have been inconsistent. However, it is important to recognize that presacral neurectomy is a technically challenging procedure associated with significant risk of bleeding from the adjacent venous plexus. Patient may also experience constipation and/or urinary retention postoperatively.

Hysterectomy with bilateral salpingo-oophorectomy generally is reserved for women with debilitating symptoms attributed to endometriosis who have completed childbearing and in whom other therapy have failed. The success of this approach is attributed to debulking the disease with the resulting surgical menopause causing atrophy of endometriotic tissue. Hysterectomy without bilateral salpingo-oophorectomy is less effective as disease recurrence and subsequent reoperation rates are higher. In conclusion, endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.

References

Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril 2012; Vol.98:511-519.

Thiruchelvam U, Wingfield M, O'Farrelly C. Natural Killer Cells: Key Players in Endometriosis. Am J Reprod Immunol 2015; Epub jun 24.

Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, Tayade C. Pathophysiology and Immune Dysfunction in Endometriosis. Biomed Res Int 2015. Epub jul 12.

Barcena de Arellano ML, Mechsner S. The peritoneum--an important factor for pathogenesis and pain generation in endometriosis. J Mol Med 2014;92:595-602.

Kobayashi H, Yamada Y, Morioka S, Niiro E, Shigemitsu A, Ito F. Mechanism of pain generation for endometriosis-associated pelvic pain. Arch Gynecol Obstet 2014;289:13-21.

Morotti M, Vincent K, Brawn J, Zondervan KT, Becker CM. Peripheral changes in endometriosis-associated pain. Hum Reprod Update 2014;20:717-36.

Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014;101:927-35.

Female sexual dysfunction and sexual pain: an introduction

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Does clinical practice show concern for sexual health?

- Global Study of Sexual Attitudes and Behaviors Study
  - only14% of Americans aged 40-80 y.o. reported that a physician inquired about their sexual health concerns within the past 3 years
- Berman et al 2003
  - On line survey of women with sexual health concerns who had consulted a physician:
  - 52% - "physician didn't want to hear about their problems"
  - 87% - "no follow up re: the complaint at subsequent visits

Male vs. Female "Wiring"

Women vs. Men – With women the "other factors" seem to more easily get in the way of enjoying the experience – and then ultimately having a sexually satisfying experience

FSD definitions

- Hypoactive sexual desire disorder
  The persistent or recurrent lack of sexual fantasies, thoughts, desires and receptivity to sexual contact.
- Sexual aversion disorder
  The persistent or recurrent fear or aversion of sexual contact.
- Sexual arousal disorder
  The persistent or recurrent inability to become sexually aroused, often characterized by inadequate vaginal lubrication for penetration.
- Orgasmic disorder
  The persistent or recurrent inability to orgasm.
- Dyspareunia
  Pain during sexual intercourse.

FSD: Diagnostic Inventories

The Female Sexual Function Index (FSFI)
19 items, internal consistency, test-retest reliability
Discriminates FSD in 5 domains:

desire, arousal, orgasm, satisfaction and pain
The Sexual Function Questionnaire (SFQ)
31 items, reliability and validity established
Discriminates FSD in 7 domains, including partner satisfaction

Dyspareunia

Affects ALL aspects of the female sexual response (eg: desire, arousal, orgasm, satisfaction)
Dyspareunia: 2 types
- Superficial (entry):
often due to inflammation at the introitus associated with: UTI, urethritis, vaginitis, provoked vestibulodynia
- Deep (thrusting):
often occurs in women with CPP related to bladder, uterine, ovarian, bowel or pelvic floor muscle pathology
Hypersensitivity disorders can cause or complicate FSD symptoms in urogynecology
(IC/PBS, HT-PFD, PVD, etc).

Examination for sexual pain

- Inspection of external genitalia
  Muscle tone, skin color – texture – turgor - thickness, pubic hair
  Cotton swab test (pain mapping): vulva, vestibule, hymenal ring, Bartholin's and Skene's glands
  Vulvar atrophy, vulvar dystrophy, vulvar vestibulitis, HPV infection
  Retract clitoral hood and expose clitoris
  Examine posterior fourchette and hymenal ring
- Bimanual vaginal examination

Palpate rectovaginal surface, levator muscles, vaginismus, bladder/urethra
Episiotomy scars, strictures, vaginal adhesions, vaginal atrophy, vaginal pH
Speculum examination and Pap smear
Evaluate for prolapse, vaginal length, vaginal mobility
Perform uterus, adnexa, rectal examination
Rectal disease, vaginismus, levator ani myalgia, IC, UTI
Postoperative or postradiation changes, stricture
Fibroids, endometriosis, masses, cysts

FSD: Diagnostic Testing

- Vulvoscopy
- Perineometry
- Biothesiometry
- Ph testing/ Microscopy
- Doppler flow studies

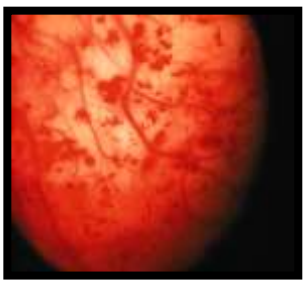
Value of Intravesical Anesthetic Solution to Aid in IC Diagnosis

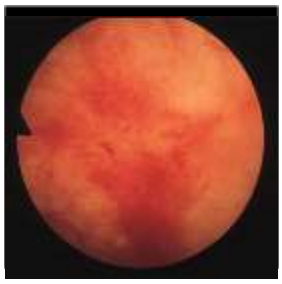
Majority of patients have improved symptoms after anesthetic instillation
Intravesical anesthetic solution may help diagnose bladder origin of pain in patients with suspected IC

Glomerulations as Seen on Cystoscopy

Cystoscopy with hydrodistention may reveal such characteristic features as glomerulations or Hunner ulcers. It is thought, however, that cystoscopy is not a definitive diagnostic tool for IC, because negative findings cannot rule out the diagnosis, and some women with no IC/PBS symptoms have cystoscopic findings suggestive of IC.[1]

1. Macdiarmid SA, Sand PK. Diagnosis of interstitial cystitis/ painful bladder syndrome in patients with overactive bladder symptoms. *Rev Urol.* 2007;9:9-16.





BUT cystoscopy is NOT required for diagnosis and a negative cystoscopy does NOT rule out IC.

Botox and IC

- 67 patients with refractory IC/PBS, mean 42.5 yrs
- BTX group: 44 pts. 200 U (15 pts) or 100 U (29 pts) suburothelial, then HD 2 wks later
- Control group: HD only
- ICSI ↓ in all groups
- 3 mo: VAS ↓, Functional and cystometric bladder capacity ↑, significant only in BTX group
- 6 mo: 71 % of BTX group moderate to marked improvement on GRA
- 12 and 24 mo: BTX 55% and 30% success vs Controls 26% and 17% (p=0.002)
- Retention: 200u-47%, 100u-10%

Getting Sexual with CPP

Management

- Treat pain generators
- Explore alternatives to sexual intercourse
- Different coital positions
- Limit thrusting time to five minutes

- Pre-medicate with anti-spasmodics and/or muscle relaxants
- Use hypoallergenic non-irritating artificial lubrication
- Pre and post coital voiding
- Post coital application of ice packs

Dilators

- Daily insertion training is used to facilitate intercourse
- Discuss sexual positioning (limit stress on affected muscle groups)
- GOAL: stabilization of spasm & return of sexual function

FSD Rx: Topical Treatment

Estrogen

- Introital cream qhs-qohs (Premarin cream et al)
- Intravaginal cream 1-4 gms. / wk.
- Intravaginal tabs 1-2 / wk.
- Ring therapy q 3 mos

Testosterone (off label)

- Testim 1% gel or Intrinsic Patch (can also use Androgel)
- Monitor FAI (TT ng/dl x 3.47 = nmol.L divided by SHBG nmol/L=FAI) Monitor q 10-12 weeks
- NL values: FAI 2.0-3.0 (ages 30-49) 3.7-4.9 (ages 20-29)

The emerging role of BPS in the male population

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Interstitial Cystitis and Bladder Pain Syndrome (IC/BPS) are considered primarily disorders of women. While their occurrence in men has never been denied, the subset of men with IC/PBS is understudied both for specific diagnostic criteria and response to therapy. Older men with lower urinary tract symptoms (LUTS) are typically diagnosed as having BPH and younger men and those with pelvic pain are usually diagnosed with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). To be clear, these are distinct disorders; the prostate can be a pain generator independent of the bladder and not every CP/CPPS patient really IC/BPS. Nevertheless, certain bladder centric symptoms do suggest IC/PBS in men with pelvic pain. These include significant LUTS (absent in about half of CP/CPPS patients), suprapubic tenderness and pain that is worse with bladder filling and that improves with emptying. We use the UPOINT clinical phenotyping system for guiding therapy in both CP/CPPS and IC/BPS and indeed therapies are the same for all domains except for Organ Specific. A diagnosis of IC/BPS in men does open therapeutic options to include intravesical therapies, botulinum toxin, pentosan polysulfate, cyclosporine and fulguration of Hunner's ulcers. In our experience men are less likely to respond to intravesical DMSO based cocktails or PPS but are more likely to respond to amitriptyline and cyclosporine. Nevertheless, a multimodal phenotype driven approach can be successful in most men once the appropriate diagnosis is made.

7 - Failings In Standardisation And Guidelines

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The aim of standardisation and guidelines is not only to further scientific research and international multi-centre collaboration, but also to improve clinical diagnosis, treatment and ultimately all aspects of the quality of life of the patient. This includes facilitating eligibility for reimbursement of treatment, claiming social security, unemployment and disability benefits and entitlement to all kinds of social services and care, many of which may have an impact on the entire family not just the patient.

However, in recent decades, guideline and classification committees have tended to go over the heads of patients and their organisations, excluding them from any meaningful discussion, and at most consulting them at the very end of the decision-making process in order to rubber stamp their document as "patient-approved". This has also been the case in the field of chronic pelvic pain syndromes, including interstitial cystitis/bladder pain syndrome where a plethora of terms and definitions has led to a breakdown in international communication and has even been to the detriment of the patient in practical terms. However, the patient is also affected if research takes a wrong turning and groups of patients are excluded.

Patient organisations are experts on the challenges and issues facing patients in their daily lives and through their contacts with hundreds and even thousands of patients have a wide view of the whole spectrum of symptoms and the chain of developments from A to Z. This means that they can provide standardisation and guideline health professionals with supplementary information, thereby helping to create a comprehensive picture of each disease and disorder and everything it involves in the widest sense.

Official recognition of a condition is vital, so coding must be correct and uniform across all authorities. Potential problems must be anticipated. However, this cannot be achieved if different societies with their different guidelines, taxonomy and standards committees produce different terminology and definitions, often with little or no evidence base, while the International Classification of Diseases (ICD) produces its own variations on terminology and definitions which may directly affect the patient.

Furthermore, living as we do in a world rapidly becoming entirely dependent on electronic systems, we need to ask ourselves whether health professionals engaged in standardisation and guidelines have sufficient knowledge of coding, electronic systems and ICD to avoid pitfalls which may ultimately cause harm to the patient? If they don't, who does? Is sufficient thought being paid by standardisation and guideline groups to this aspect? Is too much attention being paid to pet theories rather than to the practical consequences for the patient? How can potentially detrimental consequences be anticipated well ahead rather than being realised when it is too late and the patient discovers that his/her treatment is no longer being reimbursed by authorities or insurance companies who will take any opportunity to cut costs in today's climate of economic crisis? Should guideline and standardisation committees ensure that they have the possibility to consult experts in the field of coding and electronic systems? And should the World Health Organisation (WHO) be doing more with its ICD to capture a comprehensive global view rather than the limited viewpoint of just a few participants? A study is needed to take a worldwide view and see how differences can be reconciled so as to create a workable system for the benefit of both the patient and meaningful global research and databanks.

8 - The Effect of Apical Prolapse Repair on Bladder Pain

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Introduction and aim of the study

Bladder pain can have a devastating impact upon women's lives. We wanted to explore the relationship between uterovaginal prolapse operations and bladder pain. We identified 62 cases who have had sacrocolpo-hysteropexy (SCP/SHP) and 82 patients who have had sacrospinous fixation (SSF) in our unit over a 3 year period (N=144). Most of our patients routinely fill in ePAQ (electronic pelvic assessment questionnaires) preoperatively and postoperatively. The symptom examined in this study is the "Pain" symptom in the "Bladder Domain".

Materials and methods

Pre-operative scores were compared with post-operative scores at 3 months.
Fisher exact tests was used.

Results

80 patients had completed pre and post operative bladder pain scores (80/144= 55% had bladder pain).

Operation	Improved	Same	Worse
SCP/SHP (n=37)	12	20	5
SSF (n=43)	15	23	7
Total (80)	27/80 (37%)	43 (53%)	12 (15%)

There was no difference between the two operations (P 0.878)

Interpretation of results

Around half of the patients will have no change in bladder pain following prolapse surgery, but in the other half; two thirds seem to experience improvement and one third experience deterioration in their bladder pain. The absence of a control to assess the natural progression of pain in this cohort is a weakness in this study.

Conclusions

Bladder pain seems to be common in patient with prolapse and surgical treatment on prolapse may have a mild positive effect on it.

9 - Gastrointestinal symptoms, quality of life, and impact of nutritional therapy in women with Bladder Pain Syndrome/Interstitial Cystitis: similarities and differences with Irritable Bowel Syndrome

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Introduction and aim of the study

Subjects with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) often complain of gastrointestinal symptoms. These are the same symptoms presented by subjects with Irritable Bowel Syndrome (IBS). In this study, we carried out a comprehensive analysis of symptoms and quality of life of female subjects with BPS/IC + gastrointestinal symptoms and female subjects with IBS.

Materials and methods

We enrolled 10 women without BPS/IC + gastrointestinal symptoms and 10 women with IBS. Forty women without these diseases were used as healthy controls. Enrolment took place at

our Outpatient Clinic from December 2014 to May 2015.

Results

Although the spectrum of symptoms was very similar between the two groups of patients, quality of life was significantly more compromised in subjects with BPS/IC + gastrointestinal symptoms than in people with IBS. This was associated with a longer time-frame between the onset of symptoms and the diagnosis, a higher number of prescribed medications, and a more frequent prescription of antidepressants, non-steroidal anti-inflammatory drugs, and GABAergic medications. Subjects with PBS/CI + gastrointestinal symptoms had lower EQ-VAS score, increased levels of anxiety and depression, and a lower self-esteem and ability to face difficulties.

We also evaluated the impact of a personalized nutritional approach on gastrointestinal symptoms and quality of life of women with BPS/IC, compared to women with IBS. Both subjects with BPS/IC + gastrointestinal symptoms and subjects with IBS displayed substantial benefits in response to this nutritional approach, both in terms of symptom complains and scores of quality of life. However, such beneficial effects were significantly more pronounced in the group of women with BPS/IC.

Interpretation of results

Subjects with PBS/IC and gastrointestinal symptoms have a quality of life that is even more compromised than subjects with IBS and may take advantage of an individualized nutritional therapy.

Conclusions

Subjects with PBS/IC merit a multidisciplinary approach that includes the gastroenterologist and the nutritionist.

10

10 - Central sensitization in Bladder Pain Syndrome

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Background

Central Sensitization (CS) has been proposed as a pathophysiological mechanism to explain the chronic pain related to Fibromyalgia, Chronic Fatigue, Irritable Bowel Syndromes (IBS), and Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC), representing an abnormal state of responsiveness or increased activation of the nociceptive system. CS is characterized by allodynia (painful response from normally non-painful stimulus), hyperalgesia (increased sensitivity to pain), expansion of the receptive fields of neurons, and unusually prolonged pain sensation persisting after the stimulus has been removed. Several studies have demonstrated that CS is associated with several changes in the properties of neurons in the central nervous system including alterations in membrane excitability, reduction in inhibitory transmission, and increase in synaptic efficacy. Aim of this study is to analyze the impact of CS in BPS in relation to the disease duration.

Methods: Patients with BPS/IC according to ESSIC Criteria, were enrolled from July 2014 to July 2015, filled in the Central Sensitization Inventory (CSI), a questionnaire containing 25 statements related to the current health symptoms (each item is measured on a 5-point temporal Likert scale, with the cumulative score ranging between 0-100), and a part including the description of other syndromes related to CS previously diagnosed. The cutoff for a normal CSI

is considered 28.9+13.5 (+SD). The relation between the CSI score and the delay of the diagnosis, from the onset of the symptoms, has been studied with Pearson's test.

Results

Forty-three patients (2 men and 41 women, age 48+14 years, mean + SD), were enrolled in the study. The delay between the onset of symptoms and diagnosis of BPS was 11.6 (+9.6) years (range 0-37 years). The CSI score was 74.7+13 (range 46-97). The correlation between CSI score and the years of disease was 0.45, and every year of disease resulted related to a worsening of 0.5 points at the CSI. Each patient presented one-three additional diseases related to CS. The comorbid conditions observed were: psychological disturbances (46%), IBS (18.6%), fibromyalgia (12%), headache (12%), cervical spinal injuries (5%), and restless leg syndrome (5%). The number of these associated diseases increased in the time (r=0.37).

Conclusion

CS appears a pathological mechanism detectable at the beginning of the disease in BPS/IC patients, with a greater level at onset of symptoms in comparison with the normal population. This result could be a predisposing factor to other diseases related to CS. The delay in the diagnosis and the absence of a early treatment could facilitate the onset of other diseases characterized by CS.

Mayer TG, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract 2012;12:276-85. doi:10.1111/j.1533-2500.2011.00493.x.

11 - Who does the patient meet before the diagnosis of bladder pain syndrome?

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Background

The Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) is a chronic inflammatory condition of the bladder characterized by pelvic pain, urinary urgency and frequency and a typical cystoscopic findings with hydrodistension under anesthesia. Chronic pelvic pain associated to the BPS/IC is a typical case of neuropathic pain. Diagnosis and management of this syndrome may be difficult, and patients can meet several practitioners or unprofessional subjects before receiving a diagnosis. The aim of the present study is to evaluate the different specialists consulted by the patients before the diagnosis of BPS/IC.

Methods

43 patients with BPS/IC recruited from July 2014 to July 2015 at the MRCIC in Catholic University and CRND in La Sapienza University of Rome, filled in a questionnaire to investigate the specialists and the subjects who met the patients before the diagnosis of BPS and the treatments prescribed. The absolute frequency of tag occurrence is visualized with font size.

Results: 43 patients (2 men and 41 women, age 48+14 years, mean + SD), were enrolled in the study. The delay between the onset of symptoms and diagnosis of BPS was 11.6 (+9.6) years (range 0-37 years). Globally the patients met at least seven different practitioners-unprofessional subjects before the diagnosis, and at least eight treatments were prescribed. A correlation between the number of practitioners-unprofessional

subjects/treatments and the length of the disease was evidenced (r=0.49; p<0.05). Specifically, patients consulted the following specialists: general practitioner (100%), gynecologist (46%), surgeon (39%), nutritionist (35%), urologist (30%), gastroenterologist (25%), physiotherapist (28%), anesthesiologist (23%), rheumatologist (11%), and psychiatrist (11%). The main prescribed treatments were: antiepileptic drug (18%), homeopathic therapies (18%), natural therapies (16%), psychotherapist (16%), antidepressant drugs (49%), invasive surgery (37%), massages (23%), acupuncture (25%), muscle infiltrations (21%), contraceptives (14%), biofeedback (9%), meditation (5%), and TENS (4%).

Conclusion

Our patients met different health operators, both practitioners and unprofessional subjects, before the diagnosis of BPS/IC. The difficulty and delay in diagnosis can expose the patient to the risk of unnecessary and expensive treatments.

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12 - Safety and Efficacy of AQX-1125 in Interstitial Cystitis/Bladder Pain Syndrome - Results of the Phase 2 LEADERSHIP Trial

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Introduction and Objectives: AQX-1125, a novel SH2-containing inositol-5'-phosphatase 1 (SHIP1) activator represents a potential therapy for bladder pain syndrome (BPS). This 6-week randomized, double-blind, placebo-controlled Phase 2 trial assessed the safety and efficacy of AQX-1125 on average daily bladder pain and in standardized BPS questionnaires.

Methods: Women with BPS, having cystoscopic evidence of inflammation within 3 years and a baseline mean pain score of ≥5 were randomized to daily AQX-1125 or placebo for 6 weeks. Daily average and maximal pain scores and urinary frequency were recorded by e-diary and in the clinic. O'Leary-Sant Symptom and Problem Indices (ICSI/PI), Bladder Pain IC Symptom Scale (BPIC-SS) and Short Form 12 Health Survey (SF-12v2) questionnaires were administered. Safety data was collected through 6 weeks treatment and 4 weeks follow up.

Results: 69 women were randomized to AQX-1125 (n=37) and placebo (n=32). Mean age (52.6 years), weight (71.5 kg) and duration of BPS at diagnosis (69.4 months) were balanced between arms. At 6 weeks, the daily average pain score was reduced by 2.4 points (AQX-1125) versus 1.4 points (placebo) (p=0.061 ANCOVA). AQX-1125 significantly improved ICSI with a reduction of 3.7 points versus 1.3 on placebo (p=0.005) and ICPI with a reduction of 3.5 versus 1.5 points (p=0.015). Maximum pain and BPIC-SS results will also be presented. AQX-1125 was well tolerated with no SAEs reported. Adverse event rates were similar between AQX-1125 (51.4%) and placebo (78.1%).

Conclusions: Women with moderate to severe BPS treated with AQX-1125 reported greater reduction in bladder pain and symptoms at 6 weeks, compared to placebo. AQX-1125 was well tolerated. This compelling data supports continued development of AQX-1125 for BPS.

The functional assessment: Urodynamic evaluation

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Filling cystometry is helpful in overactive bladder (OAB) for diagnosing detrusor instability as IC and OAB may coexist in 14% of pats. This might have implications for treatment. In males, bladder outlet obstruction (BOO) can be a differential diagnosis . Therefore, it is recommended to perform filling cystometry with a filling rate of 50 ml/s (to comply with the revised PotassiumTest - see below) to look for instability, volume at first desire to void and cystometric capacity. In females, flowmetry, post void residual urine volume and pressure-flow study are optional. In males, a flowmetry should be done in all, and if maximum flow rat < 20 ml/s a pressure-flow study and measure of residual urine volume should be done. The revised Potassium Test has shown prognostic value in bladder irrigation studies , but is considered optional. If performed it should be performed according to Daha et al. . A recent amendment of AUA guidelines confirmed the precise roles of Urodynamics on the evaluation of IC/BPS pats. (see table)

Modified KCl test:

comparative assessment of maximum bladder capacity A Foley balloon catheter (14F) is inserted and the bladder drained. Instill into the bladder 500 ml saline (0.9%) at a rate of 50 ml/min via an infusion set until the maximum capacity is reached. Drain the bladder and measure the saline filling volume. Repeat the instillation and measurement with 500 ml 0.2 M potassium chloride at a rate of 50 ml/min (taking care that filling lines are emptied of all saline before KCl instillation), and calculate the filling volume difference. A difference in bladder capacity > 30% is considered positive. Besides reduction of bladder capacity with 0.2 M KCl there is a stronger feeling of urgency in IC patients compared to the saline filling, which is also clinically relevant.

Role of Urodynamics in the diagnosis of BPS/IC

indications

- to distinguish BPS/IC symptoms from OAB
- all pats. with typical Symptoms, sterile urine and:
  - typical Frequency/Volume record Chart
  - nocturia (at least once)
  - capacity <400 ml

Role of Urodynamics in the diagnosis of BPS/IC

Filling Cystometry

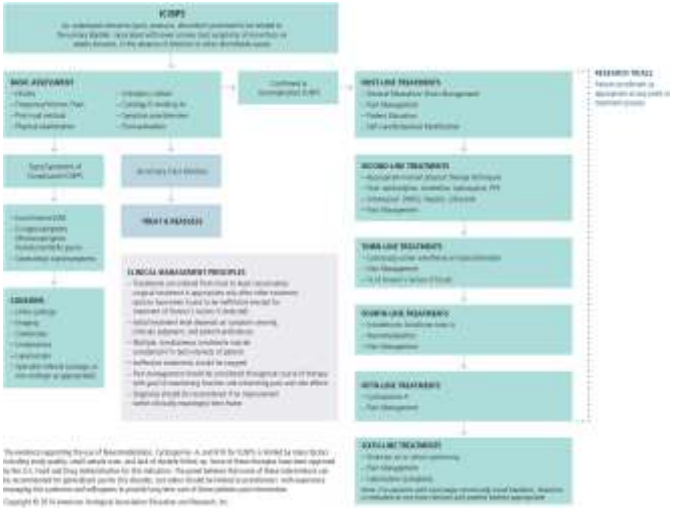
Vol. at first Urge(FD) – ideally < 150 ml
to distinguish between:

Bladder hypersensitivity — *Detrusor overactivity*

OAB in 14% of BPS/IC pats.

Nigro et al. '97

in Bladder Outlet Obstruction EMG or P/F study are required



AUA Guidelines amendment 2015

References

Nigro DA, Wein AJ, Foy M, Parsons CL, Williams M, Nyberg LM Jr, Landis JR, Cook YL, Simon LJ. (1997).Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology.May;49(5A Suppl):86-92.

Primary Evaluation of Patients Suspected of Having Interstitial Cystitis (IC). (2004). J. Nordling, F.H. Anjumb, J.J. Badec et al. European Urology 45 662–669)

Riedl CR, Daha KL, Pflu¨ger H, Hohlbrugger G. Intravesical hyaloronic acid for the treatment of interstitial cystitis. J Urol 2003; 169 (Suppl.).

Daha LK, Riedl CR, Hohlbrugger G, Knoll M, Engelhardt PF, Pfluger H. Comparative assessment of maximal bladder capacity, 0.9% NaCl versus 0.2 M KCl, for the diagnosis of interstitial cystitis: a prospective controlled study. J Urol 2003;170(3):807–9.

P.M. Hanno, D. Erickson, R. Moldwin et al. (2015). Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome: AUA Guideline Amendment. J Urol. Vol. 193, 1545-1553.

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Biomarkers: not yet ready for prime time

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What is the value of a "diagnostic test" in what is essentially a clinical syndrome defined by a symptom complex? If a patient has chronic pain associated with the bladder for several months in conjunction with any urinary tract symptomatology in the absence of a discernable cause, we diagnose bladder pain syndrome. The patient is telling us the diagnosis much as a male who is unable to have sexual intercourse makes the diagnosis of sexual dysfunction. This is not to say that establishment of a valid diagnostic marker would not be a major advance in our understanding of BPS. Just as with phenotyping, it will be important largely to the extent that it can predict prognosis in a given group of patients, predict response to a specific therapy in biomarker positive patients, and/or help us to rule out between competing causes of the patient's symptoms where the diagnosis is in doubt or might have dual etiologies. Ultimately the hope is that a biomarker may enable us to stratify patients with the symptom complex in such a way that treatments will be specific to the specific cause reflected in the marker. As various causes are identifiable, the diagnosis of BPS may itself become a rarity, much like what has happened to "acute urethral syndrome". As pointed out by Fry (Fry et al 2014) identification of biomarkers for lower urinary tract disorders is difficult as such disorders are many and various, from overactive bladder to bladder pain syndrome, to detrusor over-activity, to outlet obstruction. The disorders are often based on subjective symptoms rather than objective clinical measures and are multifactorial in origin. Identification of a biomarker requires a hypothesis-driven approach rather than the serendipitous identification of a suitable entity. Whether the approach of urinary metabolite profiling combined with computational analysis (Wen et al 2014) will be useful seems questionable. In 2015, the only biomarker that is clinically useful is the presence of Hunner lesions on endoscopy, pathology on bladder biopsy consistent with a Hunner lesion, or the surrogate finding of elevated nitric oxide in patients with symptoms of BPS in the absence of other etiologies. One can predict that based on pathologic findings, endoscopic findings, and response to therapy, the patient with Hunner lesions will be categorized as having a specific urologic disease and fall from the bladder pain syndrome group. Our goal should be to discover other markers that would better enable treatment of different patient groups and aid pharmaceutical companies in their quest for new, rational therapies. In these cases, the biomarker can serve as a surrogate endpoint for results of treatment and may help eliminate the huge placebo effect that makes clinical studies so challenging. As Kuo has recently reviewed (Kuo 2014), markers that have been the focus of the most research are antiproliferative factor, epidermal growth factor, heparin-binding epidermal growth factor-like growth factor, glycosaminoglycans and bladder nitric oxide. Inflammatory mediators in the urine and serum have been studied. While subepithelial mast cell distribution is characteristic of bladder pain syndrome with Hunner lesions, it is not really a necessary or useful marker at this time. Gamper et.al. (Gamper et al 2015) did not find that detrusor mastocytosis is useful in distinguishing non-Hunner BPS from overactive bladder or asymptomatic patients. We don't really need a marker to distinguish asymptomatic patients from BPS, and thus come full circle in the argument.

Fry, C.H., Sahai, A., Vahabi, B., Kanai, A.J. & Birder, L.A., 2014, What is the role for biomarkers for lower urinary tract disorders? ICI-RS 2013, Neurourology and urodynamics.

Gamper, M., Regauer, S., Welter, J., Eberhard, J. & Viereck, V., 2015, Are mast cells still good biomarkers for bladder pain syndrome/interstitial cystitis? The Journal of urology.

Kuo, H.C., 2014, Potential urine and serum biomarkers for patients with bladder pain syndrome/interstitial cystitis, International journal of urology : official journal of the Japanese Urological Association, 21 Suppl 1, pp. 34-41.
Wen, H., Lee, T., You, S., Park, S.H., Song, H., Eilber, K.S., Anger, J.T., Freeman, M.R., Park, S. & Kim, J., 2014, Urinary Metabolite Profiling Combined with Computational Analysis Predicts Interstitial Cystitis-Associated Candidate Biomarkers, Journal of proteome research.

Cysto-hydrodistension: the way I do it - ESSIC proposal

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The role of cystoscopy in painful bladder conditions has been debated. Until about forty years ago, cystoscopy and hydro-distension was a mandatory step in the investigation. Later the definition of the generic concept changed to encompass a variety of painful conditions, including many patients without bladder inflammation or distinct cystoscopic changes, while the original denomination interstitial cystitis (IC), which indicates deep-going bladder inflammation, was kept unchanged. Cystoscopy became an optional step in the work-up. The attitude has changed recently and there is almost general agreement that there are separate phenotypes, related by similar symptoms and a chronic course. This is based on the fact that there are unquestionable differences between entities in terms of cystoscopic features, age at onset, histopathology, complication patterns and response to various treatments (1) as well as associated symptoms.

So today, much owing to the work of the ESSIC (2,3), cystoscopy combined with bladder distension during anesthesia has regained its role to separate phenotypes of bladder pain syndrome (BPS) including IC. Because of the historical development mentioned above, the urological and gynecological communities of today's knowledge on how to identify a Hunner lesion is not up to the mark, though, and that is still limiting research as well as clinical practice. The ability to identify the various features of the lesion is of paramount importance to get to the correct diagnosis. This presentation will describe our routines and some relevant findings, like the typical circumscript mucosal areas and their reaction to distension. In this context, it should be noted that what was called "Hunner's ulcer" is not a persistent chronic ulcer but rather a distinctive inflammatory lesion with a characteristic central fragility, presenting a deep rupture through the mucosa and submucosa when provoked by bladder distension: the term should preferrably be "Hunner lesion".

Other varying endoscopic presentations indicate differences, so far of obscure significance. For example, the clinical and therapeutic implications of epithelial changes like glomerulations and mucosal cracks, if any, remain to be determined. Detection of relevant changes is certainly a matter of attention, training and technique and additional means of identification may be helpful and are needed. Narrow band imaging (NBI) is a technique under evaluation with a potential to increase the detection rate of lesions provoked by hydro-distension (4).

It demonstrates neovascularization following overexpression of angiogenetic factors. This technique is to be illustrated in our presentation.

The anesthetic bladder capacity registered at hydro-distension is a parameter of importance, since a reduced capacity together with other characteristics is a further indication of classic IC with Hunner lesions as being a destructive inflammation that can produce a progressive reduction of anesthetic bladder capacity over time and result in bladder contracture at end-stage. This is all but unheard of in other presentations of BPS.

1. Peeker R, Fall M. Towards a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. J Urol. 2002;167:2470-2.
2. Nordling J, Anjum F, Bade J, Bouchelouche K, Bouchelouche P, Cervigni M, et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol. 2004;45(5):662-9.
3. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008;53(1):60-7.
4. Ueda T, Nakagawa M, Okamura M, Tanoue H, Yoshida H, Yoshimura N. New cystoscopic diagnosis for interstitial cystitis/painful bladder syndrome using narrow-band imaging system. Int J Urol 2008;15(12):1039-43.

Is it possible to histologicallay diagnose Classic IC/Essic 3c Hunner's disease?

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Clinical information and deep bladder biopsies are essential in order to histologically diagnose classical IC and separate this condition from other forms of cystitis with similar clinical conditions like non-ulcerative interstitial cystitis. Other confusable disease might be chronic follicular cystitis, eosinophilic cystitis, tuberculous cystitis, metaplastic conditions and carcinoma in situ.

Light microscopic features for classical IC should be denudation of urothelium, signs of ulcerations like granulation tissue, fibrin and neutrophils. There is chronical inflammation with lymphocytes and plasma cells. The detrusor muscle shows fibrosis separating the smooth muscle bundles.

Staining of mast cells with the antibody Mast cell Tryptase, to detect mast cells in the detrusor muscle, is important and most classical IC show a number of mast cells above 40 per mm^2 more often up to 60-100 per mm^2 using a grid.

The non-ulcerative interstitial cystitis sharing similar symptomatology and same chronic course show a different microscopic picture. The mucosa is almost normal and the urothelium is mostly intact. The inflammation might be sparse but sometimes there could be more of a follicular chronic inflammation. There is only a slight fibrosis and the mast cell count in the muscle detrusor is low.

If the pathologist gets adequate clinical information and adequate deep biopsies with several fragments of the detrusor muscle there is a possibility to separate the above conditions with sometimes similar clinical symptoms. If the pathologist then use Mab Mast Cell Tryptase and a grid, the diagnose of classical interstitial cystitis may be reported.

The incidence of BPS in the Mediterranean area

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Introduction

Interstitial cystitis [IC], or bladder pain syndrome [BPS], is not a prevalent condition but has a significant adverse impact on the quality of life. IC is more common in women than men and therefore is likely to be encountered in both Gynaecological and Urogynaecological practice. In some Mediterranean women, the suffering is in silence because women do not complain about the symptoms or do not know that it can be cured.

Objective

To review the incidence and prevalence of IC amongst women in the Mediterranean region and describe the possible barriers to healthcare access in women with this condition.

Method

A review of the English language literature.

Results

There was only one study published from Turkey about the community prevalence of IC in women. The findings supported the higher than expected prevalence of increased potassium sensitivity, which is a reliable indicator of IC, in a fixed female population. Known barriers of access to healthcare in Mediterranean women with chronic pelvic pain and lower urinary tract symptoms include cultural factors and external barriers namely inadequate health care facilities, inconvenience of consultation, low expectations from health care and incurred service costs.

Conclusion

The true community-based prevalence of IC in women is unknown in most Mediterranean countries and therefore health care planning is not possible. Urogynaecologists are the perfect women health care providers to lead public health efforts for studying and reducing the burden of IC in Mediterranean women.

The "coating" problem and its management

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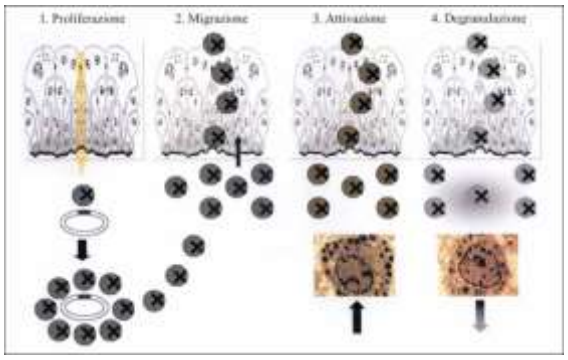
INTRODUCTION

A large body of evidence supports the notion that activation of mast cells and disruptions in the bladder permeability barrier are the key events in the bladder inflammation associated with BPS. The intravesical route offers reasonable adjunctive therapies for immediate symptom relief during symptom flare up.



(from G. Tajana & M.Cervigni: Bladder Pain Syndrome: A guide for Clinicians.Springer 2013)

Instillations of drugs into the bladder create a high concentration of drugs locally at the disease site without increasing systemic levels, which can explain the low risk of systemic side effects.

DIMETHYL SULFOXIDE (DMSO)

DMSO has long been used as a therapeutic agent for BPS. Its mechanism of action, however, has not been clarified. In a RCT Peeker et al reported that frequency and pain were improved in ulcer-type BPS patients, although no improvement was observed in maximum bladder capacity . In a non-RCT Perez-Marrero et al reported that 53% of the patients showed remarkable improvement in subjective evaluation (placebo 18%), and 93% in objective evaluation (placebo 35%). After instillation of DMSO, most pats recognize a garlic-like odour, which disappears within a day.

BACILLUS CALMETTE-GUERIN (BCG)

Peters et al conducted a RCT double blind study evaluating the efficacy of intravesical BCG showing a 60% improvement compared to 27% placebo response with good long-term results at 27 months. A recent NIDDK-sponsored RCT demonstrated benefit in 21% of the BCG group compared to 12% in the placebo group (p=0.062). In a crossover trial BCG vs DMSO , none of the patients improved on BCG at first treatment, whereas 7 improved using DMSO.

RESINIFEROTOXIN

During the last years this drug has also been used for the treatment of BPS. Payne et al. conducted the largest RCT that showed single administration of RTX at doses of 0.01 mM to 0.10 mM did not improve overall symptoms, during 12 weeks follow-up.

SUBSTITUTION THERAPY

Glycosaminoglycans (GAGs) are polysaccharides synthesized by urothelial cells where they reinforce the surface and form an additional permeability barrier; in this way GAGs reduce the direct contact of urine with the urothelium. GAG deficiency has been suggested as a primary cause of BPS and GAG substitution concepts have been obtained a predominant position in BPS therapy.

Pentosanpolysuphate (PPS)

Oral administration of PPS is a well-established first-choice treatment. There is still poor evidence concerning the results of the intravesical instillation therapy. In a RCT, Bade et al found benefit in 4 patients out of 10 on PPS versus 2 of 10 on placebo. In a prospective, uncontrolled, open-label study, 29 BPS patients received 300 mg PPS intravesically twice a week for 10 weeks and thereafter a voluntary maintenance therapy once a month. Complete response was observed at 12 months after treatment in14% of pats respectively. In most patients, benefits last a short time and required sustainment therapy.

HEPARIN

Kuo reported that the Int. Prostate Sympt. Sc., as well as bladder capacity, improved significantly. According to the report by Parsons et al symptoms were reduced in 56% of patients treated 3 times weekly for 12 weeks. However, there is no RCT to give conclusive evidence.

HYALURONIC ACID

Morales et al. reported a 71% partial or complete response to treatment with HA after 12 weeks, with a subsequent relapse after 24 weeks . A lower response rate of only 30% was demonstrated by another author on a small group of PBS/IC patients, achieving improvement in both pain and frequency.

CHONDROITIN SULFATE (CS)

Steinhoff et al used CS in 13 pats with BPS, 6/13 (46.2%) showed a good response, and 1/13 (7.7%) showed no response . In a multicenter, open-label study Nickel et al showed that of the 53 enrolled pats at 24 weeks, 60% were responders. There was a statistically and clinically significant decrease in the mean symptom and bother scores from baseline at 10 weeks and 24 weeks ($P < 0.001$).

Hyaluronic acid plus chondroitin sulfate (HA+CS)

To maximise the potential for urothelial restoration HA 1.6% and CS 2.0% (Ialuril®) were combined for intravesical therapy in the course of an open-label, uncontrolled study, in 23 patients with BPS. There was significant symptomatic improvement for pats with weekly bladder instillations administered for 20 weeks, then monthly for 3 months, with a mean f-u for another 5 months . A long-term evaluation was carried out with the same combination of agents administered intravesically weekly for 12 weeks and then monthly up to 3 years. There was a sustained improvement in symptoms still apparent at 3 ys. f-u in pats. affected by BPS/IC unresponsive to previous treatments. More recently a multicenter RCT was carried out on 108 pats. to evaluate the efficacy and tolerability of Ialuril® vs. DMSO. Pain reduction was greater with Ialuril than DMSO (60% vs.48%), the VAS reduction was higher (70,3% vs. 55,6%), as well as the chance of becoming a responder. It was also observed that earlier treatment gave greater clinical and statistical advantage.

CONCLUSION

Different therapeutic strategies are possible for intravesical treatment. GAG replenishment therapy showed promising tendencies in recent research.On the contrary, BCG and RTX do not seem to have any improving effect on symptoms in BPS/IC pats.

REFERENCES

Peeker, R., Haghsheno, M. A., Holmang, S., and Fall, M.: Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer BPS: a prospective, randomized double-blind study. J Urol, 164:1912, 2000.

Perez-Marrero, R., Emerson, L. E., and Feltis, J. T.: A controlled study of dimethyl sulfoxide in BPS.J Urol, 140: 36, 1988.

Sant, G. R.: Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of BPS. Urology, 29: 17, 1987.

Peters, K. M., Diokno, A. C., Steinert, B. W., and Gonzalez, J. A.: The efficacy of intravesical bacillus Calmette-Guerin in the treatment of BPS: long-term followup.J Urol, 159: 1483, 1998.

Mayer R, Propert KJ, Peters KM et al: A randomized controlled trial of intravesical bacillus calmette-guerin for treatment of refractory BPS. J Urol 2005; 173: 1186-1191.

Peeker R, Haghsheno MA, Holmang S, Fall M: Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer BPS: a prospective, randomized double-blind study. J Urol 2000; 164: 1912-1915.

Hurst RE: Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. World J Urol 1994; 12: 3-10

Toft BR, Nordling J: Recent developments of intravesical therapy of painful bladder syndrome/BPS: a review. Curr Opin Urol 2006; 16: 268-272

Bade JJ, Laseur M, Nieuwenburg A, et al. A placebo controlled study of intravesical pentosanpolysulphate for the treatment of BPS. Br J Urol 1997; 79: 168-171.

Daha LK, Lazar D, Simak R, Pfuger H: The effects of intravesical pentosanpolysulphate treatment on the symptoms of patients with bladder pain syndrome/BPS: preliminary results. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19: 987-990.

Kuo, H. C.: Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome andBPS. J Formos Med Assoc, 100: 309, 2001.

Parsons, C. L., Housley, T., Schmidt, J. D., and Lebow, D.: Treatment of BPS with intravesical heparin. BrJ Urol, 73: 504, 1994.

Morales A, Emerson L, Nickel JC (1996) Intravesical hyaluronic acid in the treatment of refractory BPS. J Urol 156:45–48

Porru D, Campus G, Tudino D, Valdes E, Vespa A, Scarpa RM, Usai E (1997) Results of treatment of refractory BPS with intravesical hyaluronic acid. Urol Int 59(1):26–29

Steinhoff G, Ittah B, Rowan S. The efficacy of chondroitin sulfate 0.2% in treating BPS. Can J Urol. 2002 Feb;9(1):1454-8.

Nickel JC, Egerdie B, Downey J, Singh R, Skehan A, Carr L, Irvine-Bird K: A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of BPS. .BJU Int. 2009 Jan;103(1):56-60. Epub 2008 Sep 3.

Cervigni M, Natale F, Nasta L, Padoa A (2008) A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/BPS. Int Urogynaecol J 19:953-947

Cervigni M., Natale F., Nasta L., Mako A. (2012) Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: long-term treatment results. Int Urogynecol J 23:1187-1192

Cervigni M., Sommariva M., Tenaglia R. et al. (2014) A randomized, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulphate vs. dymetyl sulfoxide in women with bladder BPS/IC. Proceedings ICS 2014 RIO in press.

Hyperbaric Oxygen Treatment

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Purpose: We conducted a double-blind, sham controlled study to evaluate the safety, efficacy and feasibility of hyperbaric oxygenation for interstitial cystitis.

Materials and Methods: A total of 21 patients with interstitial cystitis were randomized to 90 minutes treatment in a hyperbaric chamber pressurized with 100% O2 to 2.4 atmosphere absolute for 30 treatments sessions or 1.3 atmosphere absolute, breathing normal air in the control group. Moderate or marked improvement in a global response assessment questionnaire was defined as treatment response (primary outcomes). Secondary measurements included changes of pain and urgency evaluated by visual analog scales, functional bladder capacity and frequency. Changes in the O'Leary-Sant Interstitial Cystitis Index and rating of overall satisfaction with the therapeutic outcome were also reported.

Results: There were 3 of 14 patients on verum and no control patients who were identified as responders ($p \leq 0.05$). At 12-month followup 3 patients (21.4%) still reported treatment response. Hyperbaric oxygenation resulted in a decrease of baseline urgency intensity from 60.2 ± 15.0 to 49.9 ± 35.2 mm at 3 months and decrease of pain intensity from 43.1 ± 20.5 to 31.2 ± 19.8 mm, respectively ($p \leq 0.05$). The Interstitial Cystitis Symptom Index score sum decreased from 25.7 to 19.9 points in patients on verum. Sham treatment did not result in improvement of the baseline parameters.

Conclusions: A total of 30 treatment sessions of hyperbaric oxygenation appear to be a safe, effective and feasible therapeutic approach to interstitial cystitis. In the treatment responders application of hyperbaric oxygenation resulted in a sustained decrease of interstitial cystitis symptoms with a discordant profile regarding the peak amelioration of the various interstitial cystitis symptoms compared with a normobaric, normoxic sham treatment.

The role of surgery

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Bladder Pain Syndrome (BPS) is a chronic and debilitating disease. Major surgical options should be considered only when all conservative treatment has failed. The patient should be informed of all aspects of surgery and understand consequences and potential side effects of surgical intervention.

Hydrodistention

Bladder distension has been used for many years (1) not only as a diagnostic/ classification tool but also for treatment of BPS. Recent literature reports poor results with only a minority of patients reporting a small improvement in symptoms for a relatively short period of time(2;3;4;5). Most studies are retrospective and uncontrolled. Level of evidence 3; recommendation C

Sympathetic and Parasympathetic Denervation

Sympathetic and parasympatheticdenervation is not indicated for BPS

Level of Evidence: 4 Grade of Recommendation: -A (not recommended)

Bowel Surgery

Bladder augmentation-cystoplasty has been commonly used for refractory BPS for 50 years. First reports of ileocystoplasty from 1958 were very promising(6). Later publications were less sanguine with good results varying from up to 100% (7; 8) to 25%(9;10). Cystoplasty is usually done with or without bladder resection.

There is no significant different between different bowels segments with regard to outcome except for gastric tissue substitution which is associated dysuria and persistent pain due to production of acids.

There is some weak evidence that cystoplasty with supratrigonal resection may benefit some selected

patients with end stage ESSIC type 3C BPS. There is no compelling evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy.
Level of Evidence: Level 3; Grade of Recommendation: C

Urinary Diversion with or without Total Cystectomy and Urethrectomy

This is the ultimate, final and most invasive option. It should be used as a last therapeutic resort in selected patients. Techniques include simple or continent urinary diversion. Continent diversion may be preferable for cosmetic reasons in younger patients.
Simple urinary diversion with formation of an ileal conduit is the most common surgical treatment for BPS (11). Initially, diversion can be done without cystectomy and only when bladder pain is persistent, cystectomy may be considered. Bladder de-functionalization alone produced symptom-relief in several reports(12;9;13;14;15).
Relatively good responses to diversion with or without cystectomy have been reported in small series(10;16). It seems that primary cystectomy does not benefit the clinical outcome(17;18)
Urinary diversion with and without cystectomy may be the ultimate option for refractory patients. Continent diversion may have better cosmetic and life style outcome but recurrence of pain in the pouch is a real possibility. Level of Evidence: 3; Grade of Recommendation: C.

1. Bumpus HC. Interstitial cystitis: its treatment by overdistention of the bladder. Med Cl N A 1930;13:1495-8.
2. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn 2005;24(7):638-42
3. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005 Sep;66(3):494-9.
4. Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM, et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol 2007 Feb;177(2):556-60
5. McCahy PJ, Styles RA. Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol 1995;28(4):325-7
6. Goodwin WE, Turner RD, Winter CC. Results of ileocystoplasty. J Urol 1958;80:461-6.
7. von Garrelts B. Interstitial cystitis: thirteen patients treated operatively with intestinal bladder substitutes. Acta Chir Scand 1966 Oct;132(4):436-43
8. Webster GD, Maggio MI. The management of chronic interstitial cystitis by substitution cystoplasty. J Urol 1989 Feb;141(2):287-91.
9. Badenoch AW. Chronic interstitial cystitis. Br J Urol 1971 Dec;43(6):718-21.
10. Nielsen KK, Kromann-Andersen B, Steven K, Hald T. Failure of combined supratrigonal cystectomy and Mainz ileocecocystoplasty in intractable interstitial cystitis: is histology and mast cell count a reliable predictor for the outcome of surgery? J Urol 1990 Aug;144(2 Pt 1):255-8.
11. Gershbaum D, Moldwin R. Practice trends for the management of interstitial cystitis. Urology 2001 Jun;57(6 Suppl 1):119.
12. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978 Oct;12(4):381-92.
13. Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). Journal of Urology 1949;61:291-310.
14. Freiha FS, Faysal MH, Stamey TA. The surgical treatment of intractable interstitial cystitis. J Urol 1980 May;123(5):632-4.
15. Tait L. On the cure of the chronic perforating ulcer of the bladder by the formation of an artificial vesico-vaginal fistula. Lancet 1870;54:738.
16. Webster GD, Galloway N. Surgical treatment of interstitial cystitis. Indications, techniques, and results. Urology 1987 Apr;29(4 Suppl):34-9.
17. Andersen AV, Granlund P, Schultz A et al. Longterm experience with surgical treatment of selected patients with bladder pain syndrome/ interstitial cystitis. Scand J Urol Nephrol 2012;46:284
18. Norus T, Fode M, Nordling J. Ileal conduit without cystectomy may be an appropriate option in the treatment of intractable bladder pain syndrome/interstitial cystitis. Scand J Urol. 2014 Apr;48(2):210-5.

The Interstitial Cystitis Association of America: Lessons Learned Over the Past 30 Years

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In 2014, the Interstitial Cystitis Association of America (ICA) celebrated its 30th anniversary. It has been a very challenging journey. In 1984, IC was generally considered a rare psychosomatic disorder in post-menopausal women. We've come a long way since that time and great progress has been made. In looking back over this period of time, there were seven key reasons why the ICA became so successful: the tremendously dedicated ICA staff, Board of Directors and volunteers; a very strong Medical Advisory Board and participation of many other urologists from across the country and around the world; the media; epidemiology; the ICA's Pilot Research Program; representation in Congress; and a strong working partnership with the National Institutes of Health (NIH). Given the time limitation, I will focus on the importance of the media.

Failings in standardisation and guidelines

Author: Jane M. Meijlink
International Painful Bladder Foundation (IPBF)

The aim of standardisation and guidelines is not only to further scientific research and international multi-centre collaboration, but also to improve clinical diagnosis, treatment and ultimately all aspects of the quality of life of the patient. This includes facilitating eligibility for reimbursement of treatment, claiming social security, unemployment and disability benefits and entitlement to all kinds of social services and care, many of which may have an impact on the entire family not just the patient. However, in recent decades, guideline and classification committees have tended to exclude patients and their organisations from any meaningful discussion, at most consulting them at the very end of the decision-making process in order to rubber stamp their document as "patient-approved". This has also been the case in the field of interstitial cystitis/bladder pain syndrome/hypersensitive bladder where a plethora of terms and definitions has led to a breakdown in international communication and has even been to the detriment of the patient in practical terms.

Patient organisations are experts on the challenges and issues facing patients in their daily lives and through their contacts with hundreds and even thousands of patients have a wide view of the whole spectrum of symptoms and chain of developments. This means that they can provide standardisation and guideline health professionals with supplementary information, thereby helping to create a comprehensive picture of each disease and disorder and everything it involves in the widest sense.

Official recognition of a condition is vital, so coding must be correct and uniform across all authorities. Potential problems must be anticipated. However, this cannot be achieved if different societies with their different guidelines, taxonomy and standards committees produce different terminology and definitions, while the International Classification of Diseases (ICD) produces its own variations on terminology and definitions which directly affect the patient.

Furthermore, living in a world rapidly becoming entirely dependent on electronic systems, we need to ask ourselves whether health professionals engaged in standardisation and guidelines have sufficient knowledge of coding, electronic systems and ICD to avoid pitfalls which may ultimately cause harm to the patients. Is sufficient thought being paid by standardisation and guideline groups to this aspect? Should guideline and standardisation committees ensure that they have the possibility to consult experts in the field of coding and electronic systems? And should the World Health Organisation (WHO) be doing more with its ICD to capture a comprehensive global view rather

than the limited viewpoint of just a few participants? A study is needed to take a worldwide view and see how differences can be reconciled so as to create a workable system for the benefit of both the patient and meaningful global research and databanks.

The Disability and Welfare Reimbursement

Author: Loredana Nasta
Italian Interstitial Cystitis Association / Founded 1995-2015

The Interstitial Cystitis, also called Bladder Pain Syndrome, is defined by ESSIC as an unpleasant sensation of 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 that lasts for more than six months in the absence of infection or other identifiable causes. The description of the disease is always accompanied by terms describing the high negative impact on the quality of life of patients and their families.

The Interstitial Cystitis/Bladder Pain syndrome was neglected and underestimated for decades. Patient organizations have been crucial to sensitize the scientific community, research and governments on the severity of the disease and the need to find solutions to cure it, as well as instrumental in achieving patient's rights in the Health System

The Italian Interstitial Cystitis Association (AICI) was born in 1995 in Rome, ten years after the American association (ICA) and two years after the ICA Germany. As Italy has a different National Health System from other Nations, AICI had to work closely and stimulate the Government and the Institutional Community to achieve rights for patients suffering from Interstitial Cystitis / Bladder Pain Syndrome. The most important goal in the first years of activity was having IC/BPS recognized as Rare Disease in 2001, giving patients a number of facilities and tutelage. Although some countries assume a number of IC/BPS patients above the threshold established for rare diseases of 5:10,000 people, the diagnosis criteria in Italy is quite strict and the data presented in the Italian National Register of Rare Diseases brings a number of diagnoses ascertained and certified well below this threshold, so the disease is still in the National Directory of Rare Disease.

The Recommendations of EU Council (141/00) declaring the Rare Diseases a Public Health Priority Area, considered the rare diseases as chronic life-threatening, highly disabling conditions that affect not more than 5:10000 people in the European Union.

Having implemented these Recommendations in its plans and having the Italian Ministry of Health programmed actions in favor of Women's Health, it has defined Interstitial Cystitis as "high social impact and severely debilitating disease both physical and psychological that affects mainly women in childbearing age compromising pregnancy, and has urged Italian Regions to study specific actions for women's health that include this disease. Today many Italian Regions, mainly in the North of Italy, apply care protocols or recommendations for IC/BPS, describing it's severe symptoms that can make the person affected unable to conduct a normally daily life, including having relationships, family life, school, university and work activities. In many cases the psychological sphere is strongly involved with lack of self-confidence and poor self-image. IC/BPS compromises heavily quality of life that can become very poor, with a severe risk of depression due to loss of sleep, anxiety, stress, sexual dysfunction, panic attacks and difficulty to have normal social relationships, and that can lead to suicidal ideas.

Disability Commissions, that evaluate the percentage of disability in our Country, are unprepared on the clinic aspects of the majority of rare diseases, as they are so many and so heterogeneous, but it gets even more difficult for the "invisible diseases" like IC/BPS. Furthermore in Italy, even though being part of the National Directory of Rare Diseases should guarantee free care and treatment, the reality is very different and

to secure these basic rights to IC patients is very difficult and complex. The actual economic situation in certain areas of Italy, sometimes on the blade of collapse with armored economic health plans, puts the Patients's organization team in the condition of being not only professional experts with a deep knowledge of the IC/BPS in all its clinic aspects, but in the European, National, Regional laws and human rights as well, in order to be accepted in scientific and political round tables.

An IC / BPS patient may not be able to work for 8 hours a day every day, or she cannot carry out certain jobs, or may not be able to work at all. The exemptions of the Italian National Social Security Institution (INPS) for the most common diseases are very restrictive and inadequate for who has a chronic disorder such as IC / BPS. Actions have been done and are pursued to improve awareness and knowledge on rare disease by disability's commissions on these aspects.

The presentation will analyze the current situation, achievements, weaknesses, bottlenecks and future proposals.

An international registry for BPS: a future option or a utopia?

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Setting up an international registry for a disease may be a useful tool for the investigation of many aspects of the disease. Examples are epidemiological aspects and clinical aspects such as natural history, response to treatment, risk factors for complications etc. However, many requirements have to be fulfilled to start a registry that can be divided into legal, safety, technical, scientific, methodological, financial and many other aspects.

The most important part of setting up a registry is defining the research questions that it should be able to answer. However, if these questions are not meticulously defined, a database is useless because as a result the required data are not collected in the right way

On the basis of the research questions, the design of the database for the registry should become clear. Essential research aspects of the registry are not different from any other clinical study and include definitions of what kind of, and how many patients have to be included (on the basis of inclusion and exclusion criteria), how many points in time have to be collected, how the various variable clinical parameters are to be scored, and many more.

It should be realized that several severe methodological flaws are prone to occur such as:

- heterogeneity of the patient populations of different contributing centres may result in spurious statistical results
- heterogeneity of the interpretation of subjective patient data by the researchers
- statistical errors that result from answers obtained to questions that were not defined at the start of the study but on the basis of analysis of the results
- inconsistent data collection, missing values etc.
- loss of patients or even complete centres from follow-up
- diminishing of the relevance of the research questions in long-term studies
- lack of well-defined research questions
- remember GIGO (garbage in, garbage out)

These difficulties may be difficult to overcome but even more difficult today is the protection of the data - that need to be accessible to the participating researchers - to access by unauthorized persons. Privacy and digital data storage are contradictory phenomena!

Conclusion

A registry for a disease is not a goal but an expensive and difficult method. All research questions have to be defined in advance.

ESSIC management of BPS patients: role of ESSIC

Authors: Philip Hanno[1], Jørgen Nordling[2]
University of Pennsylvania, School of Medicine, Philadelphia, PA[1]; University of Copenhagen, School of Medicine, Denmark[2]

In this presentation we will review the ESSIC approach to diagnosis and management of bladder pain syndrome.
As pointed out by Dr. Cervigni in his letter of invitation to this pivotal ESSIC meeting, It is time for the organization to review its diagnostic algorithm and management algorithm in a practical sense, outlining exactly when the provider should suspect BPS and what practical steps are necessary in confirming the diagnosis in the real world (ie those tests and studies that make sense relative to the risks of missing a confusable disease early in the process of diagnosis and related to the risk of another disorder actually being the cause of symptoms in an individual patient). Much of the theoretical work has been done and published, but can be simplified for the clinician on the front line. For example, when is an ultrasound necessary to rule out urolithiasis as a cause of symptoms? When does testing for sexually transmitted disease have to be done to rule out this confusable disorder? When is a gynecologist necessary to consider endometriosis?
In particular, ESSIC needs to make some difficult decisions that directly affect diagnosis and indirectly affect management of BPS.

ESSIC CLASSIFICATION OF BLADDER PAIN SYNDROME TYPES

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

The iconic ESSIC classification may need revision. Should glomerulations (ESSIC type 2) be eliminated as a category at this time. Data compiled by Wennevik and accepted for publication in the Journal of Urology suggests this to be the case. (The role of glomerulations in Bladder Pain Syndrome – A review. Gjertrud E. Wennevik, Jane M. Meijlink, Philip Hanno, Jørgen Nordling).
Should ESSIC 3B and 3C be eliminated from the bladder pain syndrome and recognized as a separate disease entity, perhaps to be referred to as "interstitial cystitis"? Much like urinary infection or radiation cystitis could give symptoms compatible with BPS but are not, is the Hunner lesion indicative of a different disease process that requires different basic science investigations and required pharmaceutical trials and treatment trials that reflect that it is a defined and separate pathologic process? Whether the answer is yes or no, this will require a scholarly paper to argue the merits and an organization like ESSIC is ideally suited for this task.
ESSIC needs to publish a treatment algorithm that is up to date and draws from the experience of its members and the work done by the medical groups around the world that have already published such algorithms. These activities help to keep the organization relevant. ESSIC as a group needs to make its thoughts known to the International Association for the Study of Pain with regard to their classification suggestions for The International Classification of Diseases 11th Revision, due by 2017. Dr. Nordling and Dr. Baranowski have been involved with this effort.
ESSIC needs to continue to recruit new members who are interested in bladder pain syndrome and there is no shortage of basic scientists, health care providers, and pharmaceutical scientists and companies with such an interest.
Courses geared to both specialists and primary care providers around the world should also continue to be an integral part of the ESSIC mission.
Finally, the resources of a large number of interested clinicians and scientists can take advantage of international collaboration and perhaps the new science of crowd-sourcing (the process of obtaining needed services, ideas, or content by soliciting contributions from a large group of people, and especially from an online community, rather than from traditional employees or suppliers).

ESSIC EXECUTIVE COMMITTEE

Jean-Jacques Wyndaele - President | Belgium
Mauro Cervigni - Vice President | Italy
Joop P van de Merwe - Treasurer | Netherlands
Jørgen Nordling - Past President | Denmark
Philip Hanno - Member | USA
Magnus Fall - Member | Sweden

ESSIC MEETINGS

2004 | Copenhagen – Denmark | Jorgen Nordling
2005 | Baden – Austria | Claus Riedl
2006 London - United Kingdom | John Osborn
2007 | Münster – Germany | Arndt van Ophoven
2008 | Rome – Italy | Mauro Cervigni
2009 | Göteborg – Sweden | Magnus Fall
2010 | Antwerp – Belgium | Jean-Jacques Wyndaele
2011 | Moscow – Russia | Andrew Zaitcev
2012 | Porto – Portugal | Paulo Dinis Oliveira
2013 | Kyoto – Japan | Tomohiro Ueda
2014 | Philadelphia – USA | Philip Hanno

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