

Evaluation and treatment of pelvic pain syndrome

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Disclosures

Francisco Cruz has been a consultant, speaker or investigator for the following corporations:

- Astellas
- Allergan
- Bayer
- Boston Scientific
- Ipsen
- Recordati

Agenda

- Disease definition
- Future trends in the evaluation
- Biomarkers
- Treatment

Definition of Bladder pain syndrome in EAU guidelines

- Pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency
- The nature of pain is important :
*Related to the bladder, increasing with bladder content;
Relieved by voiding but returning soon
Located suprapubically, but also radiating to other areas
Aggravated by food or drink*
- Exclusion of confusable diseases as the cause of symptoms,

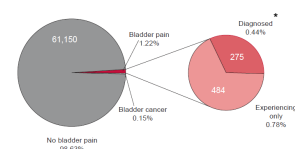
Engeler et al. EAU guidelines, 2018

Bladder Pain Syndrome

- **ICS** : The complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology
- **ESSIC**: Chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder, with at least one other urinary symptom such as urgency or urinary frequency. Confusable diseases as the cause of the symptoms have to be excluded.
- **AUA**: Unpleasant sensation (pain, pressure, or discomfort) perceived to be related to the urinary bladder and associated with lower urinary tract symptoms lasting > 6 weeks in the absence of infection or other identifiable cause

Abrams P et al. NAU 2002, Van de Merwe JP et al. Eur Urol. 2008, ESSIC Annual Meeting 2017.

Prevalence of Bladder Pain in 5 European countries (France, Germany, United Kingdom, Italy, Spain)



- Subjects were more likely to have impaired HRQoL
- Work productivity was greatly impaired
- Subjects with bladder pain utilize more healthcare resources

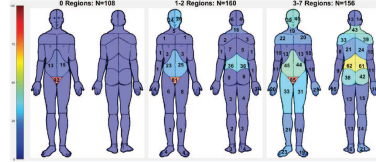
* 440/100.00 adult subjects

Hakimi et al. Urology. 2017

Phenotyping BPS/IC patients

- Unravelling the cause of a disease usually begins with grouping patients with similar symptoms and signs.
- An etiopathogenesis is better recognized in homogeneous groups
- Response to a treatment may be better in certain subgroups

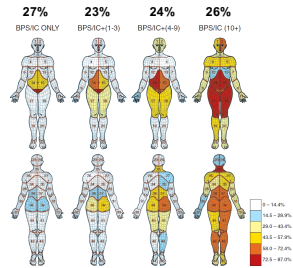
Merely 25% report pelvic pain only, 75% report pain beyond the pelvis



Patients with greater number of pain locations had more **sleep disturbance** ($p=0.035$), **depression** ($p=0.005$), **anxiety** ($p=0.011$), **psychological stress** ($p=0.005$) and **worse quality of life** ($p=0.021$).

Henry Lai et al., J Urol, 2017

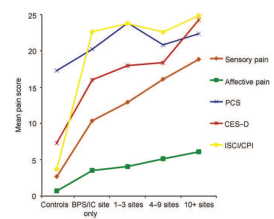
Pain Phenotypes in Female with BPS/IC



315 females participated.

Tripp et al., Eur Urol, 2012

Mean pain scores for each phenotypic pain group



ICSI/ICPI = Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index;
 PCS = Pain Catastrophizing Scale;
 CES-D = Center for Epidemiologic Studies Depression Scale.

Tripp et al., Eur Urol, 2012

O'Leary-Sant Questionnaire

- Q1: During the past month, how often have you had the strong need to urinate with time or no warning?**
- not at all
 - less than 1 time a day
 - about half the time
 - more than half the time
 - always
- Q2: During the past month, how often did you urinate less than 2 hours after you finished urinating?**
- not at all
 - less than 1 time a day
 - about half the time
 - more than half the time
 - always
- Q3: During the past month, how often did you most typically get up at night to urinate?**
- never
 - once
 - 2 times
 - 3 times
 - 4 times
 - 5 or more times
- Q4: During the past month, how often did you experience pain or burning in your bladder?**
- not at all
 - less than 1 time a day
 - about half the time
 - more than half the time
 - always
- Q5: During the past month, how much has each of the following been a problem to you?**
- no problem
 - very small problem
 - small problem
 - moderate problem
 - large problem
- Q6: Getting up at night to urinate**
- no problem
 - very small problem
 - small problem
 - moderate problem
 - large problem
- Q7: Having to urinate with little warning**
- no problem
 - very small problem
 - small problem
 - moderate problem
 - large problem
- Q8: Urinary pain, discomfort, or pressure in your bladder**
- no problem
 - very small problem
 - small problem
 - moderate problem
 - large problem
- Add the number of values of the checked answers:
 Total score: _____

UPOINT Phenotyping the subjects using the Urinary, Psychosocial, Organ-specific, Infection, Neurological/systemic and Tenderness categories

Category	Criterion	Category	Criterion
Urinary	Postvoid residual urine volume >100 ml Nocturia frequency > 2/night Subject complaint of bothersome urgency, frequency, or nocturia	Infection	Confirmed to have significant bacteriuria with typical uropathogenic bacteria in the previous 2 years associated with exacerbation of bladder symptoms and return to baseline symptoms following appropriate antimicrobial therapy
Psychosocial	Clinical depression (or with recent history of depression), anxiety, stress, history of sexual or physical abuse Maladaptive coping mechanisms (e.g., catastrophizing), or problems with social interaction	Neurological/systemic conditions	Vulvodynia Urinary bowel syndrome Ehlers-Danlos Chronic fatigue syndrome Fibromyalgia Low back/leg pain
Organ specific	Pain with bladder recycling (typically pain with bladder filling and temporary relief with voiding) Pain on bladder filling reported with low volumes of irrigation fluid Glomerulonephritis and/or Hasser's lesions noted during cystoscopy (with or without hydrodistension) Typical inflammation confirmed on bladder biopsy	Tenderness of detrusor muscle	Palpable muscle spasm or muscle/tendon tenderness in abdomen, pelvis and pelvic floor

Nickel JC, Shoskes D, Irvine-Bird K., J Urol, 2009

INPUT vs UPOINT

UPOINT is more useful in patients with chronic pelvic pain than in patients with IC/PBS since by definition all patients have the Urinary and Organ specific phenotype

"INPUT":

- I** Infection,
- N** Neurologic/Systemic,
- P** Psychosocial,
- U** Ulcers
- T** Tenderness of Muscles.

Crane, Lloyd and Shoskes et al. Can J Urol, 2018

Genitourinary Pain Index (GUPI)

Female Genitourinary Pain Index

1. How often have you had pain in the area of your bladder or vagina in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
2. How often have you had pain in the area of your urethra in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
3. How often have you had pain in the area of your vagina in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
4. How often have you had pain in the area of your vulva in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
5. How often have you had pain in the area of your perineum in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
6. How often have you had pain in the area of your rectum in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
7. How often have you had pain in the area of your anus in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
8. How often have you had pain in the area of your penis in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
9. How often have you had pain in the area of your testicles in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
10. How often have you had pain in the area of your scrotum in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
11. How often have you had pain in the area of your urethra in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
12. How often have you had pain in the area of your bladder in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
13. How often have you had pain in the area of your vagina in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
14. How often have you had pain in the area of your vulva in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
15. How often have you had pain in the area of your perineum in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
16. How often have you had pain in the area of your rectum in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
17. How often have you had pain in the area of your anus in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
18. How often have you had pain in the area of your penis in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
19. How often have you had pain in the area of your testicles in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always
20. How often have you had pain in the area of your scrotum in the last 3 months?
 - a. Never or rarely
 - b. Often
 - c. Always

Legend:
 0 = Never or rarely
 1 = Often
 2 = Always

Impact on daily tasks and QoL:
 0 = No impact
 1 = Mild impact
 2 = Moderate impact
 3 = Severe impact

Clemens et al. Urology, 2009

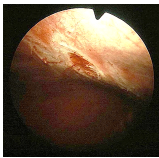
Association of BPS/IC and auto-immune diseases

- Allergies, rheumatoid arthritis, and inflammatory bowel disease (Crohn's disease, Ulcerative Colitis) were significantly more frequent among BPS/IC patients
- Sjögren's syndrome is associated with Hunner's lesion phenotype of interstitial cystitis

Engeler et al, EAU guidelines, 2018

Cystoscopy with hydrodistension

Hunner's lesion
 (fissures and areas of fibrosis that bleed)
 - 20-60% of BPS patients*

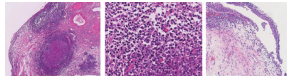


* ESSIC 2017: literature and ESSIC survey

Recent research favours the histological distinction between IC/BPS with Hunner lesions and IC/BPS without Hunner lesions.

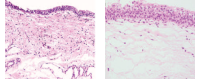
IC/BPS with Hunner's lesions is an inflammatory disorder characterized by pancystitis with B cell abnormalities and epithelial denudation

HIC



IC/BPS without Hunner lesions shows minimal histological changes

NHIC



HIC: Hunner type interstitial cystitis
 NHIC: non-Hunner type interstitial cystitis
 Yukio Homma and Daichi Maeda, Histology and Pathology, 2018

Hunner's lesions and pain intensity measured by VAS

0 1 2 3 4 5 6 7 8 9 10
 no pain extreme pain

Variables	Baseline		P
	Ulcerative BPS/IC N = 10	Nonulcerative BPS/IC N = 14	
Visual analog scale for pain	6.3 ± 0.9	5.6 ± 0.5	ns
Frequency	11.2 ± 2.4	10.3 ± 1.9	ns
Nocturia	5.9 ± 1	4.9 ± 0.5	ns
O'Leary-Sant symptoms Score	16.6 ± 1	15.9 ± 0.8	ns
O'Leary-Sant problems Score	12.6 ± 1	12.5 ± 0.7	ns
QoL (IPSS)	5.8 ± 0.4	5.9 ± 0.3	ns

Printo et al. Urology, 2014

The Role of Glomerulations in Bladder Pain Syndrome

- No convincing evidence was found supporting that glomerulations should be included in the diagnosis or phenotyping of BPS/IC
- Glomerulations do not correlate with symptoms
- Glomerulations are found in patients without BPS/IC

	Has BPS/IC	Does Not Have BPS/IC	Totals
Has glomerulations	558*	213	771
Does not have glomerulations	359	355	681
Totals	917	568	

Sensitivity = 60% (558/917)
 Specificity = 62% (355/568)
 Positive predictive value: 72% (558/771)
 Negative predictive value: 52% (355/681)

Wernevik, Meljirik, Hanno and Nording, J Urol, 2016

ESSIC classification by cystoscopy and biopsy

		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

¹ cystoscopy glomerulations grade II-III
² with or without glomerulations
³ histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or interstitial cystitis fibrosis

Van Der Merwe et al, European Urology 53 (2008) 60-67

Urodynamic testing and Lidocaine

- Lidocaine significantly improves urodynamic parameters in the majority of patients.
- These patients appear to have a peripherally mediated disease state.
- Failure to improve with lidocaine occurred in a sub-group, suggesting a central origin or central component to pain.
- It is suggest that this simple and safe test could be used to stratify patients for research or therapeutic trials.

With the kind permission of Barry O'Reilly, in press

Biomarkers

Neurotrophic-angiogenic agents: NGF, VEGF

Nitric Oxide

Urine and blood Cytokines and Chemokines

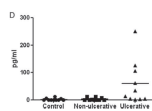
Expression of pain receptors and pain receptor agonists

Agents that insult the urothelium / GAG layer (APF, Cations)

Gene regulating the collagen deposition

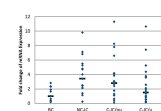
Bacteria and virus

NGF in the urine and bladder of IC patients



Urine, ELISA-Promega kit (n=10)

Tyagi et al, J Urol, 2012



qRT-PCR for mRNA expression in 11 controls, 17 nonclassic and 22 classic IC.

Homma et al, J Urol, 2013

OPEN ACCESS freely available online PLOS ONE

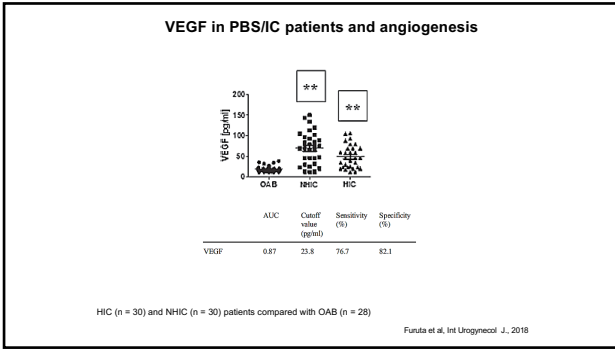
Increased Urine and Serum Nerve Growth Factor Levels in Interstitial Cystitis Suggest Chronic Inflammation Is Involved in the Pathogenesis of Disease

Hsiu-Tzu Liu^{1,2*}, Hsien-Chong Kuo^{2*}
¹Department of Pathology, Baotian Yu Chi General Hospital and the Chi University, Hualien, Taiwan, ²Institute of Pharmacology and Toxicology, The Chi University, Hualien, Taiwan

	Control (n = 28)	IC/BPS(n = 30)	P value
Age (range)	32.6 ± 1.56 (22-55)	51.3 ± 1.87 (22-86)	p < 0.001
Gender	F:17 M:11	F: 26 M: 4	
Urinary NGF (pg/ml)	1.40 ± 0.63 (0.00-13.6)	26.3 ± 11.2 (0.00-270.8)	P = 0.014
Urinary NGF/Cr (pg/mg)	0.02 ± 0.01 (0.00-0.22)	0.69 ± 0.38 (0.00-9.52)	P = 0.011
Serum NGF (pg/ml)	1.90 ± 0.38 (0.00-5.85)	3.48 ± 0.55 (0.00-18.0)	P = 0.015

Data are expressed as mean ± standard error.

Liu and Kuo, PlosOne, 2012



INTRAVESICAL NITRIC OXIDE PRODUCTION DISCRIMINATES BETWEEN CLASSIC AND NONULCER INTERSTITIAL CYSTITIS

YR LOGADOTTIR, INGRID EHRÉN, MAGNUS FALL, N. PETER WIKLUND AND RALPH PERKER*

From the Department of Urology, Sahlgrenska University Hospital, Göteborg, SE, MF, RP, and Department of Urology, Karolinska University Hospital, Stockholm (SE, NPO), Sweden

Group	n	Yes	No
Classic IC			
77-F	275	Yes	
73-M	295	Yes	
85-F	1,813	Yes	
85-P	1,604	Yes	
62-P	1,679	No	
61-F	2,093	No	
69-P	967	Yes	
54-F	2,595	No	
41-M	307	Yes	
35-F	397	Yes	
Nonulcer IC			
60-P	1	Yes	
66-M	1	Yes	
53-F	1	Yes	
46-P	1	Yes	
44-F	1	Yes	
38-P	1	Yes	
20-F	1	Yes	
Control			
66-P	5		
66-F	1		
54-P	1		
39-F	1		
35-M	1		
30-F	2		

Air sample (25 ml) from the urinary bladder (using a silicon catheter)

Air, surrounding the patient as control

air was immediately examined in a chemiluminescence NO analyzer (NIOX, Aerocrine, Stockholm, Sweden)

Results in ppb (parts per billion)

Lower Urinary Tract Microbiota during symptom flare in women with urologic Chronic Pelvic Pain Syndrome: A MAPP network study

Abstract

Background: Lower urinary tract microbiota composition is associated with urologic chronic pelvic pain syndrome (IC/BPS). We investigated the changes in the lower urinary tract microbiota during symptom flares in women with IC/BPS.

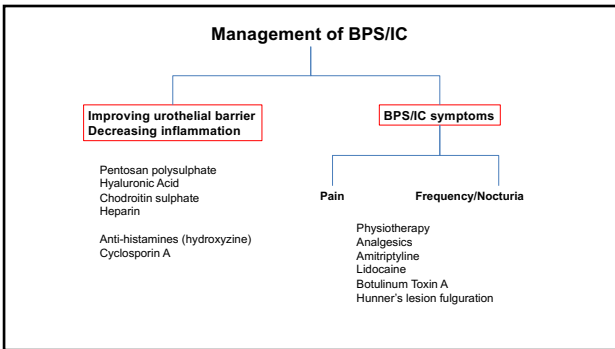
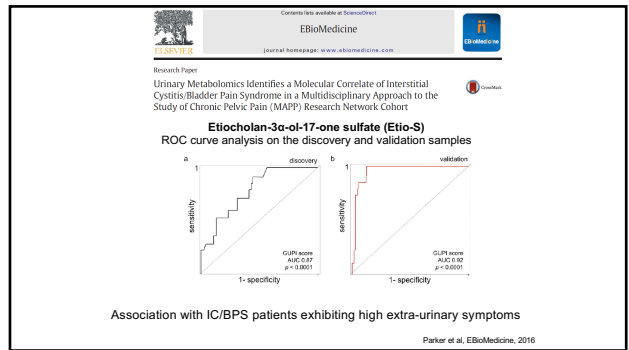
Methods: A total of 233 women with IC/BPS were included in the study. The study was conducted as a prospective, observational study. The lower urinary tract microbiota was analyzed using 16S rRNA sequencing. The results were compared between the flare group and the nonflare group.

Results: Univariate analysis confirmed a significantly greater prevalence of fungi (Candida and Saccharomyces) in the flare group (15.7%) compared to the nonflare group in the midstream urine (3.9%) (p<0.01).

Conclusion: The lower urinary tract microbiota composition changes during symptom flares in women with IC/BPS. The prevalence of fungi is significantly higher in the flare group.

N=233 patients

Nickel et al. J Urol, 2016



EAU guidelines: Management of BPS/IC

Recommendations	Strength rating
Offer subtype and phenotype-oriented therapy for the treatment of Bladder Pain Syndrome (BPS).	Strong
Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of BPS.	Strong
Administer amitriptyline for treatment of BPS.	Strong
Offer oral pentosan polysulphate for the treatment of BPS.	Strong
Offer oral pentosan polysulphate plus subcutaneous heparin in low responders to pentosan polysulphate alone.	Weak
Administer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	Weak
Administer intravesical pentosan polysulphate before more invasive treatment alone or combined with oral pentosan polysulphate.	Strong
Administer submucosal injection of botulinum toxin type A (BTX-A) plus hydrodistension if intravesical instillation therapies have failed.	Strong
Only undertake ablative organ surgery as the last resort and only by experienced and BPS-knowledgeable surgeons.	Strong
Offer intravesical hyaluronic acid before more invasive measures.	Weak
Offer intravesical chondroitin sulphate before more invasive measures.	Weak
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3/4 only.	Strong
Offer neuromodulation before more invasive interventions.	Weak
Offer dietary advice.	Weak

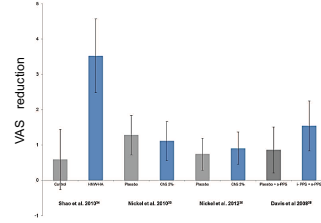
Engeler et al. EAU guidelines, 2018

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Offer transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.	Strong

Engeler et al, EAU guidelines, 2018

Can we correct the barrier? A systematic review and meta-analysis on the efficacy of intravesical therapy for BPS/IC



HMW-HA high molecular weight hyaluronic acid 0.08 %,
ChS 2% chondroitin sulphate 2 %,
o-PPS oral dose of pentosan polysulphate,
i-PPS intravesical instillation with pentosan polysulphate

Barua et al, Int Urogyn J, 2016

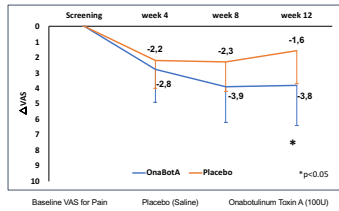
Treatment: tricyclic antidepressants

- Amitriptyline has analgesic and sedative effects
- May stabilize mast cells and inhibiting release of inflammatory mediators
- Amitriptyline was not superior to placebo in a RCT
- Eventually, doses > 50mg/day may have some effect

Foster, Hanno, Nickel et al, J Urol, 2010

Probable: Treatment of Bladder Pain Syndrome with Onabotulinum toxin A. RCT

Primary end-point: Change from baseline to 12 weeks in VAS score

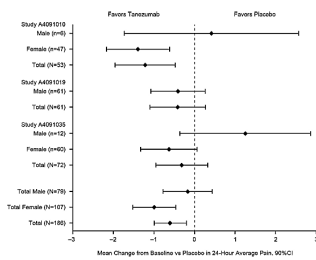


Baseline VAS for Pain (0-10) Placebo (Saline) 6.8±0.8 Onabotulinum Toxin A (100U) 6.8±1.2

Probable: Treatment of Bladder Pain Syndrome with Onabotulinum toxin A

Pinto et al, J Urol, 2018

Pooled analyses from 3 clinical trials of tanezumab in patients with urological chronic pelvic pain



Nickel et al, J Urol, 2016

Conclusions

A condition with numerous unmet needs

A definition accepted by all scientific organizations is necessary

Phenotyping patients is necessary but we need to agree on the tools

- Questionnaires
- Cystoscopy
- Histological findings
- Urodynamics with lidocaine

Investigate biomarkers that might help to form homogeneous groups

New trials to investigate new forms of treatment are necessary