W13: Phenotyping BPS/IC for Clinical Success

Workshop Chair: Christopher Payne, United States
12 September 2017 11:00 - 12:30

Start	End	Topic	Speakers
11:00	11:10	Overview: Where we went wrong and how to start again	Christopher Payne
11:10	11:20	Hunner Lesion IC: A distinct disease	Magnus Fall
11:20	11:30	Autoimmune Phenotype	Jane Meijlink
11:30	11:40	Myofascial Phenotype	Mauro Cervigni
11:40	11:50	Central Sensitization Science	Christopher Payne
11:50	12:00	Central Sensitization Clinical	Jane Meijlink
12:00	12:30	Discussion	All

Speaker Powerpoint Slides

Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website www.ics.org/2017/programme Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop

Why has so little progress been made after decades of research in Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC)? Many hundreds of research projects costing tens of millions of dollars have come and gone but patient care is little improved. We argue that the mistake has been in creating a large group of patients with similar symptoms but nothing else in common. In his workshop will present a new approach to the problem—rather than lumping different patients together, work to identify useful patient phenotypes appropriate for research and specific clinical pathways.

Learning Objectives

1. To identify Hunner Lesion/Ulcerative Interstitial Cystitis as a separate identifiable disease.
2. To identify specific clinical features of patients with Bladder Pain Syndrome which suggest a phenotype that may respond differently to treatment.
3. To understand the significance of central sensitisation and multiple CS manifestations in the same patient.
4. To critically read the literature to determine if models used in studying BPS/IC are appropriate for the patient groups seen in practice.

Learning Outcomes

1. Effectively screen patients in larger group of BPS/IC for Hunner Lesion/Ulcerative Interstitial Cystitis.
2. Identify clinically relevant phenotypes within the larger group of BPS patients through history and physical exam.
3. Develop individualised treatment plans for patients based on their clinical phenotypes
4. Develop research protocols which are clinically relevant to clearly defined, clinically identifiable phenotypes.

Target Audience

Broadest possible. Will be appropriate for physicians and allied health professionals who care for BPS/IC but also for basic science researchers who struggle with identifying appropriate animal models to study this group of patients.

Advanced/Basic

Advanced

Suggested Reading

1. Fall M and Peeker R. Classic Interstitial Cystitis: Unrelated to BPS. Current Bladder Dysfunction Reports. March 2015;10(1), pp 95-102
2. Payne CK. A New Approach to Urologic Chronic Pelvic Pain Syndromes: Applying Oncologic Principles to "Benign" Conditions. Current Bladder Dysfunction Reports. March 2015;10(1), pp 81-86.
3. Potts, JM. Male Pelvic Pain Syndrome: Escaping the Snare of Prostatocentric Thinking. Current Bladder Dysfunction Reports. March 2015;10(1), pp 75-80
4. Kotarinos R. Myofascial Pelvic Pain: Rationale and Treatment. Current Bladder Dysfunction Reports. March 2015;10(1), pp 87-94
5. Meijlink JM. Patient Heal Thyself: Engaging in a Team Approach. Current Bladder Dysfunction Reports. March 2015;10(1), pp 103-108
6. Warren JW and Clauw DJ: Functional Somatic Syndromes: sensitivities and specificities of self-reports of physician diagnosis. Psychosom Med 74:891-895 (2012)
7. Warren JW, Langenberg P, Clauw DJ: The number of existing functional somatic syndromes (FSSs) is and important risk factor for new, different FSSs. J of Psychosom Res 74 (2013) 12-17

Overview: Where we went wrong and how to start again: Dr. Payne, Urologist, United States

In 1978 Stamey and Messing published the landmark paper suggesting that "the finding of multiple petechia-like hemorrhages (glomerulations) on the second distention of the bladder is the hallmark of interstitial cystitis, and that a reduced bladder capacity and a Hunner's ulcer represent a different (classic) stage of this disease." This concept was adopted by United States' National Institutes of Health in the NIDDK research criteria which subsequently became the default research criteria. Unfortunately, time has proven this hypothesis to be wrong. Tens of millions of dollars of research spending have produced little and there has been similarly little improvement in patient care.

In this workshop we propose a different approach. We believe:

- there are identifiable phenotypes
- researching more homogeneous groups of patients (specific phenotypes) will produce useful results
- Treatment algorithms aimed at specific phenotypes will be much more useful/successful than current documents

We will now have a series of short presentations proposing clinically relevant phenotypes. We do not claim that these are completely accurate or comprehensive. Rather, these represent a starting point from which we believe that, by working together, we can gain a more complete understanding of these challenging patients.

Please see:

Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978; 12: 381–92.
Meijlink JM: Interstitial cystitis and the painful bladder: A brief history of nomenclature, definitions and criteria. Int J Urol 2014; 21(S1), 4-12.

Hunner Lesion IC: A distinct disease: Dr. Fall, Urologist, Sweden

Prior to Messing & Stamey and the NIDDK criteria Interstitial Cystitis or Hunner Lesion disease was considered to be a specific disease, however enigmatic it may be. The hypothesis that these lesions represent a chronic, end-stage disease is contradicted by many observations:

- There are no good case reports of patients developing Hunner Lesions after years of having "glomerulations" and pain.
- A recent review of the literature "found no convincing evidence in the reviewed literature that glomerulations should be included in the diagnosis or phenotyping of bladder pain syndrome/interstitial cystitis."

Our research clearly shows that patients with Hunner Lesions are different than those with pain but no lesions.

- Patients most typically develop Hunner Lesions later in life without a prodrome of years of pain preceding.
- Patients with Hunner Lesions commonly have physical changes in the bladder with loss of anesthetic capacity whereas this is extremely rare in patients with Bladder Pain Syndrome
- Objective intravesical nitrous oxide testing completely separates IC from BPS with no overlap between the groups.
- Patients without Hunner Lesions rarely have any identifiable abnormalities on bladder biopsy.

Sadly, there has been little progress in recognizing this important group of patients or in optimizing their treatment. Although many researchers report good results with a wide variety of surgical approaches the result is rarely permanent and often not long-lasting. Important questions to be addressed in the future include:

- Can HL patients be stratified by blood, urine or tissue testing to determine their prognosis?
- What is the optimal surgical approach?
- What is the role of adjuvant or neoadjuvant therapy in relation to surgery?

Please see:

Fall M and Peeker R. Classic Interstitial Cystitis: Unrelated to BPS. Curr Bladder Dys Rep. March 2015;10(1), pp 95-102
Wennevik GE et. al.: The Role of Glomerulations in Bladder Pain Syndrome: a review. J Urol 2016; 195, 1-7.
Leiby B, et. al:. Discovery of morphological subgroups that correlate with severity of symptoms in interstitial cystitis: a proposed biopsy classification system. J Urol. 2007;177(1):142–8.

Autoimmune Phenotype: Ms. Meijlink, Patient Advocate/Researcher/Writer, Netherlands

In 1997 Alagiri reported that patients with Interstitial Cystitis were "100 times more likely to have inflammatory bowel disease and 30 times more likely to have systemic lupus erythematosus" than the general population. Some work has been done in this area, particularly by van de Merwe examining the connection with Sjogren's Syndrome, but the association remains largely unexplored. Instead, the focus has been on many other common associations with disorders that are far less specific than these autoimmune diseases.

Important questions to be addressed in the future include:

- Do patients with autoimmune disorders represent a clinically meaningful phenotype within BPS/IC?

- Does this phenotype skew toward the HL patients, suggesting a common inflammatory pathway?
- Could treatment protocols be developed with newer biologic immunomodulating agents be useful in this subgroup of patients?

Please see:

Alagiri M et. al.: Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology. 1997 May;49(5A Suppl):52-7.

van de Merwe JP: Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol. 2007 Sep;4(9):484-91.

Myofascial Phenotype: Dr. Cervigni, Urogynecologist, Italy

Individual researchers and clinicians have recognized the relevance of myofascial dysfunction in chronic pelvic pain for decades. However, it was only after two positive NIDDK clinical trials demonstrated superiority of myofascial physical therapy to global therapeutic massage in the treatment of BPS/IC that the therapy began to gain wide acceptance. While this represents a meaningful advance for our patients there remain many more questions than answers in defining this as a phenotype. Our agreed on principles are:

- The phenotype is properly described as myofascial pelvic pain (MPP).
- Pelvic floor dysfunction would be a subtype of MPP; triggers for pelvic pain and bladder symptoms can occur in the abdominal wall, low back, hips, and thighs
- MPP often has a specifically identifiable cause (orthopedic or behavioral) so treating the physical finding without treating the cause will not be effective
- Behavioral and psychological factors can increase muscle tension and lead to persistence of MPP despite appropriate intervention.

This talk will focus on clinical diagnosis and treatment of patients identified as having a primary myofascial cause for pain and lower urinary tract symptoms.

Important questions to be addressed in the future include:

- What are the key clinical exam findings and how should they be described in research? Patients can have muscle tenderness without classic trigger points. Tenderness can refer to the area of pain or not. Classic trigger points (band/knot/twitch response) can be found that appear unrelated to the clinical pain.
- What is the role of interventional physical therapy vs. behavioral modification/home program?
- What is the role of pharmacologic therapy?
- When are blocks/Botox injections indicated?
- What is the connection between voiding dysfunction and MPP?

Please see:

- Kotarinos R. Myofascial Pelvic Pain: Rationale and Treatment. Current Bladder Dysfunction Reports. March 2015;10(1), pp 87-94
- FitzGerald MP et. al.: Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol. 2012 Jun;187(6):2113-8.
- FitzGerald MP, et. al.: Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol. 2009 Aug;182(2):570-80.

Central Sensitization Science: Dr. Payne, Urologist, United States

Bladder Pain Syndrome, that is bladder pain and lower urinary tract symptoms without identifiable bladder pathology is best thought of as a Central Sensitization Syndrome (CSS). Central sensitization/CSS is one of the best explanations for the phenomenon of FSS, which have both visceral and somatic manifestations. Sensitization is caused by chemical and anatomical changes leading to hyperexcitability in the dorsal horn cells from persistent afferent C fiber bombardment by painful stimuli. The presence of sensitization expands the pain field and creates a neuroanatomical basis for pain persistence and recurrence in the presence of minimal or no discernable pathology. This process will eventually cause a local up-regulation and central “wind up” that creates a neuroanatomical basis for pain persistence in the presence of minimal disease or stimuli.

A growing body of research supports the concept of CSS. Objective, measureable differences or abnormalities have been identified in autonomic nervous system (blood pressure and heart rate), cortisol levels, brain activity and other areas when comparing patients with CSS to controls. Of course, the significance of these findings in relation to clinical care remains to be elucidated.

The concept of central sensitization is gaining recognition in the urological community. It is extremely detrimental to continue perpetuating a link between an infectious or inflammatory end organ cause in the absence of scientific data. In fact, triggers for pelvic pain include many other urological as well as non-urological causes: Passage of kidney stones, changes in sexual

functioning/sexual trauma, obsessive masturbation, pelvic surgery, cycling, running, anal fissure disease, hemorrhoidectomy, sports or other orthopedic trauma, etc.

Important questions to be addressed in the future include:

- Are observed physiologic changes related to pain and behavioral changes or are they the cause? When an abnormality is observed can we use this as a target in therapy?
- To what degree are CNS changes reversible? Can they become irreversible?

Please see:

- Clemens JQ et. al.: The MAPP research network: a novel study of urologic chronic pelvic pain syndromes. BMC Urol 2014; 14, 57.
- Neurobiology of Fibromyalgia & Chronic Widespread Pain Syndrome. Sulka & Clauw. Neuroscience 2016; 338, 114-129

Central Sensitization Clinical: Ms. Meijlink, Patient Advocate/Researcher/Writer, Netherlands

Perhaps the greatest advance in the science of IC/BPS is increasing recognition of coexistent central sensitization syndromes (fibromyalgia, chronic fatigue, irritable bowel, etc.). The current focus of the United States MAPP research network is focused on elucidating these connections. This talk will focus on what is currently known about bladder pain and other central sensitization syndromes. It will review the general treatment recommendations for patients with central sensitization.

Important questions to be addressed in the future include:

- How and when should we screen our patients for central sensitization syndromes?
- When is it important to treat the bladder symptoms in patients with LUTS and central sensitization?
- How do we best treat significant LUTS in patients with central sensitization?

Please see:

- Wessely S, et. al.: Functional Somatic Syndromes: one or many? Lancet. 1999;354, 936-939.
- Warren JW and Clauw DJ: Functional Somatic Syndromes: sensitivities and specificities of self-reports of physician diagnosis. Psychosom Med 74:891-895 (2012)
- Warren JW, et. al.: The number of existing functional somatic syndromes (FSSs) is an important risk factor for new, different FSSs. J of Psychosom Res 74 (2013) 12-17
- Potts JM. Male Pelvic Pain: Beyond Urology and Chronic Prostatitis. Curr Rheumatol Rev. 2016;12(1):27-39. Review.

Discussion: Entire Panel

BPS/IC 2017: Phenotyping BPS/IC for success

Christopher K. Payne, MD
Emeritus Professor of Urology at Stanford
Vista Urology & Pelvic Pain Partners

Christopher K. Payne, MD

Affiliations to disclose:

Worldwide Fistula Fund, President

International Continence Society, Board of Trustees

Consultant for: Astellas, Seikagaku, Aquinox

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NEW FOR 2017

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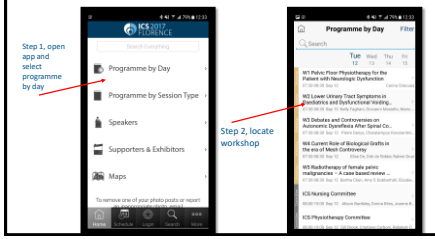

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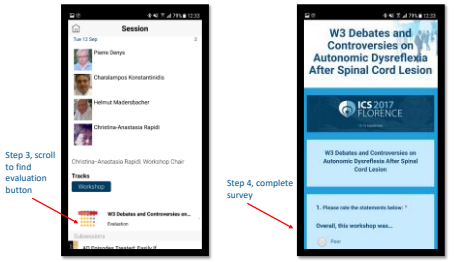

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- A full handout for all workshops is available via the ICS website.
- Please silence all mobile phones
- Please refrain from taking video and pictures of the speakers and their slides. PDF versions of the slides (where approved) will be made available after the meeting via the ICS website.

The Emperor Has No Clothes

Messing & Stamey, Urology 1978

INTERSTITIAL CYSTITIS*

Early Diagnosis, Pathology, and Treatment

EDWARD M. MESSING, M.D.
THOMAS A. STAMEY, M.D.

From the Stanford University School of Medicine, Stanford, California

ABSTRACT — In a retrospective review, 32 patients with interstitial cystitis have been studied. Patients with persistent lower tract irritative symptoms, repeatedly sterile urine, and negative urine cytology must be suspected of having interstitial cystitis, and a diagnosis of urethral syndrome in such patients is highly questionable until cystoscopy under anesthesia has been performed. We believe that the finding of multiple petechia-like hemorrhages (glomerulations) on the second distention of the bladder is the hallmark of interstitial cystitis, and that a reduced bladder capacity and a Hunner's ulcer represent a different (classic) stage of this disease. In all stages, the characteristic histologic finding is submucosal edema and vasodilation. The presence of eosinophils and mast cells is variable, and even in the classic disease the muscularis often appears to be normal. Immunofluorescent studies and laboratory tests, including the fluorescent antinuclear antibody test (FANA), have not helped us to diagnose (or investigate) interstitial cystitis. Bladder installations with a 0.4 per cent solution of oxychlorosene sodium (Clorpactin WCS-90) have provided remarkable relief for many patients with this disease, particularly those with the classic form.

Hypothesis

- Glomerulations:
  - "are a hallmark of IC (biomarker)"
  - "represent a different (early) stage of IC
- Glomerulations then incorporated into NIDDK criteria

Review Article

The Role of Glomerulations in Bladder Pain Syndrome: A Review

Gjertrud E. Wennevik,* Jane M. Meijlink, Philip Hanno and Jørgen Nordling

From the Department of Urology UNI, University of Copenhagen (GEW), Copenhagen, Denmark, International Painful Bladder Foundation, Rotterdam, The Netherlands (JMM), and Department of Urology, University of Pennsylvania, Philadelphia, Pennsylvania (PH)

Purpose: As a diagnostic marker for bladder pain syndrome/interstitial cystitis, glomerulations were first popularized by Messing and Stamey in 1978. Later this was included in the NIDDK criteria for research and consequently used by many urologists as a default diagnostic criterion. Today the connection between glomerulations and bladder pain syndrome/interstitial cystitis is much debated

Abbreviations and Acronyms

BPS = bladder pain syndrome

ESSIC = International Society for

We found no convincing evidence . . . that glomerulation should be included in the diagnosis or phenotyping of BPS/IC.

J Urol 195:1-7; 2016

Breaking News from the US

Donald J. Trump
@realDonaldTrump

Follow

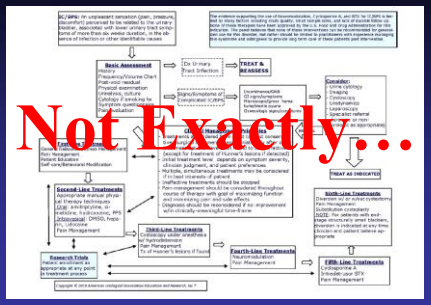
@ICS2017--BPS/IC--Totally, totally, very completely wrong. What are you doing? SAD!!

7:19 AM - Sep 12, 2017

11,413 29,605 104,470

Research

AUA Guidelines, J Urol 2011



Not Exactly…

Key Messages

1. Ulcerative IC is a unique disease.
2. BPS is not a disease; it is a syndrome
3. Phenotyping BPS patients will drive clinical (and research) success

Phenotyping Untangles the Mess

Phenotyping

- Phenotype = observable characteristics that define a clinically relevant group

What Phenotypes Can We Identify?

Bladder Phenotype

- What we all learned—pain on bladder filling relieved by urination
- Consistently reduced volumes on diary
- Primarily bladder tenderness on exam
- Pain relief with intravesical lidocaine

Bladder Phenotype

- Bladder Training
- Urinary analgesics
- Bladder instillations
- Pentosan Polysulfate
- Pain Management
- Botulinum Toxin
- Neuromodulation

Phenotyping

- Discussion today:
  - Proposals/suggestions
  - Our phenotypes may not be quite right
  - Many others are possible
- This is a call to action

Phenotyping

Don't persist in error while waiting to discover the truth. Admission of ignorance is the first step to truth.

Faculty

Faculty

- Magnus Fall--Urology
- Mauro Cervigni--UroGyn
- Jane Meijlink--Writer

Agenda

Introduction/Overview	C Payne
Ulcerative IC	M Fall
Myofascial Phenotype	M Cervigni
Central Sensitization Overview	C Payne
CS and Chemical Sensitivities	J Meijlink
Autoimmune Phenotype	J Meijlink
Questions & Comments	Faculty

Interstitial cystitis in the past

- **1896 Fenwick**. Lectures on " The simple solitary bladder ulcer"
- **1887 Skene** introduced the denomination Interstitial Cystitis.

Diseases of the Bladder and Urethra in Women. William Wood Publishing Company, New Yourk, 1887

- **1915, 1918 Hunner and the so called Hunner ulcer**
  - Reported on "red bleeding areas high on the bladder wall" interpreted as ulcers, much depending on the limited optical methods one hundered years ago
  - Added the term "elusive ulcer" since the initial inspection of the bladder might be normal
  - Described focal rather than generalized changes

Boston Med Surg J 1915;172:660
Am J Obstet 1918;78:374

Magnus Fall

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Affiliations to disclose†:

Institute of Clinical Sciences
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

† All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation

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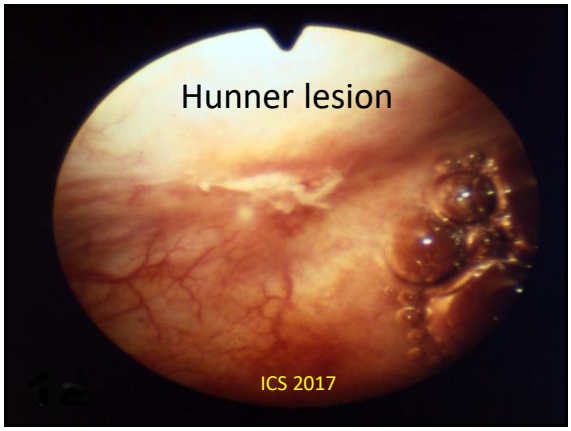
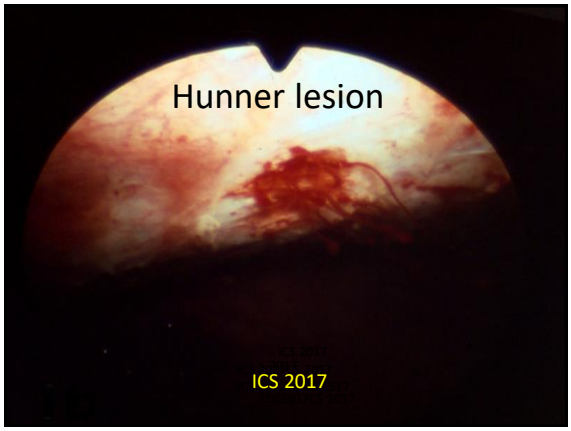
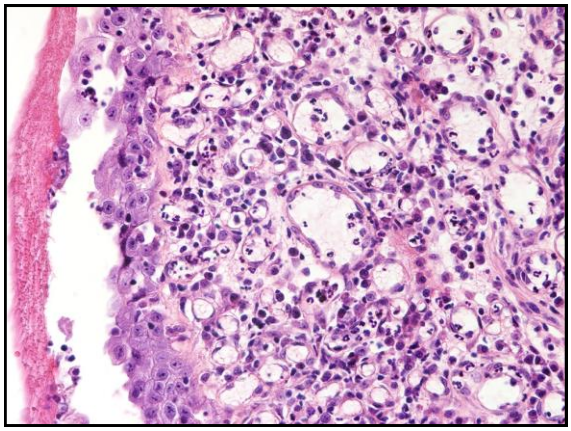






Cell components in the inflammatory infiltrate

- Lymphocytes
- Plasma cells
- Neutrophil- and eosinophil granulocytes
- Macrophages
- Mast cells

Fall, Johansson, Vahlne. J Urol 133:771, 1985

Cell components in the inflammatory infiltrate

- Lymphocytes
- Plasma cells
- Neutrophil- and eosinophil granulocytes
- Macrophages
- Mast cells
- There is a focal, perineural arrangement of inflammatory cells – proximity facilitates neuro-immune interfaces

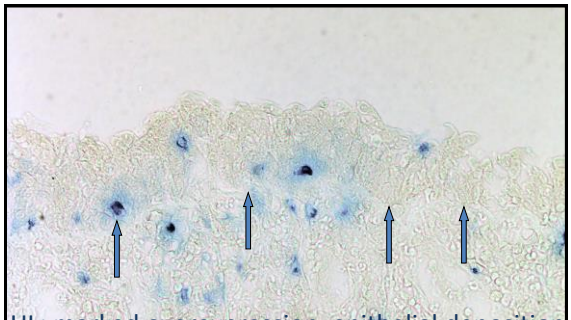
Fall, Johansson, Vahlne. J Urol 133:771, 1985

Cell components in the inflammatory infiltrate

- Lymphocytes
- Plasmacells
- Neutrofil- and eosinofil granulocytes
- Macrophages
- Mastcells

MC:s are multifunctional immune cells

- Contain immunoglobuline E receptors
- Express stem cell factor and CD 117
- Granules: histamine, sulphated glycosaminoglykans and distictive proteinases



HL: marked overexpression, epithelial deposition of mast cells (from co-expression of epithelial SCF and IL-6)

Peeker, Enerbäck, Fall, Aldenborg. J Urol J Urol. 163:1009, 2000.

Cell components in the inflammatory infiltrate

- Lymphocytes
- Plasmacells
- Neutrofil- and eosinofil granulocytes
- Macrophages
- Mastcells

Macrophage Migration Inhibitory Factor (MIF)

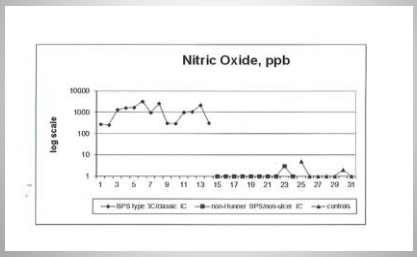
Urinary MIF is increased in patients with Hunner lesions while levels in non-HL are similar to controls

MIF is a new non-invasive urine biomarker with a potential to identify patients with Hunner lesions

Vera, Preston , Moldwin, Erickson et al., submitted 2017

NO - a distinctive inflammatory marker

Nitric Oxide level in parts per billion (ppb) from classic IC patients with Hunner lesions, non-Hunner patients and controls



Logadottir, Ehrén, Fall, Wiklund, Peeker. J Urol.171:1148, 2004

Hunner lesions are more common than previously believed

- Anonymous: 0 per cent
- General opinion in the 80th: 5-10 per cent
- Parsons & Mulholland -87: 28 per cent
- Fall -87: 57 per cent
- Koziol -96: 20 per cent
- Peeker -02: 56 per cent
- Braunstein -08: 39 per cent
- Logadottir -12: 55 per cent
- In Moscow, Japan and Taiwan: about 50 per cent

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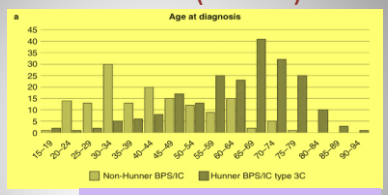
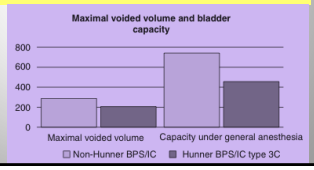
Phenotyping Hunner lesions vs non-HL 55% (n=389)





Logadottir et al. Scand J Urol Nephrol. 46:365, 2012

Urothelial dysfunction

Multiple superficial cracks

This not a Hunner lesion!

but maybe another specific phenotype

Glomerulations

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ESSIC classification		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 intrafascicular fibrosis

Wennevik et al J Urol.195:19, 2016.

TUR of Hunner lesions

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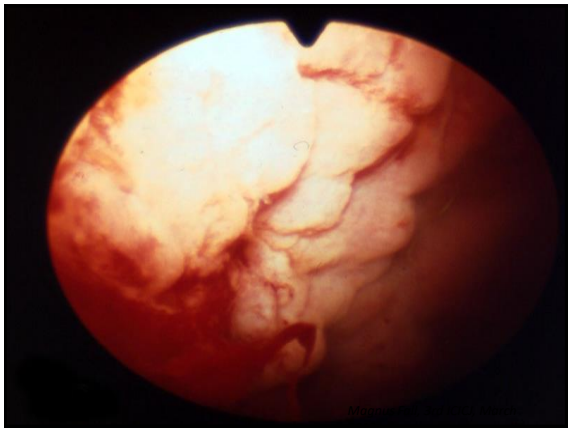

All lesions have to be removed including the postdistension edema zone!

TUR – results

Out of the 103 resected patients, 92 got a considerable amelioration of urinary frequency and bladder pain

Average symptom alleviation 23 mths (0-180 mths)

Peeker, Aldenborg, Fall. Int Urogyn J. 11:290, 2000

Why is TUR effective ?

- Removal of inflamed nerve endings
- Reduction of aggregates of potent inflammatory mediators and mast cell recruiting factors
- Elimination of epithelial and subepithelial mast cells

Repeated observations on differences in treatment outcomes

	HL	Non-HL
TENS	++	+
DMSO	++	(+)
BCG	(+)	0
Ablation	+++	0
Cyclosporine	++	(+)
Cystoplasty	+++	0
Cystectomy	+++	(+)

Classic interstitial cystitis with Hunner lesions is a distinctive and well defined entity and should be dealt with accordingly.
Identification has decisive consequences for the patient

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Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

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WS # 13 – Phenotyping BPS/IC for clinical success

MYOFASCIAL PHENOTYPE

Mauro Cervigni
Professor Urogynecology
Director Referral Center Interstitial Cystitis
Female Pelvic Medicine & Reconstructive Surgery Center
Catholic University
Rome-Italy

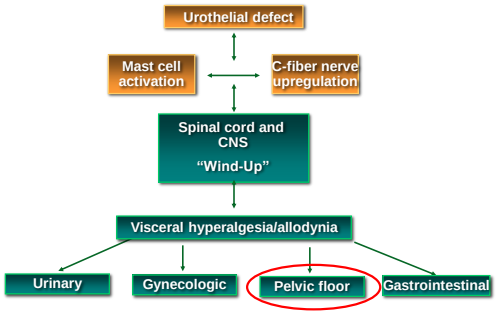
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

No Disclosure

Mauro Cervigni
Professor Urogynecology
Director Referral Center Interstitial Cystitis
Female Pelvic Medicine & Reconstructive Surgery Center
Catholic University
Rome-Italy

Interstitial Cystitis/Bladder Pain Syndrome Pathogenesis: Integrated Pathophysiology



Pelvic Floor Dysfunction

- Non-neurogenic detrusor-sphincter dyssynergia
- Probably the same or very similar to CP/CCPS Category IIIB
- The prevalence of Hypertonic Pelvic Floor Dysfunction (HPFD) is thought to be 50% to 87% in patients with BPS/IC

Peters KM et al. Urology 2007;70(1):16–8.

Myofascial Phenotype in IC/BPS

Patients With IC/BPS frequently have coexisting :

- **Levator Pain (87–94 %)**
- **Vulvar Pain (50–51 %)**
- **Sexual Dysfunction/ Dyspareunia (71–72 %)**

Peters KM et al. 2008 Urology 71(4):634–640
Peters K et al. 2008 Int Urogynec J 19(5):665–669

- myofascial trigger points were observed in 78 % of patients with IC/BPS
- their presence and number correlated with *symptom duration* and severity

Bassaly R et al. 2011 Int Urogyn. J 22(4):413–418.

Pelvic Floor Dysfunction

Symptoms

- Pelvic Pain
- Urinary urgency and frequency
- Pain with sexual intercourse or orgasm
- Variable urinary flow rate
- Constipation
- Lower back pain

Hypertonic Pelvic Floor

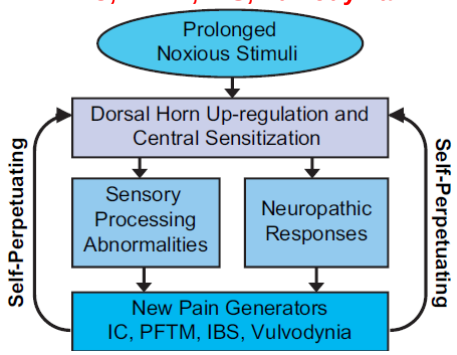
Characterics of High tone:

- Hypertonicity
- Decreased strength
- Decreased ability to relax post contraction
- Pain to palpation
- Trigger points
- Decreased motor control

BPS/IC & Pelvic Floor Dysfunction

IC/BPS	PFD
•Urgency and frequency of urination	•Urgency and frequency of urination
•Pelvic pain	•Pelvic pain
•Dyspareunia common	•Dyspareunia common
•Symptoms often worsened by stress	•Symptoms often worsened by stress
•Nocturia common	•Nocturia uncommon
	•Sensation of incomplete emptying
	•Constipation
	•Low back pain
	•Straining with voiding

Etiology of Visceral Pain Syndromes: IC, PFTM, IBS, Vulvodynia



CharlesW. Butrick, Obstet Gynecol Clin N Am 36 (2009) 699–705

Myofascial Phenotype in IC/BPS

IC/BPS and myofascial pain

patients with a significant myofascial component to their pelvic pain will often report leg or groin pain that occurs with bladder filling and urinary frequency that is severe **during the day but not at night**

Butrick cw et al. 2005 Int Urogyn J 2009;20:1047–53.

Myofascial Phenotype in IC/BPS

IC/BPS and MYOFASCIAL PAIN

the *"pressure"* arising from the pelvic floor hypertonicity is perceived as a need to void but *during sleep the pelvic floor relaxes*, therefore the need to void is generated only by bladder volume and not by the pelvic floor.

Butrick CW et al. Int Urogyn J 2009;20:1047–53.

Myofascial Phenotype in IC/BPS

DIAGNOSIS

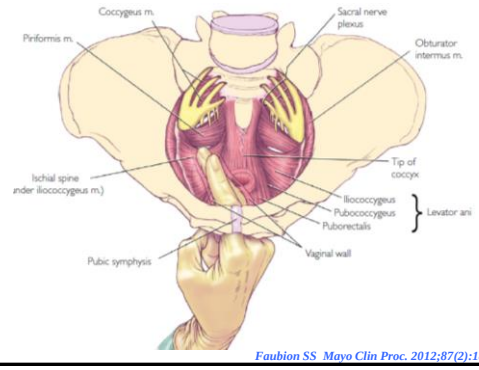
PHYSICAL EXAMINATION

clinical evaluation of the pelvic floor begins with simple observation of pelvic floor muscle activity during the process of squeezing and relaxation.

Assessment of Pelvic Floor
INNER PELVIS

- **Trigger points** of pelvic floor muscles.
- **Strength**, **High tone-relaxation.**
- **Measure strength:**
  - Digital measurement, POP-Q/Baden Score
  - Perineometry, EMG.
- **Measure high tone dysfunction:**
  - Digital measurement.
  - Perineometry, EMG.

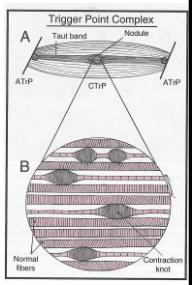
Digital palpation of deep pelvic floor muscles



Faubion SS Mayo Clin Proc. 2012;87(2):187-193

Myofascial Trigger Point

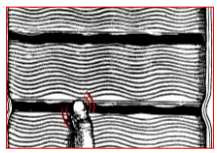
- A **hyperirritable spot** in skeletal muscle that is associated with a **hypersensitive palpable nodule in a taut band**.
- The spot is painful on compression and can give rise to characteristic **referred pain, referred tenderness, motor dysfunction, and autonomic phenomena**.

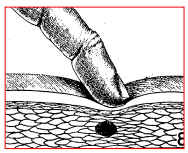


Internal Assessment

Trigger Point:

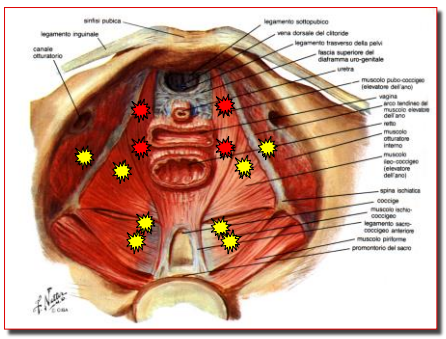
A discrete, focal, hypersensitive spots located in a taut band of skeletal muscle. They produce pain locally and in a referred pattern and often accompany chronic musculoskeletal disorders.





Travell, Janet; Simons David; Simons Lois (1999). Myofascial Pain and Dysfunction: The Trigger Point Manual (2 vol. set, 2nd Ed.). USA: Lippincott Williams & Williams

Myofascial Trigger Points



Referred Pain Patterns: Pelvic Floor Muscles *(Itza et al. 2010)*

Pelvic Floor Muscle	Referral Pattern	Possible Patient Complaint
Superficial Muscle Layer		
Bulbocavernosus	Perineal pain, urogenital structures	Dyspareunia, pain with orgasm, clitoral pain
Ischiocavernosus	Perineal pain, urogenital structures	Dyspareunia, pain with orgasm, clitoral pain
Transverses perineum (Superficial transverse perineal)	None documented	Dyspareunia
Anal sphincter (Sphincter ani externus)	Posterior pelvic floor, anus/rectum, pubic pain	Burning or tingling in anus/rectum, pain before/during/ after defecation
Deep Muscle Layer		
Levator ani anterior: Pubococcygeus/puborectalis	Suprapubic region, urethra, bladder, perineum, pain/symptoms	Increased urinary urgency & frequency, Painful urination after intercourse, dyspareunia
Levator ani posterior: Iliococcygeus	Sacrococcygeal, deep vaginal, rectal, perineal, anal pain	Pain before/ during/after defecation, dyspareunia, thrusting pain
Other Deep Pelvic Floor Muscles		
Coccygeous	Sacrococcygeal, buttock pain	Pain with sitting, during defecation, intestinal fullness, anal pressure/pain
Obturator internus	Anal, coccyx, vulvar, urethral, vaginal, or posterior thigh pain	Generalized pelvic pain, often burning or aching
Piriformis	Sacroiliac region, lateral over ipsilateral buttock, posterior over	Buttock, leg pain if sciatic nerve affected
	ipsilateral hip, proximal 2/3 of posterior thigh	

Myofascial Phenotype in IC/BPS

DIAGNOSTIC STUDIES

Surface EMGs

- the use of concentric needle EMGs to identify a unique EMG pattern in the urethral sphincter in patients with nonrelaxing pelvic floor and idiopathic urinary retention.

Multichannel Urodynamics

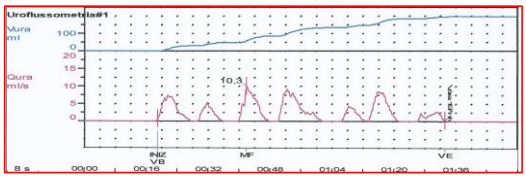
- Characteristic findings often seen with multichannel urodynamics include abnormal voiding studies, elevated urethral pressure at rest, and urethral instability.

Defecography

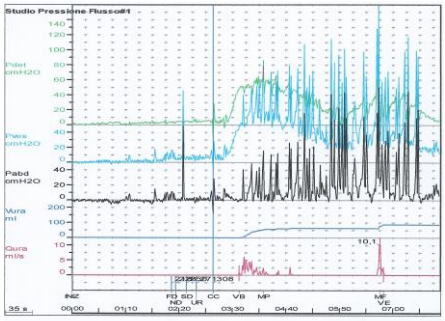
- When symptoms involve obstructed defecation and rectal pain, defecography can be used to identify the presence of a nonrelaxing pelvic floor or even paradoxic activity of the pelvic floor during defecation.
- **MRI**

Butrick CW Obstet Gynecol Clin N Am 36 (2009) 707–722

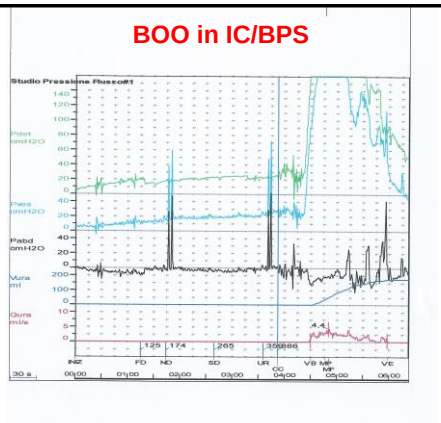
UDM & IC/BPS
INTERRUPTED UROFLOW



BOO in IC/BPS



BOO in IC/BPS



Int Urogynecol J
DOI 10.1007/s00192-015-2794-6

ORIGINAL ARTICLE

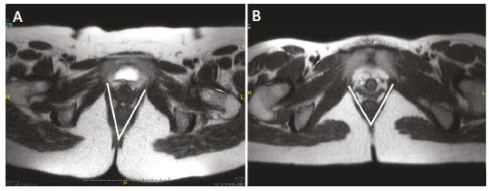
MRI suggests increased tonicity of the levator ani in women with interstitial cystitis/bladder pain syndrome

A. Lenore Ackerman[1,6] · Una J. Lee[2] · Forrest C. Jellison[3] · Nelly Tan[4] · Maitraya Patel[4] · Steven S. Raman[4] · Larissa V. Rodriguez[5]

Patients with IC/BPS have pelvic floor hypertonicity on MRI, which manifests as *shortened levator, increased posterior puborectalis angles, and decreased puborectal distances*.

There is an evidence of *pelvic floor hypertonicity* in patients with IC/BPS, which may contribute to or amplify pelvic pain.

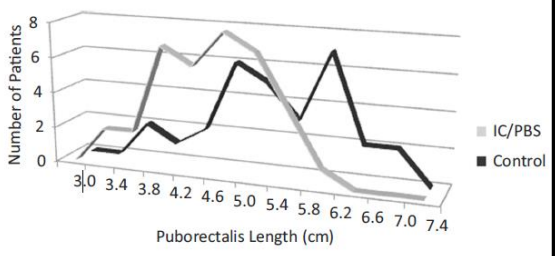
Puborectalis shortening in patients with interstitial cystitis/bladder pain syndrome (IC/BPS).



A. control patient, shortening of the bilateral puborectalis muscles

B. the patient with IC/BPS shifts the posterior insertion of the muscle anteriorly, widening the posterior puborectalis angle

Ackerman AL et al .Int Urogyn J 2015



distribution of levator length in patients with interstitial cystitis/bladder pain syndrome (ic/bps) in contrast to control women.

Ackerman AL et al .Int Urogyn J 2015

Int Urogynecol J
DOI 10.1007/s00192-015-2794-6
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This study identifies pelvic floor hypertonicity on MRI in patients with IC/BPS, supporting the theory that *pelvic muscle over-tensioning contributes to and amplifies patient pain*. Identification of patients with severe pelvic floor dysfunction may distinguish those likely to respond to treatments aimed at pelvic floor rehabilitation

Ackerman AL et al .Int Urogynecol J 2015

Treatments for PFD

- Behavior modification
- Physical Therapy
- Trigger Point Injection
- Pharmacologic Therapy
- Neuromodulation

Behavioral Modification

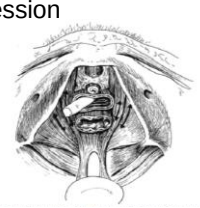
- **Bladder retraining**
  - Dietary modification
  - Fluid schedules
  - Bowel programs
  - Timed voiding
- **Pelvic floor muscle rehabilitation**
  - Manual therapy
  - Thiele massage
  - Pelvic floor muscle exercises (PFME)
  - Biofeedback/ Electrical stimulation

Manual Treatment
Internal massage

- Breaks pain-spasm-pain cycle
- Restores normal muscle tone
- Restores normal length tension relationship
- Increases blood flow
- Increase elasticity of tissue at vaginal opening

Manual Treatment
Internal Massage

- Myofascial Release Techniques:
- Direct pressure/compression
- Strumming
- Lateral stretching
- Contract-relax



Internal Massage

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 Questionnaire)
  - Pain and urgency VAS
  - Physical and mental component from Quality-of-Life Scale

TRANSVAGINAL THIELE MASSAGE for women with IC & HTPFD

- 21 patients, Age 42 yrs.
- 2 Rxs/ wk for 5 wks.
- Thiele stripping technique
- F/u 4.5 mos., 13 pts.
- 63% improvement
- O'Leary Sant Symptom/ Problem indices, UDI-6, Digital assessment.

Whitmore,KE, et al. ICA Grant, Urol., 2004.

Transvaginal Theile Massage for women with IC/BPS

Results

- 9 patients (90%) showed >50% improvement in frequency and/or nocturia, urgency and pain
- The digital exam showed >75% improvement in the ability to contract and relax pelvic floor muscles in the improved group

Holzberg A, et al. NIDDK/ICA International Research Symposium; October 19–20, 2000; Minneapolis, MN.

Transvaginal Theile Massage for women with IC

Results

- As a result of the close anatomic proximity of the bladder to its muscular support, it appears that internal vaginal massage improves IC symptoms
- This treatment provides an easy, noninvasive method of IC symptom improvement

Holzberg A, et al. NIDDK/ICA International Research Symposium; October 19–20, 2000; Minneapolis, MN.

Pelvic Floor Myofascial Trigger Points: Manual Therapy for IC/BPS

- 45 women, 3 men
- 10 IC, 42 UFS
- Manual PT 1-2 weekly visits x 8-12 weeks
- UFS 83% improved (moderate, marked, CR)
- IC 70% improved (moderate or marked)
- Mean resting pelvic floor tension decreased from 9.73 to 3.61 µV.

Weiss J, J Urol, 166:2226-2231, 2001

PHARMACOLOGIC THERAPY

Amitriptyline is the most commonly studied drug using doses of between 25 to 75 mg per day typically given as a single dose 1 hour before sleep.

Tiazadine/Zanaflex has also been found by many to be very
beneficial for muscle spasticity and secondarily for myofascial pain.

Pregablin in doses up to 600 mg per day is well tolerated and provides excellent results.

Butrick CW Obstet Gynecol Clin N Am 36 (2009) 707–722

Medical Adjuvant Treatment: HTPFD

Anxiolytic + myorelaxant
(binds to benzodiazepine sites on $GABA_A$ receptor)
-diazepam / Valium 2mg QD-TID
-lorazepam / Ativan 1mg QD - PRN
-alprazolam /Xanax .25-.50mg
Anticonvulsants:
-gabapentin/Neurontin
-pregabalin/ Lyrica
SRNIs
-duloxetine HCL /Cymbalta
-mulnacipran / Savella

Rogalski et al 2010 Intl J Urogyn 2010; Butrick CW. 2009. Obstet Clin N America

HTPFD Medical treatment:

- *Carrico et al 2010*
- Safety /efficacy of diazepam suppositories
- 11 pts (IC-PFD) V5-10 supp. TID
- After 30d: 64% "moderate/marked improvement" and no s/e
- Serum levels WNL =mean 0.29
- Ref range (0.2-1.0 mcg/ml)
- 36% mild drowsiness; no respiratory suppression; no worsening of pain

Diazepam suppositories

- *Rogalski et al 2010*

- N=26
  - 100% HTPFD; 85% dyspareunia, 81% CPP, 61% IC
- Interventions: PT, TrP injx and 10 mg diazepam vaginal suppositories, inserted nightly for 30 days.
- 25 /26=" improved sexual comfort"
- Abstinence reversed in 6/7

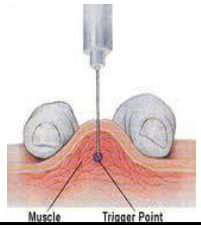
Triggerpoint needling

- **TrP needling:** a method of directly inactivating TrP's -particularly those refractory to myotherapy.
- TrP is penetrated with fine needle, eliminating TrP as a painful focus.
- Needle inserted w/o medication (or lidocaine and antinflammatory medications can be added.)

Trigger Point Injection

3 Different approaches:

- Dry Needling
- Injection of local anesthetic
- Injection of botulinum toxin



BOTULINUM TOXIN THERAPY

- In a randomized controlled *trial of Botox* (80 units) versus physical therapy for chronic pelvic pain caused by levator spasm, there was a statistically *significant decrease in dyspareunia and nonmenstrual pelvic pain* in the Botox subjects.
- Treated with 35 units of BTX/A injected into the submucosa demonstrated a favorable outcome but in this author's experience *100 units injected into the pubococcygeus muscle has proved to be very effective for vulvodynia associated with pelvic floor pain and significant hypertonicity.*

Rosier et al. J Urol 1994; Mayer RD, Howard 152(6 Pt 1):2071–5. 45.

HTPFD Medical Treatment:

PFM TrP Injx

-*Kang et al.* N=104 Levator spasm
Lidocaine .5cc /triamcinolone .5cc
Painfree 30.1%/moderate to mild relief 64.7%

-*Langford et al* N=18 Levator spasm
Bupivicaine and lidocaine 5 ml/TrP
Painfree 33% / 39% >50% improvement in s/s

Kang et al Dis Colon Rectum 2000,1288-91
Langford CF et al. Neurourodyn 2007,59-65

Botox and High Tone Pelvic Floor Dysfunction

- 12 women with CPP and HTPFD
- 40 U B/L PR, PC
- F/U at 2, 4, 8, 12 wks
- Dyspareunia VAS 80→28 (p=0.01)
- Dysmenorrhea VAS 67→28 (p=0.03)
- 25% ↓ manometry at 3 mo (p<0.0001)

Jarvis et al. J. OB & GYN. 2004; 44: 46-50

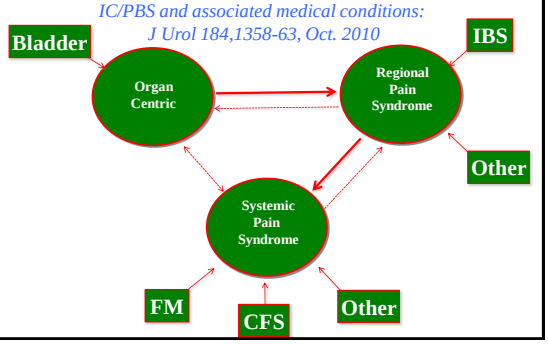
NEUROMODULATION

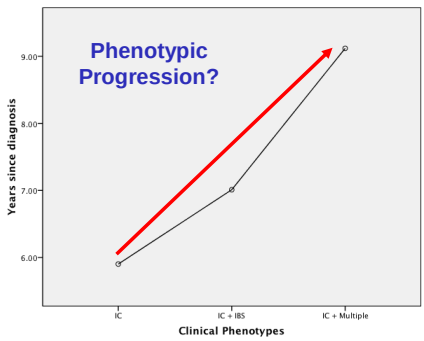
Although not indicated for the management of chronic pelvic pain disorders, there are reports of up to 50% of patients demonstrating resolution of chronic pelvic pain and 85% of patients with diagnosis of IC also demonstrating improvement in pain and quality of life.

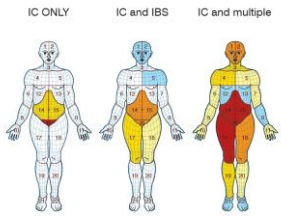
Mayer RD et al. Neurotherapeutics 2008;5(1):107–13.
Peters Km et alRev Urol 2002;4(Suppl 1):S36–43.

Distinct clinical phenotypes of pats. with IC/PBS

J.C.Nickel et al
IC/PBS and associated medical conditions:
J Urol 184,1358-63, Oct. 2010







Greater Pain
Greater BPS/IC Disease Specific Symptoms
Poorer Quality of Life

Poorer Coping Mechanisms
Greater Depression
More stress and anxiety
Decreased sexual functioning

J.C.Nickel et al

Commentary

Interstitial Cystitis/Bladder Pain Syndrome and Nonbladder Syndromes: Facts and Hypotheses

John W. Warren, Joop P. van de Merwe, and J. Curtis Nickel

UROLOGY 78 (4), 2011

Hypothesis 1:
the NBSs and IC/BPS initiate different processes (p) that lead to different syndromes.

Hypothesis 2:
that the NBSs and IC/BPS initiate a common process (p) that leads to additional syndromes.

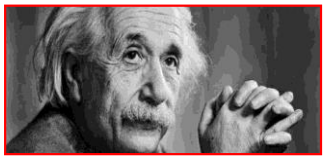
Hypothesis 3:
that a shared pathophysiology process (p) leads to the NBSs and IC/BPS.

Conclusions

- IC is associated with other "unexplained enigmatic" medical conditions, *likely through neurogenically mediated mechanisms .*
- An understanding of the pathophysiology of phenotypic initiation and progression requires more research

SIGNIFICANCE
Impacts our Diagnostic and Management Algorithm

- **Early Diagnosis**
- **Treat early and aggressively**
- **Identify Other Associated Conditions**
  - **IBS, VV, PFD, FM, CFS etc**
- **Manage the unique clinical phenotype of each patient**



"Let's not pretend that things will change if we keep doing the same things……"

Box 1
Therapeutic options for pelvic floor hypertonic disorders

Behavioral
- Education, rest, heat
- Avoidance of triggers
- Fluids and stool management

Physical Therapy
- Biofeedback/"Reverse" Kegels
- Soft tissue/myofascial therapy
- Ultrasound therapy

Pharmacologic Therapy
- Amitriptyline
- Tiazadine
- Compounded baclofen suppositories

Trigger Point Injections
- Wet trigger point injections, 3 to 5 sessions
- Botox A
- Consider caudal block, ganglion impar block

Neuromodulation
- Sacral nerve stimulation
- Posterior tibial nerve

Butrick CW Obstet Gynecol Clin N Am 36 (2009) 707–722

PHARMACOLOGIC THERAPY

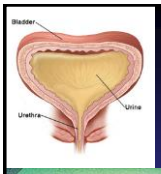
The transvaginal use of compounded baclofen suppositories (30 mg) or compounded diazepam suppositories (5 mg) every 8 hours has been very beneficial and well tolerated when placed either in the vagina or in the rectum for these patients

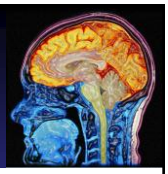
Butrick CW Obstet Gynecol Clin N Am 36 (2009) 707–72

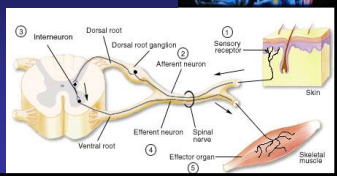
Central Sensitization Science for Clinicians

Christopher K. Payne, MD
Emeritus Professor of Urology at Stanford
Vista Urology & Pelvic Pain Partners

Transition







Pain is Simple

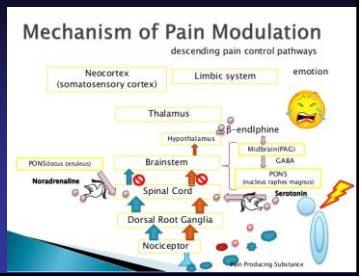
Peripheral stimulus

↓

Central perception

Pain is Complex

- Same stimulus, different person, different pain
- Multiple level modulation
- Pain without an identifiable stimulus



Phantom Limb

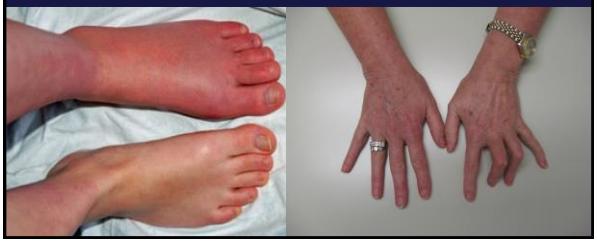
- Sensation persists after amputation
- Mechanism unknown
- Rewiring of input in brain
- Can resolve
- Can respond to treatment

Pelvic Pain Without Pelvic Organs

- Report of 4 patients with persistent pain after anterior exenteration
- 3 with interstitial cystitis and one with voiding dysfunction
- Recommend considering "alternative organ-preserving therapies"

Baskin LS and Tanagho EA: J Urol 1992;147(3) 683-686

Reflex Sympathetic Dystrophy/CRPS



Review

Functional somatic syndromes: one or many?

S Wessely, C Nimnuan, M Sharpe

We review the concept and importance of functional somatic symptoms and syndromes such as irritable bowel syndrome and chronic fatigue syndrome. On the basis of a literature review, we conclude that a substantial overlap exists between the individual syndromes and that the similarities between them outweigh the differences. Similarities are apparent in case definition, reported symptoms, and in non-symptom association such as patients' sex, outlook, and response to treatment. We conclude that the existing definitions of these syndromes in terms of specific symptoms is of limited value; instead we believe a dimensional classification is likely to be more productive.

"A significant overlap exists between the individual syndromes and the similarities between them outweigh the differences."

Wessely S: Lancet 1999; 354:936-939

TOPIC PAPER

Jeannette M. Potts

Chronic pelvic pain syndrome: a non-prostatocentric perspective

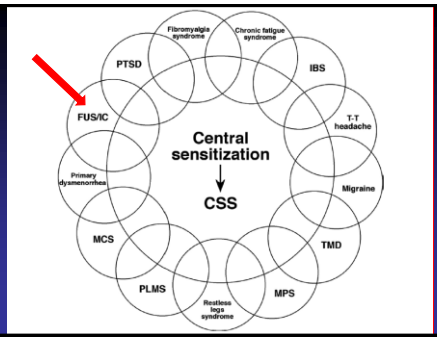
- Evidence of a bacterial etiology is non-existent, while evidence of prostatic inflammation is conflicting and non-specific.
- More plausible causes include . . . musculoskeletal pain, pelvic floor muscular dysfunction, myofascial pain syndromes, or functional somatic syndromes.

Potts JM: World J Urol (2003) 21:54-56

Fibromyalgia and Overlapping Disorders: The Unifying Concept of Central Sensitivity Syndromes

Muhammad B. Yunus, MD

Objectives: To discuss fibromyalgia syndrome (FMS) and overlapping conditions, eg, irritable bowel syndrome, headaches, and chronic fatigue syndrome, within the concept of central sensitivity syndromes (CSS).
Methods: A critical overview of the literature and incorporation of the author's own views.
Results: The concept of CSS seems viable. It is based on mutual associations among the CSS conditions as well as the evidence for central sensitization (CS) among several CSS members. However, such evidence is weak or not available in other members at this time, requiring further studies. The biology of CSS is based on neuroendocrine aberrations, including CS, that interact with psychosocial factors to cause a number of symptoms.
Conclusions: CSS is an important new concept that embraces the biopsychosocial model of disease. Further critical studies are warranted to fully test this concept. However, it seems to have important significance for new directions for research and patient care involving physician and patient education. Each patient, irrespective of diagnosis, should be treated as an individual considering *both* the biological and psychosocial contributions to his or her symptoms and suffering.
 Semin Arthritis Rheum 36:339-356
Keywords: fibromyalgia, central sensitivity syndromes, central sensitization, overlapping syndromes, fibromyalgia associations, functional syndromes



Central Pain Anatomy

- Dorsal Horn Spinal Cord
  - WDR neurons
  - Train station
- Brain Processing
  - Thalamus
  - Limbic System
  - Cortex

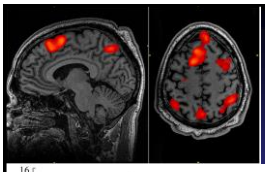
New Mechanisms & Targets

Table 1 Neurochemicals and Neuroreceptors Involved in Central Sensitization

Neuromodulators/Neurotransmitters Released by Activated C-nociceptors Presynaptically	
Substance P (SP)	Somatostatin
Calcitonin-gene-related peptide (CGRP)	Galanin
	Never growth factor
	Glutamate
Vasoactive intestinal peptide (VIP)	Aspartate
Post Synaptic Neuroreceptors/ Neuroeffector Targets	
Neurokinin 1 (NK1)	Metabotropic glutamate (mGlu)
N-methyl-D-aspartate (NMDA)	Tyrosine kinase B (Trk-B)
Alpha-amino-3-hydroxy-5-methyl 4-isoxazolepropionate (AMPA)	Protein kinase gamma (PKC-gamma)
	Vanilloid subfamily (TRPV-1, TRPVL-1)

Glutamate & Substance P excitatory
GABA inhibitory
NK1 Receptor
TRPV-1 Receptor

Measurable Physiology



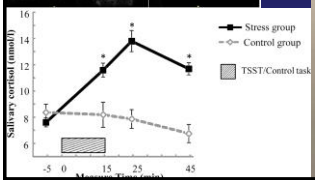


Table 3 Evidence for Central Sensitization by Controlled Studies in Selected Members of the CSS group in Response to Various Peripheral (Somatic) or Rectal (Visceral) Stimuli*

Stimulus	FMS	CFS	IBS	TTH	Migraine	TMD	MPS/RSTPS	PD
	# of studies (N of patients)†							
Pressure (somatic)‡	15 (580)			4 (178)	3 (117)	2 (42)	9 (462)	1 (20)
Pressure (rectal)§			26 (822)					
Heat (somatic)	12 (480)		2 (21)	1 (50)	3 (117)	3 (76)	3 (137)	2 (42)
Heat (rectal)			1 (46)					
Cold (somatic)	8 (255)		1 (33)		1 (41)		2 (184)	
Electric (cutaneous)	4 (61)		1 (12)				2 (36)	
Electric (intra-muscular)	2 (41)	1 (23)					2 (36)	1 (10)
Electric (spinal Reflex)	2 (107)		1 (14)	1 (40)			1 (27)	
Electric (rectal)			2 (21)					
Ischemic	1 (60)					2 (72)		
Hypertonic saline	2 (41)					1 (22)	1 (11)	
Auditory stimulus	1 (20)		1 (15)		1 (65)			

*See text for other evidence of CS (e.g. allodynia and temporal summation) in a CSS member, as well as evidence for CS in other CSS members. MPS/RSTPS-myofascial pain syndrome/regional soft tissue pain syndrome. See Table 2 for other abbreviations.
†Studies in all CSS conditions with first author (PMID#) that were not referenced in the text but counted for N in Table 3 are: (1) FMS/somatic pressure—Kosek E (9106808); Bendtsen L (9008605); Marques AP (15667613); Mikkelsson M (15148890); Staud R (15890634) (2) FMS/somatic heat—Kosek E (9106808); Berglund B (11932073) (3) FMS/Cold—Kosek E (9106808); Berglund B (11932073) (4) FMS/cutaneous electric—Arroyo JF (7848390) (5) IBS/rectal pressure—Greenwood B (8907258); Bernstein CN (8880836); Drewes AM (11495078); Fukodo S (12572883); Kwan CL (15621377); Chun A (1008061); Caldarella (15667496) (6) Migraine/pressure and heat—Kitai MB (16109112) (7) MPS/somatic pressure—Giesbrecht RJ (16180957). Please note that space limitations do not allow listing of all references in the text and under References.
‡By non-digital pressure.
§By balloon.

Neuroplasticity

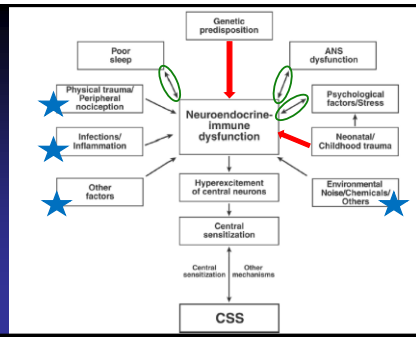
- Brain alterations in adulthood, after "critical period" of development
  - Cortical mapping
  - Individual neuron
    - Synaptic
    - Non-synaptic
- Not a one way process!

Neuroplasticity

"In fact, this finding extends our understanding of the brain's plasticity because it is evidence that profound changes in the mental representation of the body can be induced purely by internal brain mechanisms—the brain truly does change itself."

Moseley and Brugger 2009

Dalai Lama and effects of meditation on the brain



Summary

- **Pain is inherently a neurological phenomenon**
- **A large number of disorders previously assigned to an organ system are actually related Central Sensitization Syndromes:**
  - **No identifiable organ abnormality**
  - **Common neurological abnormalities**
- **Replace pejorative "it's all in your head" with logical "it's a complex neurological disorder"**

Workshop 13: Phenotyping IC/BPS for Clinical Success

Autoimmune, Multiple Sensitivity and Central Sensitization Potential Phenotypes

Jane M. Meijlink
International Painful Bladder Foundation (IPBF)

Jane M. Meijlink

ICS 2017 FLORENCE

Affiliations to disclose[†]:

None

† All financial ties (over the last year) that you may have with any business organization with respect to the subjects mentioned during your presentation

Funding for speaker to attend:

- ☐ Self-funded
- ☐ Institution (non-industry) funded
- ☐ Sponsored by:

Autoimmune Phenotype: Research has been limited

- The USA MAPP study with its comorbidity focus on irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, migraine headache and vulvodynia is only looking at part of the comorbidity problem, with its emphasis on pain and fatigue.
- Since the early 90s, comorbidity expert Joop P. van de Merwe in the Netherlands, in association with Dutch urologist Erik Arendsen, has been one of the few people who has looked closely, in a clinical setting, at the association between IC/BPS and systemic and other autoimmune diseases, particularly Sjögren's syndrome.
- *Van De Merwe JP, Arendsen HJ. Interstitial cystitis: a review of immunological aspects of the aetiology and pathogenesis, with a hypothesis. BJU Int. 2000 May;85(8):995-9.*
- *Van de Merwe JP, Yamada T, Sakamoto Y: Systemic aspects of interstitial cystitis, immunology and linkage with autoimmune disorders. Int J Urol 2003, 10 Suppl:S35-38.*
- *Van de Merwe JP. Interstitial cystitis and autoimmune diseases. Nat Clin Pract Urol. 2007 Sep;4(9):484-91.*

IC/BPS and comorbidities

Patients with chronic pelvic pain syndromes, including those with IC/BPS, have a higher prevalence of one or multiple comorbid syndromes and diseases than the general population. These include:

- allergies/non-allergic intolerances
- chronic pain syndromes
- chronic fatigue syndromes
- systemic autoimmune diseases

Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, ElNeil S, van de Merwe JP, Lin AT, Tomoe H. A standard for terminology in chronic pelvic pain syndromes: A report from the chronic pelvic pain working group of the International Continence Society. Neurourol Urodyn. 2017 Apr;36(4):984-1008. doi: 10.1002/nau.23072. Epub 2016 Aug 26.

ICS: A Standard for Terminology in Chronic Pelvic Pain Syndromes 2017

- Systemic [also called generalized] autoimmune diseases are a heterogeneous group of diseases with multi-organ and multi-system involvement and evidence indicating a role played by the immune system in the pathogenesis.
  - *Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, ElNeil S, van de Merwe JP, Lin AT, Tomoe H. A standard for terminology in chronic pelvic pain syndromes: A report from the chronic pelvic pain working group of the International Continence Society. Neurourol Urodyn. 2017 Apr;36(4):984-1008. doi: 10.1002/nau.23072. Epub 2016 Aug 26.*
- Some of these diseases are inflammatory, many not and some manifest themselves in either inflammatory or non-inflammatory forms.
- The etiology, pathogenesis and mechanisms of these diseases are unknown and diagnoses often uncertain.
- Currently, these systemic autoimmune diseases are not curable.

Systemic Autoimmune Diseases/Syndromes Examples:

1. **Systemic Lupus Erythematosus (SLE).** Most frequent symptoms are debilitating fatigue, arthritis, red skin lesions after sun exposure such as a red butterfly lesion of the face, pericarditis and pleuritis, glomerulonephritis. The prevalence is 10x higher in females than in males and 2x more frequent in non-white people.

2. **Sjögren's Syndrome (SjS)** is a systemic autoimmune disease characterized by a functional disorder of the tear and salivary glands, with or without signs of inflammation. The most common symptoms are irritation of the eyes, a dry mouth, muscle and joint pain, (debilitating) fatigue and Raynaud phenomenon.

3. **Rheumatoid Arthritis (RA)** is a disease characterized by chronic symmetric polyarthritis resulting in painful swelling of the joints. Other symptoms are morning stiffness, rheumatoid nodules and typical changes on hand and wrist radiographs.

Systemic Autoimmune Diseases/Syndromes

- Lupus cystitis is found quite frequently in the literature, going back a very long way, but mainly case reports.
- Van de Merwe has suggested that when IC/BPS occurs in SLE and RA, available data indicates that it may in fact be undiagnosed Secondary Sjögren's Syndrome causing the bladder disorder, rather than the SLE or RA itself.

Sicca Syndrome, Sjögren's-like, Undifferentiated Connective Tissue Disease

- Many disorders found in Sjögren's syndrome can also exist as separate diseases in themselves (e.g. Raynaud's phenomenon, interstitial nephritis, hypersensitivity vasculitis, etc).
- This can also apply to the characteristic Sjögren's abnormalities in the tear and salivary glands. If only these symptoms are present, patients are classified as having **Sicca Syndrome** and not **Sjögren's syndrome**.
- Some IC/BPS patients are not diagnosed with Sjögren's syndrome because they do not meet the full criteria and may for example have only 3 out of the 4 criteria required.
- This has led to a diagnosis of a **Sjögren's-like syndrome** also known as **Incomplete Sjögren's syndrome.**
- Sjögren's-like syndrome should not be confused with Sicca Syndrome.
- Sometimes Sjögren's-like is diagnosed as **Undifferentiated Connective Tissue Disease (UCTD)**. The same diagnosis applies to other systemic autoimmune diseases when not all criteria are met.

Autoimmune phenotype

- In the Netherlands, we have quite a large group of patients diagnosed with IC + Sjögren's syndrome or Sjögren's-like. There appears to be no bias towards lesion or non-lesion in this group.
- One could hypothesize that the autoimmune disease itself creates a susceptibility in different organs, and that anything could trigger off bladder pain and lesions in these patients (infection, trauma etc).
- Maybe it's an epithelial deficiency caused by the autoimmune disease that creates this susceptibility and could perhaps be one of the reasons for other comorbidities such as gastrointestinal and gastroesophageal disorders in this phenotype?

Questions to consider:

- Is the IC/BPS a consequence of the systemic autoimmune disease and part of the disease?
- Or is this IC/BPS (subtype) a separate organ-specific autoimmune disease?
- Or do both exist?

Autoimmune phenotype treatment

- For optimal treatment, comorbid diseases should be diagnosed and treated by the appropriate specialists working as a multidisciplinary team with the urologist. It sounds simple, but in practice it's complex and you don't very often find it working optimally, if at all.
- When treating each comorbid disease, it is essential to remember that an individual IC/BPS patient may not only have one or more autoimmune diseases, but also other pain syndromes, neurological disorders, allergies, etc., all of which must be taken into account.

Autoimmune treatment: problems

- Sometimes a treatment can benefit more than one condition. On the other hand, the opposite can occur. Treatment that may work well for IC/BPS in some patients may not be tolerated by patients who also have Sjögren's syndrome: e.g. amitriptyline which increases the dryness in Sjögren's pts.
- Some drugs may cause increased pain or irritation in the IC/BPS bladder (including antibiotics) or intestinally if the patient also has GI disorders. There are many more examples.

Autoimmune disease treatment: warning

- Certain drugs sometimes used to treat patients with autoimmune diseases can cause more than irritation. They can actually cause bladder pain and lesions (known then as **chemical cystitis**).
- The anti-inflammatory agent tiaprofenic acid is known to do this, also the immunosuppressant cyclophosphamide (causing **hemorrhagic cystitis** and **fibrosis**). The chemical cystitis category also includes the potentially very severe bladder damage caused by street ketamine.
- Neither chemical cystitis nor hemorrhagic cystitis are phenotypes or subtypes, but are considered confusable diseases or differential diagnoses, and an experienced pathologist is not likely to confuse them with IC/BPS.
- Nevertheless, this emphasizes how important cystoscopy is, together with a comprehensive multidisciplinary history, to determine the true cause of the symptoms.

More information about Sjögren's syndrome and other autoimmune disorders, including the combination with IC/BPS, can be found on the IPBF website under "associated disorders".

Sjögren's syndrome - information for patients and professionals

by Dr Joop P van de Merwe

http://www.painful-bladder.org/pbs_ic_ass_dis.html

Multiple Sensitivity Phenotype

- Another important potential phenotype is the one termed **Multiple Sensitivity Phenotype** by Fuoco *et al* in Canada. This term covers allergies and non-allergic intolerances or hypersensitivities.
- *Fuoco MB, Irvine-Bird K, Nickel JC. Multiple sensitivity phenotype in interstitial cystitis/bladder pain syndrome. Can Urol Assoc J. 2014 Nov;8(11-12):E758-61*
- The Canadians noted that their database of IC/BPS patients included patients who seemed to have an inordinate number of allergies and sensitivities, whereas others had either no allergies or few. They carried out a pilot study and have characterized a distinct phenotypic group of patients with IC/BPS and multiple sensitivities.
- Allergies have been commonly associated with IC/BPS for decades, while mast cells and mast cell activation have long been a topic of interest.

True allergies versus non-allergic intolerances

- True allergies can be identified by tests. Non-allergic intolerances, however, are more difficult to establish and may ultimately be a question of trial and error.
- IC/BPS patients may have true allergies or non-allergic intolerances or a mixture of both.
- However, big problems arise with multiple drug intolerance.

Drug reactions

- Non-allergic intolerance reactions to drugs can be difficult to distinguish from true allergic reactions.
- Drug intolerance may affect, for example, cognitive functioning, eyesight and balance and cause dizziness, faintness, headache, fatigue, extreme drowsiness, GI disorders and even shock.
- This makes treatment very difficult indeed in this group of patients since reactions to drugs may be unpredictable, variable and multiple.
- A patient with this problem can become very desperate, and very nervous about trying new drugs, and naturally very depressed about what the future may bring.
- New drugs should therefore be tried in miniscule amounts in these patients. While some patients may get an immediate strong reaction, in others the reaction may worsen dose by dose to a completely intolerable level. This process may happen slowly or very quickly. Intravesical treatment may be the best option for the bladder aspect in these patients since it goes straight to the bladder without passing through the rest of the body.

Central Sensitization or Multiple Chronic Pain Syndromes Phenotype?

- While everyone is talking about central sensitization these days, they all appear to have different ideas about what this means.
- In clinical terms, we are talking about patients with several or multiple chronic pain syndromes.
- So, when thinking about a potential phenotype, we could call it a **Multiple Chronic Pain Syndromes Phenotype**.

ICS CPPS document: Chronic Pain and Fatigue Syndromes.

- Chronic pain and fatigue syndromes are characterized by often widespread pain; fatigue; sleep disturbances; and disability.
- The symptoms are usually medically unexplained, have no known pathophysiology or organic basis and show no abnormal laboratory or imaging investigations.
- The literature suggests that many of these conditions share demographic characteristics, clinical course and psychosocial profiles.

ICS CPPS document: Chronic Pain and Fatigue Syndromes.

- **Fibromyalgia**: symptoms are widespread musculoskeletal pain, fatigue, non-restorative sleep, psychological distress, and regions of localized tenderness
- **Temporomandibular Joint Disorders**: symptoms consist of complaints of facial, jaw, neck, or shoulder pain. The pain is experienced in or around the ear with chewing, speaking, or opening the mouth, with or without migraine
- **Chronic Fatigue Syndrome**: is defined as clinically evaluated, unexplained, persistent or relapsing fatigue plus four or more specifically defined associated symptoms (self-reported impairment in short term memory or concentration; sore throat; tender cervical or axillary nodes; muscle pain; pain in multiple joints without redness or swelling; headaches of a new pattern or severity; unrefreshing sleep)

Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Hamma Y, Garrido G, Gomes MJ, Elneil S, van de Merwe JP, Lin AT, Tomoe H. A standard for terminology in chronic pelvic pain syndromes: A report from the chronic pelvic pain working group of the international continence society. Neurourol Urodyn. 2017 Apr;36(4):984-1008. doi: 10.1002/nau.23072. Epub 2016 Aug 26.

Pain Treatment and QoL

- In practical terms, IC/BPS patients may have several pain disorders affecting their whole body. Systemic pain treatment may work – or be partially effective - in some patients, but may make others very sick indeed, and this is not going to improve their quality of life. In these cases, you will probably need to combine milder systemic pain treatment plus local intravesical treatment. We should not forget that IC/BPS patients have bladder pain plus urgency plus frequency.
- Treatment of the bladder itself may then at least provide alleviation of these symptoms, regardless of any central sensitization hypothesis. We should not lose sight of this aspect: **The patient's quality of life should be paramount.**

Take home messages

1. While there has not yet been enough research and scientific evidence to "officially define" these potential phenotypes, there is every unofficial reason to take a specially tailored multidisciplinary approach when treating patients with IC/BPS + one or more potential comorbidity phenotypes.
2. A key aspect is that all specialists involved need to take all the other conditions fully into account.
3. Treatment is always going to be individual since not only are IC/BPS patients all different, but patients with systemic autoimmune diseases, chronic pain syndromes, fatigue syndromes and allergies are also all different. But maybe we can narrow down the trial and error approach by using the phenotype concept.
4. A very flexible approach to guidelines is needed. And maybe we need special treatment guidelines per phenotype and/or combinations of overlapping phenotypes, that could be used as a reference by all the specialists involved.
5. **Above all, remember that drug intolerance can put a spanner in the works of even the best treatment guideline.**

JOINT MEETING OF THE
4th INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS, JAPAN (ICICJ)
AND
THE ESSIC ANNUAL MEETING 2018
KYOTO INTERNATIONAL CONFERENCE CENTER,
KYOTO, JAPAN

www.icicj.jp/en/meeting/2018

This two-day meeting will discuss the state-of-the-art progress of interstitial cystitis/bladder pain syndrome(IC/BPS) – Hunner Lesions.

16-17 April, 2018

Joint Meeting of the 4th International Consultation on Interstitial Cystitis, Japan (ICICJ) and the ESSIC Annual Meeting 2018, Kyoto International Conference Center, Kyoto, Japan.