Interstitial Cystitis/ Bladder Pain Syndrome –

Overview, Case Definitions, Outcome Assessment

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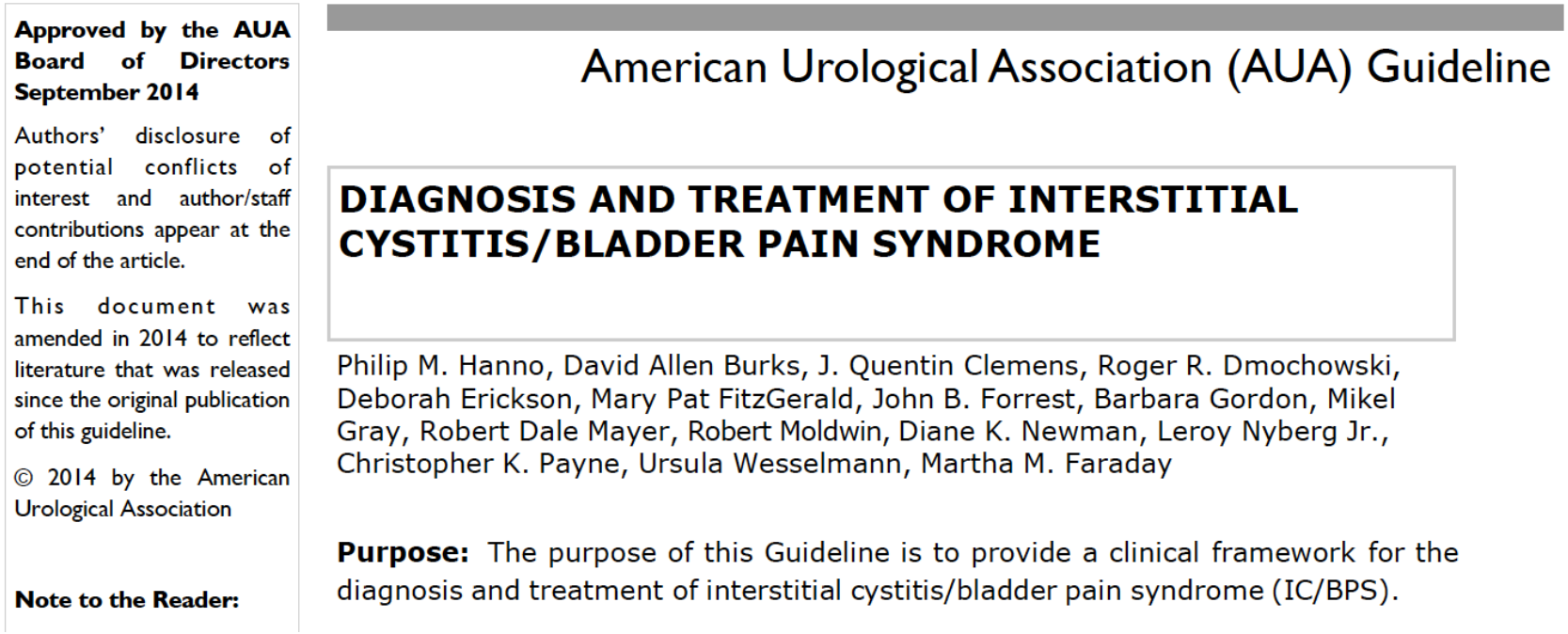
What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – A layman's description

- **Bourque's description (1951):**

"We have all met, at one time or another, patients ***who suffered chronically from their bladder****, and we mean the ones who are* distressed, ***not only periodically but constantly****, having to* ***urinate often, at all moments of the day and the night****, and* ***suffering pains every time they void****. We all now how these* ***miserable*** *patients are unhappy, and how those* ***distressing*** *bladder symptoms get finally to influence their general state of* ***health physically*** *at first, and* ***mentally*** *after a while."*

What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – Contemporary case definitions

- **Endorsed by the American Urological Association (AUA) and SUFU (Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction)**



Approved by the AUA Board of Directors September 2014

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

This document was amended in 2014 to reflect literature that was released since the original publication of this guideline.

Note to the Reader:

American Urological Association (AUA) Guideline

DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Philip M. Hanno, David Allen Burks, J. Quentin Clemens, Roger R. Dmochowski, Deborah Erickson, Mary Pat FitzGerald, John B. Forrest, Barbara Gordon, Mikel Gray, Robert Dale Mayer, Robert Moldwin, Diane K. Newman, Leroy Nyberg Jr., Christopher K. Payne, Ursula Wesselmann, Martha M. Faraday

Purpose: The purpose of this Guideline is to provide a clinical framework for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome (IC/BPS).

What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – Contemporary case definitions

- **Endorsed by the American Urological Association (AUA) and SUFU (Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction)**

*"An unpleasant sensation (**pain, pressure, discomfort**) **perceived** to be related to the urinary **bladder**, associated with **lower urinary tract symptoms** of more than six weeks duration, in the **absence of infection or other identifiable causes**."*

What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – Contemporary case definitions

- **Case definition for ESSIC (European Society for the Study of IC) and EAU (European Association of Urology)**

EUROPEAN UROLOGY 53 (2008) 60–67

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Pelvic Pain

Diagnostic Criteria, Classification, and Nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC Proposal

Joop P. van de Merwe[a], *Jørgen Nordling*[b,*], *Pierre Bouchelouche*[c], *Kirsten Bouchelouche*[c], *Mauro Cervigni*[d], *L. Kurosch Daha*[e], *Suzy Elneil*[f], *Magnus Fall*[g], *Gero Hohlbrugger*[h], *Paul Irwin*[i], *Svend Mortensen*[b], *Arndt van Ophoven*[j], *John L. Osborne*[k], *Ralph Peeker*[g], *Benedikte Richter*[b], *Claus Riedl*[l], *Jukka Sairanen*[m], *Martina Tinzl*[n], *Jean-Jacques Wyndaele*[o]

What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – Contemporary case definitions

- **Case definition for ESSIC (European Society for the Study of IC) and EAU (European Association of Urology)**

"BPS would be diagnosed on the basis of chronic (>6 months) ***pelvic pain, pressure or discomfort*** *perceived to be related to the urinary* ***bladder*** *accompanied by at* ***least one other urinary symptom*** *like persistent urge to void or frequency.* ***Confusable diseases*** *as the cause of the symptoms must be* ***excluded****."*

van de Merwe et al, Eur Urol 2008

What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – Contemporary case definitions

- **Commonalities of contemporary case definitions (AUA, EUA, SUFU, ESSIC)**

  - Chronic
  - Pain, pressure, discomfort from the bladder/pelvic
  - Associated with lower urinary tract symptoms (related to bladder, e.g. frequent urination, urinary urgency, nocturia)
  - Based on pain and urinary symptoms
  - Not defined by specific pathology, imaging, cystoscopic findings
  - No biomarkers yet
  - A clinical syndrome (symptom complex with no known etiology)
  - Heterogeneous population (like other chronic pain, e.g. IBS)

Comparing contemporary definitions to NIDDK Criteria

- **Departure from the NIDDK Criteria for IC/BPS Research (1987, 1988) close to 30 years ago**

  - 1987: NIDDK established a committee to streamline research
  - Revised in 1998 to further emphasize cystoscopic findings
  - Context: there was no research definition of IC ("starting point")
  - Context: IC/BPS is a "bladder disease" (rather than a syndrome)
  - Based on expert opinion and expert consensus
  - Became the *de facto* definition of IC/BPS to recruit into studies:
    - relatively uniform population of patients
    - ensure groups of patients studied would be comparable
    - fulfilled some objective criteria to be enrolled into research
    - *To study the beast, you need to describe the beast first…*

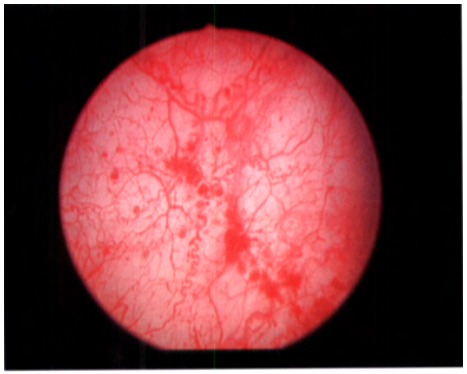
Pain + urgency +

Must have objective cystoscopy findings:

- **Hunner lesion**

-or-

- **Glomerulations**



APPENDIX 1: NIDDK DIAGNOSTIC CRITERIA FOR INTERSTITIAL CYSTITIS

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or classic Hunner's ulcer, and they must have either pain associated with the bladder or urinary urgency. An examination for glomerulations should be undertaken after distention of the bladder with the patient under anesthesia to 80 to 100 cm. water pressure for 1 to 2 minutes. The bladder may be distended up to 2 times before evaluation. The glomerulations must be diffuse, present in at least 3 quadrants of the bladder, and there must be at least 10 glomerulations per quadrant. The glomerulations must not be along the path of the cystoscope (to eliminate artifact from contact instrumentation). The presence of any of the following criteria excludes the diagnosis of interstitial cystitis:

1. Bladder capacity greater than 350 cc on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100 cc gas or 150 cc water during cystometry, using a fill rate of 30 to 100 cc per minute
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described previously
4. Duration of symptoms less than 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics or antispasmodics
7. A frequency of urination, while awake, of less than 8 times a day
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period

(plus other exclusion criteria...)

Comparing contemporary definitions to NIDDK Criteria

- **NIDDK Criteria for IC/BPS Research (1987, 1988)**
  - Unfortunately this NIDDK research definition became the diagnostic criteria for many practitioners and regulatory definition (FDA, clinical trial design & enrollment, drug approval)

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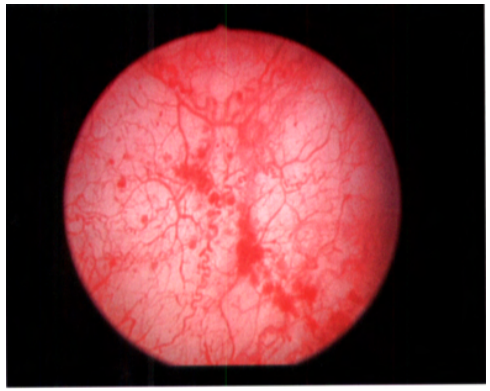


Hunner lesion is uncommon (~10%); Glomerulation is non-specific
Majority of IC/BPS patients are not covered by NIDDK definition.

The patient with Hunner lesion definitely has “classic” IC

Hunner lesion (the classic “interstitial cystitis”):

“A circumscript, reddened mucosal area that can have small vessels radiating towards a central scar, and/or a fibrin deposit of coagulum attached to this area.”

- **Focal, distinct areas of visible inflammation in the bladder**

- Seen in office cystoscopy
- Bleeding w/ distention (waterfall)
- May resemble CIS

There are good treatments for patients with Hunner lesion

18. If Hunner's lesions are present, then fulguration (with laser or electrocautery) and/or injection of triamcinolone should be performed. ***Recommendation (Evidence Strength—Grade C)***

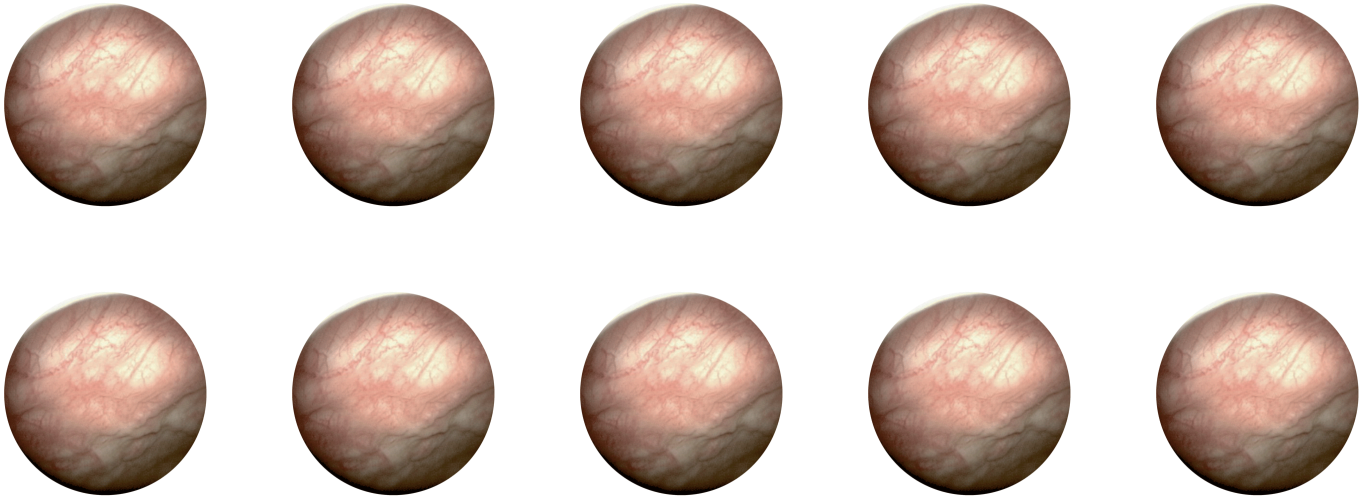
AUA IC Guideline [1]

Treatment	No. of pts	% who improve	Durability
Fulguration [2]	N=59	78% response	20.3 months
Fulguration/TUR [3]	N=14	86% response (pain: 8.1 to 1.7)	22.3 months
Triamcinolone injection [4]	N=30	70% response (PUF: 20 to 11.0)	7-12 months
Cyclosporine A [5]	N=34	85% response with Hunner lesion (30% without Hunner lesion)	

[1] Hanno et al, J Urol 2011; [2] Hillesohn et al; [3] Payne et al; [4] Cox et al; [5] Forrest et al.

Problem: Most IC/BPS patients don't have Hunner's lesion

~10% (Hunner lesion, "classic IC")



~90%
Normal
Cystoscopy

Problem: Glomerulation is not specific to IC/BPS

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 (JN), 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 National Institute of Diabetes and Digestive and Kidney Diseases 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 as research has found glomerulations in asymptomatic populations. In this review we systematically examine the available research to see if there are valid data to support the use of glomerulations as a marker for bladder pain syndrome/interstitial cystitis.

Materials and Methods: A systematic literature search of the PubMed® data-

Abbreviations and Acronyms

BPS = bladder pain syndrome

ESSIC = International Society for the Study of BPS

HD = hydrodistention

IC = interstitial cystitis

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases

Conclusions: We found no convincing evidence in the reviewed literature that glomerulations should be included in the diagnosis or phenotyping of bladder pain syndrome/interstitial cystitis. Glomerulations do not correlate with symptoms and are found in patients without bladder pain syndrome/interstitial cystitis.

Problem: NIDDK criteria miss about 2/3 of IC/BPS patients

- Compared the NIDDK research criteria to clinical definition of IC/BPS (similar to contemporary AUA/SUFU case definition):

THE DIAGNOSIS OF INTERSTITIAL CYSTITIS REVISITED: LESSONS LEARNED FROM THE NATIONAL INSTITUTES OF HEALTH INTERSTITIAL CYSTITIS DATABASE STUDY

PHILIP M. HANNO,*† J. RICHARD LANDIS, YVONNE MATTHEWS-COOK, JOHN KUSEK, LEROY NYBERG, JR. AND THE INTERSTITIAL CYSTITIS DATABASE STUDY GROUP

Results: Almost 90% of patients potentially meeting NIDDK criteria are believed by experienced clinicians to have interstitial cystitis, confirming the research value of these criteria in defining a homogeneous population for study. However, strict application of NIDDK criteria would have misdiagnosed more than 60% of patients regarded by researchers as definitely or likely to have interstitial cystitis.

Conclusions: The NIDDK criteria are too restrictive to be used by clinicians as the diagnostic definition of interstitial cystitis.

Problem: NIDDK criteria miss about 2/3 of IC/BPS patients

- Using the NIDDK research definition to diagnose IC/BPS in the clinical setting, or as regulatory definition will exclude a lot of IC/BPS patients from clinical trial enrollment and drug approval:
  - **Not address the large unmet needs of patients and society**
  - **May be doing a disservice to patients and society**
  - **Restricting to a narrow minority sub-group of patients**
  - **Reality: heterogeneous pt population, a clinical syndrome and chronic pain that desperately needs novel treatments**
  - **No objective marker ≠ need to suffer pain for next 30 yrs**

Results: Almost 90% of patients potentially meeting NIDDK criteria are believed by experienced clinicians to have interstitial cystitis, confirming the research value of these criteria in defining a homogeneous population for study. However, strict application of NIDDK criteria would have misdiagnosed more than 60% of patients regarded by researchers as definitely or likely to have interstitial cystitis.

Conclusions: The NIDDK criteria are too restrictive to be used by clinicians as the diagnostic definition of interstitial cystitis.

Hanno et al, J Urol 1999

Problem: IC/BPS patients who fulfilled NIDDK criteria are not different from patients who did not fulfilled NIDDK criteria

- Compared IC/BPS patients who fulfilled the NIDDK criteria and IC/BPS patients who did not fulfilled the NIDDK criteria:

DO THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES CYSTOSCOPIC CRITERIA ASSOCIATE WITH OTHER CLINICAL AND OBJECTIVE FEATURES OF INTERSTITIAL CYSTITIS?

DEBORAH R. ERICKSON,* JOHN E. TOMASZEWSKI, ALLEN R. KUNSELMAN, CHRISTINA M. BENTLEY, KENNETH M. PETERS, ERIC S. ROVNER, LAURENCE M. DEMERS, MARCIA A. WHEELER AND SUSAN K. KEAY

Conclusions: Patients who met the cystoscopic criteria had worse daytime frequency and nocturia, and lower bladder capacity under anesthesia. However, the 2 groups had similar urine markers and bladder biopsy findings. The cystoscopic criteria do not appear to identify a distinct pathophysiological subset of patients with IC symptoms.

Problem: IC/BPS patients who fulfilled NIDDK criteria are not different from patients who did not fulfilled NIDDK criteria

- Compared IC/BPS patients who fulfilled the NIDDK criteria and IC/BPS patients who did not fulfilled the NIDDK criteria:
  - **No differences in urinary biomarker levels (APF, HB-EGF, EGF, IL-6, IL-8, cGMP, methyl-histamine)**

TABLE 1. *Urine marker levels in patients with IC symptoms who did versus did not meet NIDDK cystoscopic criteria*

Marker	Median No. Did Meet (IQR)	Median No. Did Not Meet (IQR)	p Value (Wilcoxon-Mann-Whitney test)
APF (%)*	−95 (11)	−93 (16)	0.35
HB-EGF (ng)	0.4 (0.7)	0.6 (0.8)	0.71
EGF (ng)	33 (42)	30 (26)	0.74
IL-6 (pg)	4.4 (6.5)	5.6 (6.0)	0.58
IL-8 (pg)	5.4 (19.4)	4.0 (47.6)	0.74
Cyclic guanosine monophosphate (pmoles)	310 (214)	277 (353)	0.72
Methylhistamine (ng)	149 (239)	188 (80)	0.37

* APF is expressed as percent inhibition of thymidine uptake. All other markers are expressed as the unit in parentheses per mg urine creatinine.

- Compared IC/BPS patients who fulfilled the NIDDK criteria and IC/BPS patients who did not fulfilled the NIDDK criteria:
  - **No differences in bladder biopsy features (histology and immunostaining)**
    - Tissue HB-EFG
    - Tissue EGF, EGFR
    - Tissue IL-6
    - Denuded epithelium
    - Glomerulation
    - Leukocyte, granulation
    - Bladder fibrosis

TABLE 2. *Bladder biopsy features of patients with IC symptoms who did versus did not meet NIDDK cystoscopic criteria*

Biopsy Feature	Biopsy Feature Ordinal Scale*				p Value (Mantel-Haenszel chi-square exact test)
	% 0	% 1	% 2	% 3	
HB-EGF in urothelium:†					
Did meet	7	30	20	43	0.12
Did not meet	0	15	15	69	
HB-EGF in submucosa:†					
Did meet	23	47	30	0	0.81
Did not meet	8	69	23	0	
EGF in urothelium:†					
Did meet	19	45	19	16	0.88
Did not meet	31	23	23	23	
EGF in submucosa:†					
Did meet	45	45	6	3	0.83
Did not meet	46	46	8	0	
EGFR in urothelium:†					
Did meet	53	20	13	13	0.67
Did not meet	54	0	31	15	
EGFR in submucosa:†					
Did meet	94	6	0	0	0.60
Did not meet	85	15	0	0	
IL-6 in urothelium:†					
Did meet	10	23	23	43	0.76
Did not meet	15	8	23	54	
IL-6 in submucosa:†					
Did meet	23	39	32	6	0.16
Did not meet	0	38	62	0	
% Epithelium denuded:‡					
Did meet	6	52	19	23	0.59
Did not meet	8	31	38	23	
Submucosal hemorrhage:‡					
Did meet	77	19	3	0	1.00
Did not meet	77	15	8	0	
Submucosal granulation tissue:‡					
Did meet	90	3	0	6	0.84
Did not meet	85	15	0	0	
Submucosal leukocyte common antigen stain:§					
Did meet	0	57	20	23	0.53
Did not meet	0	62	31	8	
Submucosal F8 stain:§					
Did meet	0	32	58	10	0.60
Did not meet	0	46	46	8	
Detrusor fibrosis:§					
Did meet	13	73	13	0	0.66
Did not meet	13	88	0	0	

Erickson et al, J Urol, 2005

Problem: IC/BPS patients who fulfilled NIDDK criteria are not different from patients who did not fulfilled NIDDK criteria

- Compared IC/BPS patients who fulfilled the NIDDK criteria and IC/BPS patients who did not fulfilled the NIDDK criteria:
  - **No differences in symptoms other than increased frequency, nocturia and decreased bladder capacity in the NIDDK group.**

TABLE 4. *Frequency of "yes" responses to specific symptoms in patients who did versus did not meet NIDDK cystoscopic criteria*

Symptom	% Did Meet	% Did Not Meet	p Value (Fisher's exact test)
Foods/drinks worsen symptoms	57	47	0.55
Irritable bowel syndrome	25	41	0.34
Medication allergies	49	65	0.38
Airborne particle allergies	25	59	0.03
Skin contact allergies	28	29	1.00
Pain improves after voiding	67	59	0.76
Burning	53	59	0.77
Bloating	64	76	0.53
Sharp or stabbing pain	47	71	0.14
Pain as dull ache	60	71	0.55
Standing improves pain	21	35	0.31
Main pain in rt lower quadrant	37	24	0.37
Hematuria with flares	14	6	0.65
Constant urge	74	71	1.00

Clinical IC/BPS population is heterogeneous on cystoscopy

- Varying cystoscopic findings when classified based on symptom severity

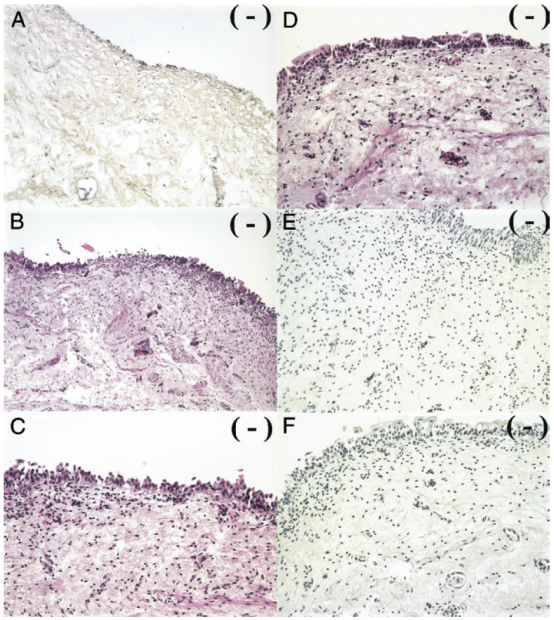
TABLE V. ***Baseline cystoscopy results of ICDB study population****

	Mild n = 59	Moderate n = 71	Severe n = 60	Overall n = 190	*P*-Value†
Hunner's patch	2 (3.4)	3 (4.2)	15 (25.0)	20 (10.5)	<0.001
Scars	3 (5.1)	6 (8.5)	19 (31.7)	28 (14.7)	0.001
Bloody effluent‡	38 (73.1)	46 (70.8)	43 (81.1)	127 (74.7)	0.307
Glomerulations (Severity)‡					
None	7 (13.5)	8 (12.3)	3 (5.7)	18 (10.6)	0.582
Mild	15 (28.9)	23 (35.4)	18 (34.0)	56 (32.9)	
Moderate	15 (28.9)	24 (36.9)	22 (41.5)	61 (35.9)	
Severe	15 (28.9)	10 (15.4)	10 (18.9)	35 (20.6)	
Glomerulations (Distribution)§					
Diffuse	34 (75.6)	41 (71.9)	40 (80.0)	115 (75.7)	0.563
Localized	11 (24.4)	16 (28.1)	10 (20.0)	37 (24.3)	

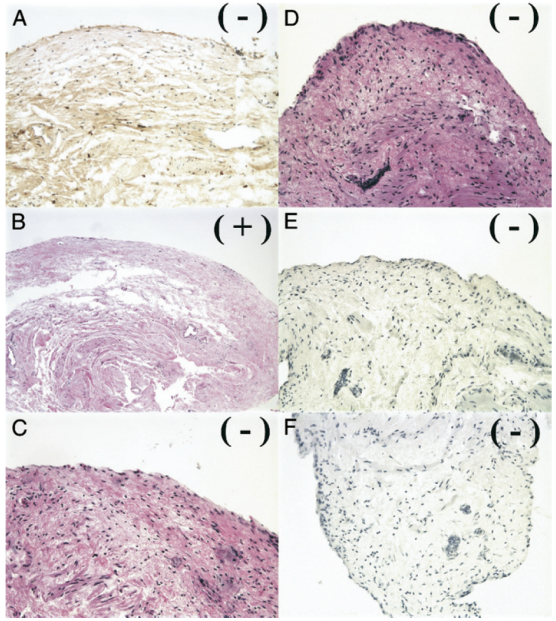
* *Reported as number (and percentage) within symptom subgroup having characteristic on cystoscopy.*
† *Mantel-Haenszel test using rank scores.*
‡ *Based on reduced sample size of 170; those patients undergoing cystopscopy with hydrodistention (52 mild, 65 moderate, 53 severe).*
§ *Based on reduced sample size of 152; those patients having glomerulations (45 mild, 57 moderate, 50 severe).*

Clinical IC/BPS population is heterogeneous on biopsy

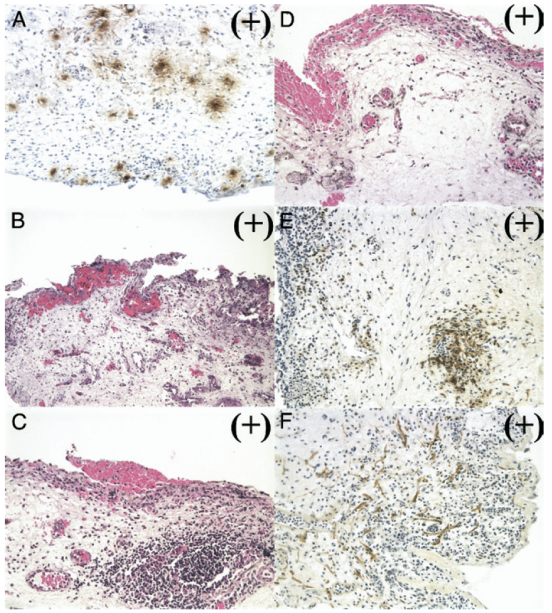
- Varying histology findings on bladder biopsy (3 patient clusters)



Normal
(88.2%)



Loss of urothelium
without inflammation
(8.4%)



Loss of urothelium
with inflammation
(3.4%)

Leiby et al, J Urol 1997

What is interstitial cystitis/bladder pain syndrome (IC/BPS)? – Contemporary case definitions

- **Recognize that IC/BPS is a syndrome with heterogeneous patient population** (like other chronic pain conditions, e.g., IBS)
  - ***Europe (ESSIC) Guideline –*** *"**Further classification of BPS** might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies."*

ESSIC CLASSIFICATION OF BLADDER PAIN SYNDROME TYPES

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

Problem: European criticism of using NIDDK criteria

EAU Guidelines on Chronic Pelvic Pain

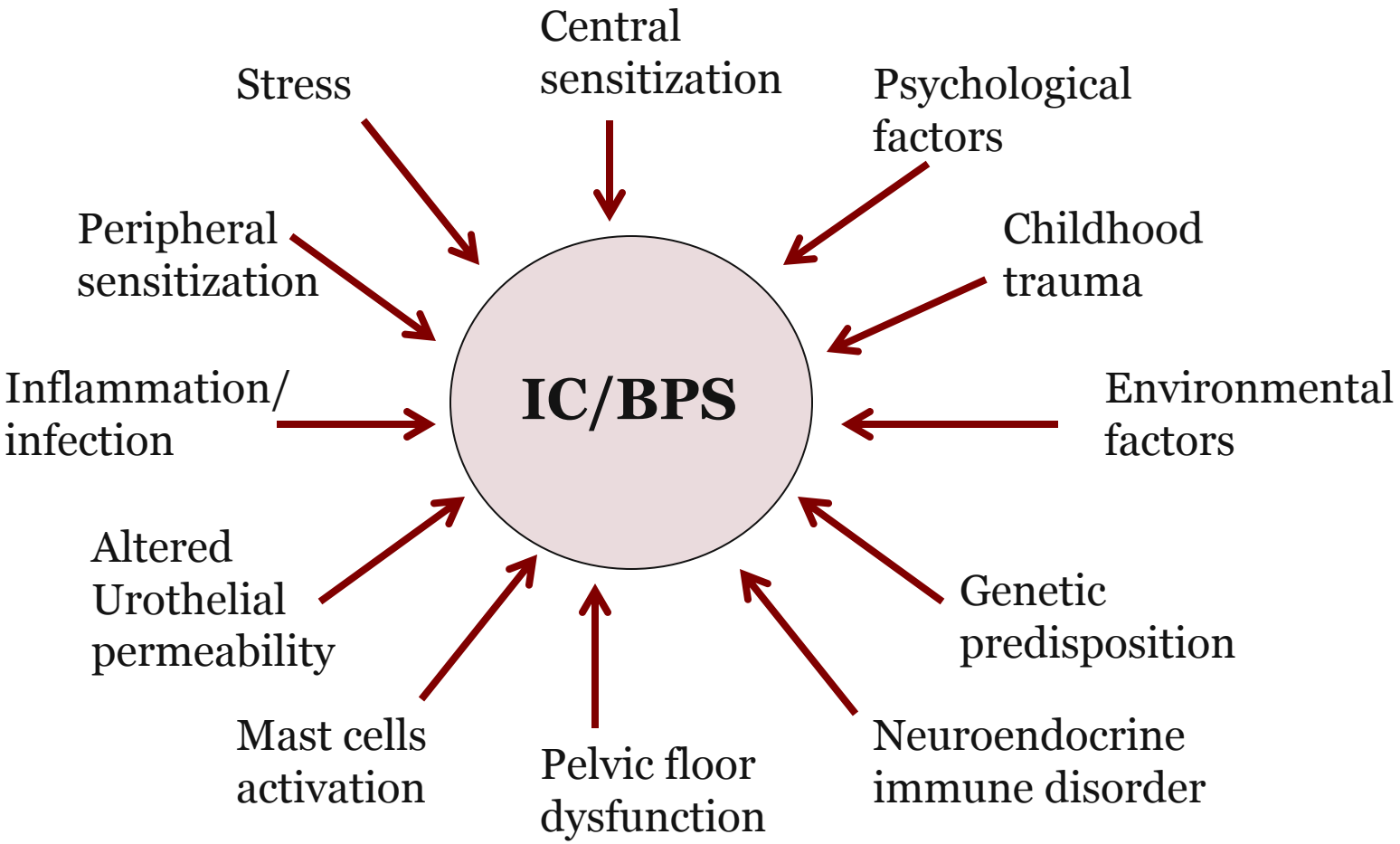
M. Fall[a,*], A.P. Baranowski[b], C.J. Fowler[b], V. Lepinard[c], J.G. Malone-Lee[d], E.J. Messelink[e], F. Oberpenning[f], J.L. Osborne[g], S. Schumacher[h]

3. Bladder pain syndrome (Interstitial cystitis)

The collective term "Interstitial cystitis" includes a variety of conditions most commonly identified by symptoms. The classical ulcer disease (Hunner's ulcer) is found in as few as 10% up to 50% of cases [22,23]. The diagnostic criteria described by the NIDDK [24] were formulated for research purpose and reach a diagnosis through exclusion, inappropriate in clinical care (Table 3). Since symptoms invariably define the clinical condition the term "Painful bladder syndrome" or "Bladder pain syndrome" is more apposite.

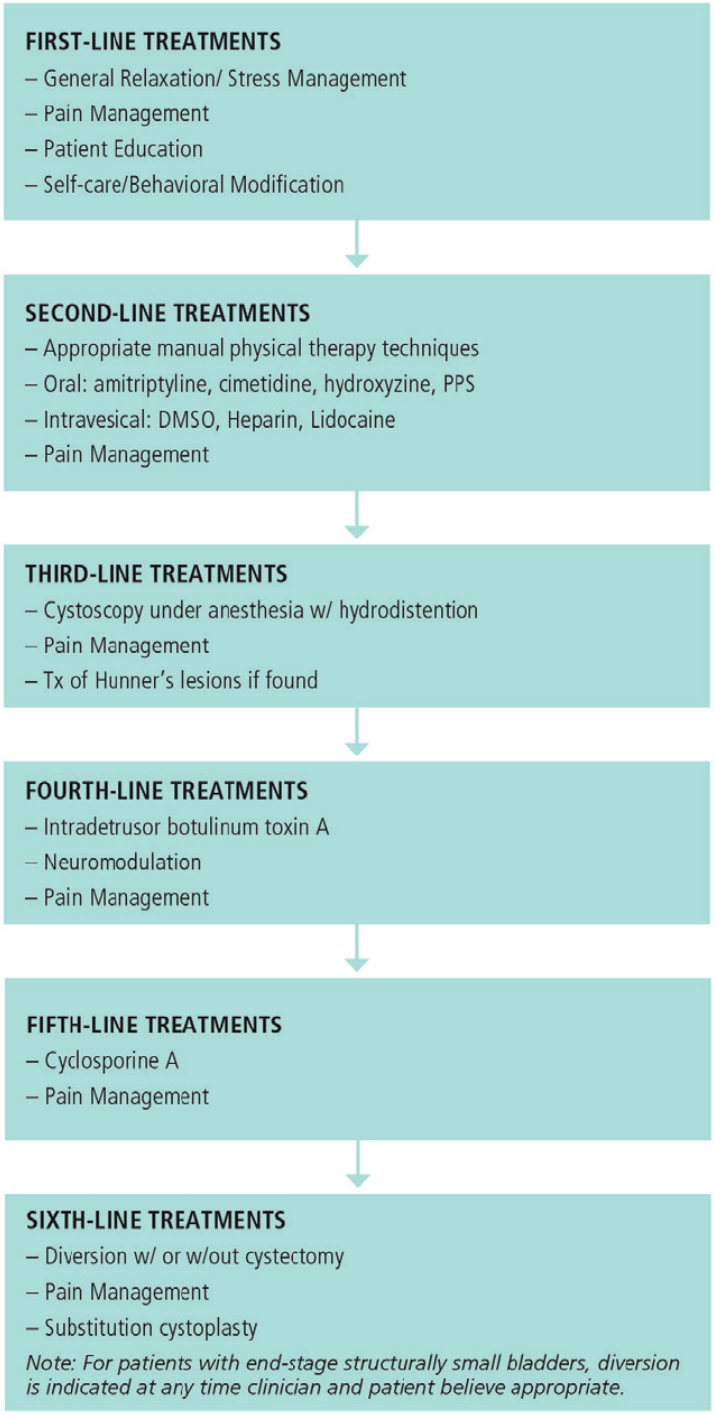
M. Fall, ironically, wrote the most about Hunner lesion

IC/BPS is a difficult syndrome to treat (heterogeneous, lack of objective biomarkers, & poor understanding of etiologies)



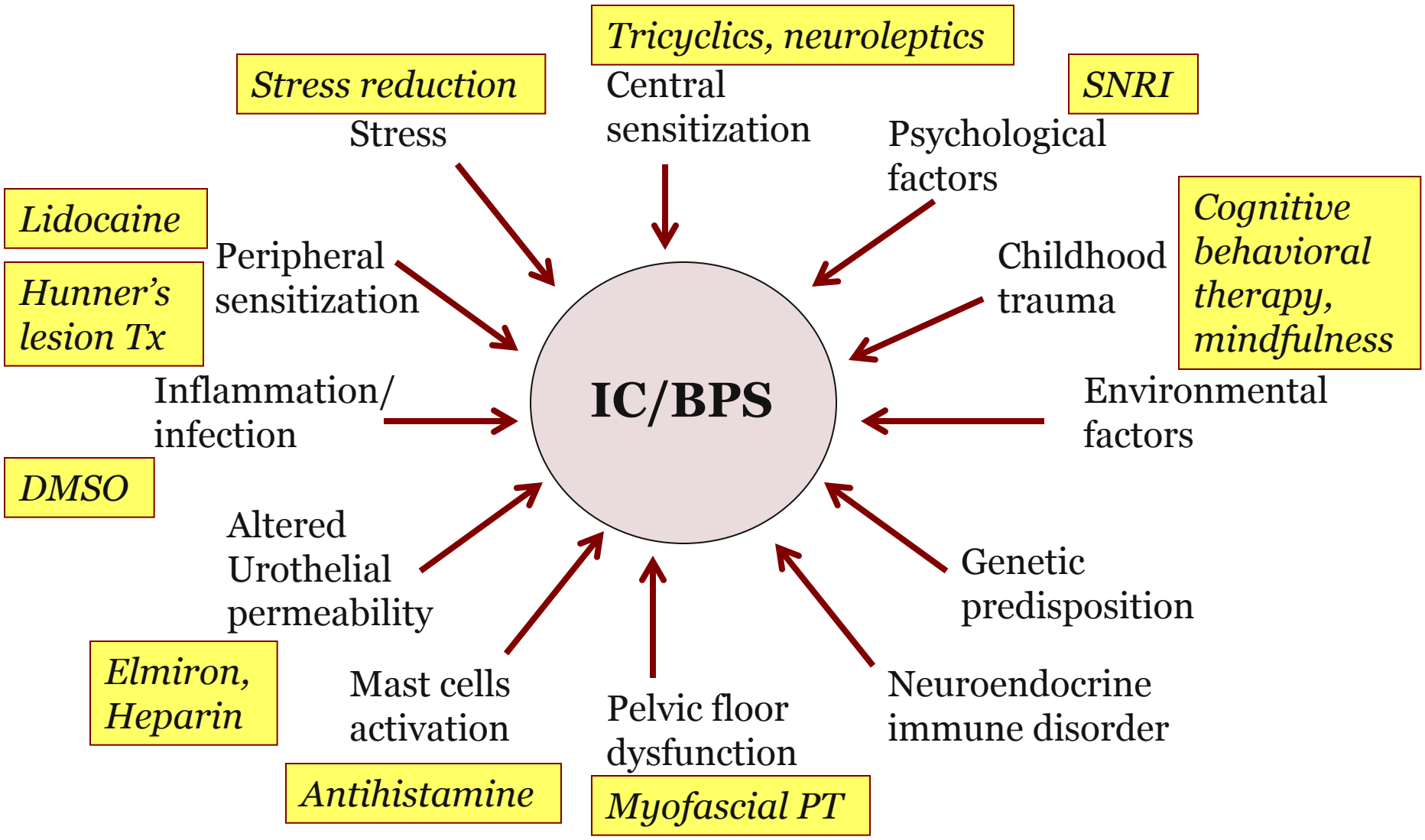
Many potential treatments of IC/BPS

- **AUA IC/BPS Guideline**
- Linear algorithm of treatment approach (first-line … second-line…)
- "One-size-fits-all"
- Without regards to their underlying etiology, pathophysiology or clinical "phenotypes"
- Other than myofascial pelvic floor physical therapy, most have failed RCT, or were poorly studied.



Hanno et al, J Urol 2015

Towards individualized treatment of IC/BPS – Map the "phenotype" to specific treatment to improve outcome



To move forward in IC/BPS, we need to…

- Define the study population (discussed some of the challenges)
- Recognize heterogeneous population and "phenotype" into subgroups
- Understand the underlying pathophysiology of the syndrome

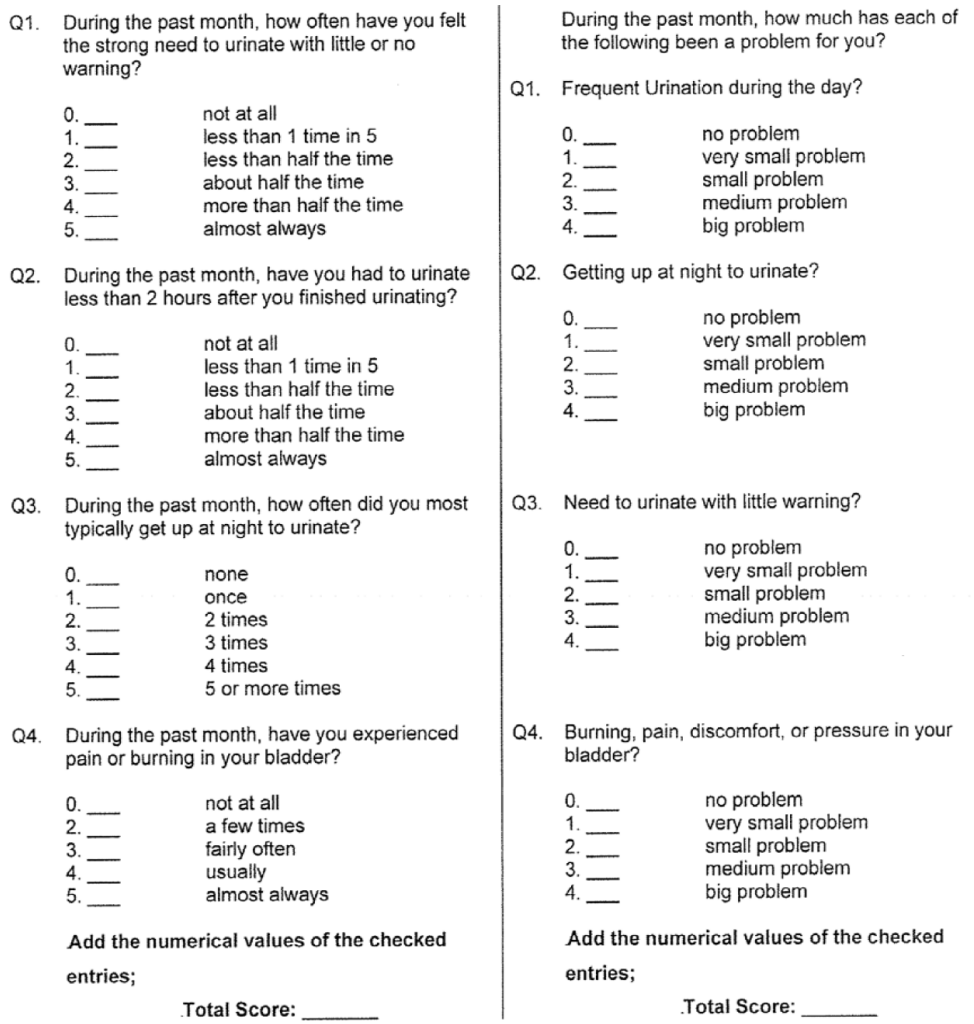
MAPP research network — The Multidisciplinary Approach to Study of Chronic Pelvic Pain (MAPP) Research Network

Dr. Clemens' talk on MAPP tomorrow morning…

- Individualized treatment based on phenotyping improves outcome?
- Relevant clinical outcome assessments (symptoms, biomarkers)

Traditional (Ubiquitous) IC/BPS clinical outcome assessment

- **IC Symptom Index (ICSI) – severity**
- **IC Problem Index (ICPI) – QOL**
- *Two composite scores that combine bladder pain + urinary symptoms (frequency + urgency + nocturia)*



Q1. During the past month, how often have you felt the strong need to urinate with little or no warning?

0. ___ not at all
1. ___ less than 1 time in 5
2. ___ less than half the time
3. ___ about half the time
4. ___ more than half the time
5. ___ almost always

Q2. During the past month, have you had to urinate less than 2 hours after you finished urinating?

0. ___ not at all
1. ___ less than 1 time in 5
2. ___ less than half the time
3. ___ about half the time
4. ___ more than half the time
5. ___ almost always

Q3. During the past month, how often did you most typically get up at night to urinate?

0. ___ none
1. ___ once
2. ___ 2 times
3. ___ 3 times
4. ___ 4 times
5. ___ 5 or more times

Q4. During the past month, have you experienced pain or burning in your bladder?

0. ___ not at all
2. ___ a few times
3. ___ fairly often
4. ___ usually
5. ___ almost always

Add the numerical values of the checked entries;

Total Score: _____

During the past month, how much has each of the following been a problem for you?

Q1. Frequent Urination during the day?

0. ___ no problem
1. ___ very small problem
2. ___ small problem
3. ___ medium problem
4. ___ big problem

Q2. Getting up at night to urinate?

0. ___ no problem
1. ___ very small problem
2. ___ small problem
3. ___ medium problem
4. ___ big problem

Q3. Need to urinate with little warning?

0. ___ no problem
1. ___ very small problem
2. ___ small problem
3. ___ medium problem
4. ___ big problem

Q4. Burning, pain, discomfort, or pressure in your bladder?

0. ___ no problem
1. ___ very small problem
2. ___ small problem
3. ___ medium problem
4. ___ big problem

Add the numerical values of the checked entries;

Total Score: _____

Psychometric study: Pain and Urinary measures should not be combined into a single score to measure outcome

Pain and urinary symptoms should not be combined into one score: Psychometric findings from the Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

James W. Griffith[1], Alisa J. Stephens-Shields[2], Xiaoling Hou[2], Bruce Naliboff[3], Michel Pontari[4], Todd C. Edwards[5], David A. Williams[6], J. Quentin Clemens[6], Niloofar Afari[7], Frank Tu[8], Robert Lloyd[1], Donald L. Patrick[5], Chris Mullins[9], John W. Kusek[9], Siobhan Sutcliffe[10], Barry A Hong[10], H. Henry Lai[10], John N. Krieger[5], Catherine S. Bradley[11], Jayoung Kim[12], and J. Richard Landis[2]

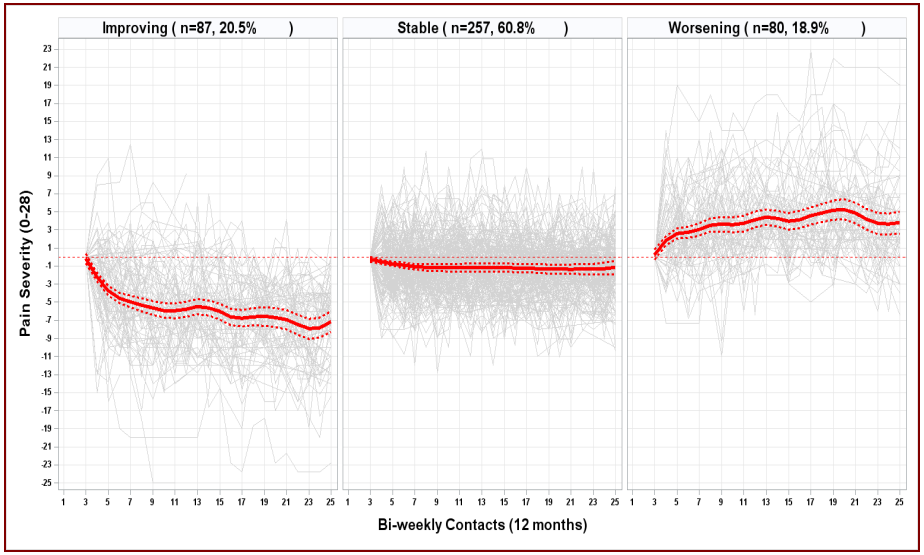
- **Pain Severity Index** = ICSI Q4 (pain) + GUPI pain subscale
- **Urinary Severity Index** = ICSI Q1-3 (urinary) + GUPI urinary subscale
- Measure the pain and urinary outcome scores separately (severity)

GUPI = genito-urinary pain index (Clemens)

Griffith et al, Urol 2016

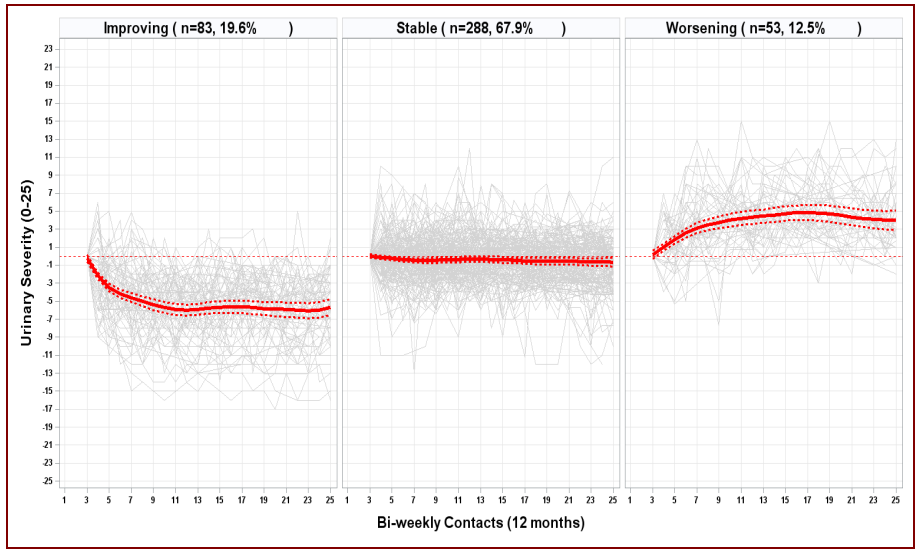
Pain and Urinary symptoms track differently over time

Pain Severity Index



Cluster	Symptom Pattern	Total (Percent)
1	Improving	87 (20.5%)
2	Stable	257 (60.6%)
3	Worsening	80 (18.9%)
Overall		424 (100.0%)

Urinary Severity Index



Cluster	Symptom Pattern	Total (Percent)
1	Improving	83(19.6%)
2	Stable	288 (67.9%)
3	Worsening	53(12.5%)
Overall		424 (100.0%)

Predictors of longitudinal outcomes over one year were (somewhat) different for Pain and Urinary symptoms

- ~60% of participants had stable symptoms over 1 year.
- 13-22% pain and/or urinary symptoms worsened over 1 year.

- **Predictors of worsening urinary outcomes:**
  - Extent of widespread pain
  - Amount of non-urological (somatic) symptoms
  - Poorer overall health
- **Predictors of worsening pain outcomes:**
  - All of the above, plus
  - Pain catastrophizing
  - High perceived stress

- Better than composite score (pain+urinary) since change may be driven by one symptom and may be missed by composite score.

Other potential novel outcome measures ? (flares)

- Flares are common among IC/BPS patients (~95% experienced)
- Flare duration varies among patients
- Pain, frequency and urgency worsened with flares
- Longer flares are associated with worse pain and urinary frequency
- Focus groups to capture aspect of flares that are important to pts
- Can we use diminished frequency of flares as potential outcomes?

	Non-Flare (n=64)	Flare duration				p-value[2]	p-value[3]
		Minutes-long (n=26)	Hours-long (n=24)	One day-long (n=16)	Multiple days-long (n=51)		
Typical symptom severity (on a scale of 0-10, mean (range)):							
Pelvic pain, pressure, or discomfort	4.3 (0 – 10)	5.2 (0 – 10)**	6.0 (2 – 10)****	7.0 (3 – 10)****	6.9 (2 – 10)****	<0.0001	0.0002
Urinary urgency	4.0 (0 – 10)	5.2 (0 – 10)****	4.3 (0 – 10)	5.6 (0 – 10)****	5.7 (0 – 10)****	<0.0001	0.21
Frequency	4.1 (0 – 10)	3.9 (0 – 10)	4.2 (0 – 10)	4.7 (0 – 9)	5.6 (0 – 10)****	0.0187	0.0054
Overall urologic or pelvic pain symptoms	4.3 (0 – 10)	5.5 (1 – 10)**	5.1 (1 – 9)	6.5 (2 – 10)***	6.2 (0 – 10)****	<0.0001	0.11

Other potential outcome measures? (objective markers)

- We care about patient-reported outcomes (PROs, symptoms, QOL)

- Non-invasive objective diagnostic methods (e.g. biomarkers)
- Objective outcome measures (e.g. biomarkers) would be ideal

- A validated biomarker for IC/BPS would be a major advantage:
  1) Provide an objective criterion for participant enrollment
  2) Allow sub-classification of subgroups of IC/BPS ("phenotyping")
  3) More objective measurement of response to treatments (context: flares, remission, chronic overlapping pain conditions)

- <u>Reality:</u> We don't have validated biomarkers for IC/BPS
- No objective marker ≠ pts need to suffer pain for next 30 yrs

Let's Move!

Interstitial Cystitis/ Bladder Pain Syndrome –

Overview, Case Definitions, Outcome Assessment

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IMMPACT-XX Meeting on Chronic Pelvic Pain and IBS, July 13, 2017

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Backup slides

APPENDIX 1: NIDDK DIAGNOSTIC CRITERIA FOR INTERSTITIAL CYSTITIS

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or classic Hunner's ulcer, and they must have either pain associated with the bladder or urinary urgency. An examination for glomerulations should be undertaken after distention of the bladder with the patient under anesthesia to 80 to 100 cm. water pressure for 1 to 2 minutes. The bladder may be distended up to 2 times before evaluation. The glomerulations must be diffuse, present in at least 3 quadrants of the bladder, and there must be at least 10 glomerulations per quadrant. The glomerulations must not be along the path of the cystoscope (to eliminate artifact from contact instrumentation). The presence of any of the following criteria excludes the diagnosis of interstitial cystitis:

1. Bladder capacity greater than 350 cc on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100 cc gas or 150 cc water during cystometry, using a fill rate of 30 to 100 cc per minute
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described previously
4. Duration of symptoms less than 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics or antispasmodics
7. A frequency of urination, while awake, of less than 8 times a day
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period

TABLE III. ***Interstitial cystitis data base (ICDB) study eligibility criteria***

- Providing informed consent to participate in the study
- Willing to undergo a cystoscopy under general or regional anesthesia, when indicated, during the course of the study
- At least 18 years of age
- Having symptoms of urinary urgency, frequency, or pain for more than 6 months
- Urinating at least 7 times per day, or having some urgency or pain (measured on linear analog scales)
- No history or current genito-urinary tuberculosis
- No history of urethral cancer
- No history or current bladder malignancy, high-grade dysplasia, or carcinoma in situ
- Males: no history or current prostate cancer
- Females: no occurrence of ovarian, vaginal, or cervical cancer in the previous 3 years
- Females: no current vaginitis, clue cell, trichomonas, or yeast infections
- No bacterial cystitis in previous 3 months
- No active herpes in previous 3 months
- No antimicrobials for urinary tract infections in previous 3 months
- Never having been treated with cyclophosphamide (cytoxan)
- No radiation cystitis
- No neurogenic bladder dysfunction (eg due to a spinal cord injury, a stroke, Parkinson's disease, multiple sclerosis, spina bifida, or diabetic cystopathy)
- No bladder outlet obstruction (determined by urodynamic investigation)
- Males: no bacterial prostatitis for previous 6 months
- Absent of bladder, ureteral, or urethral calculi for previous 3 months
- No urethritis for previous 3 months
- Not having had a urethral dilation, cystometrogram, a bladder cystoscopy under full anesthesia, or a bladder biopsy in previous 3 months
- Never having had an augmentation cystoplasty, cystectomy, cystolysis, or neurectomy
- Not having a urethral stricture of less than 12 French