

REALLY TWO DISORDERS AND MANY NAMES

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

HUNNER LESION DISEASE

IC/BPS

Painful bladder syndrome

Hypersensitive bladder

Non-Hunner lesion interstitial cystitis

Urologic chronic pelvic pain syndrome

Classic interstitial cystitis

Hunner lesion (disease, type interstitial cystitis)

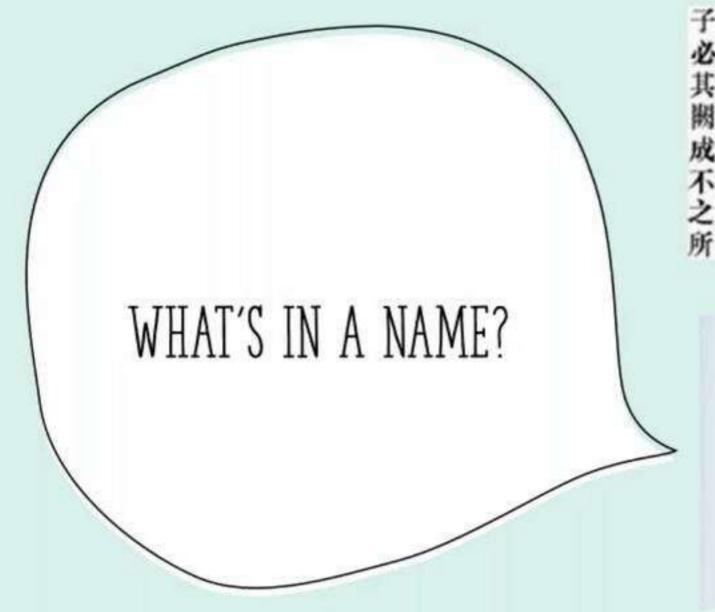
Hunner's ulcer

Hunner cystitis

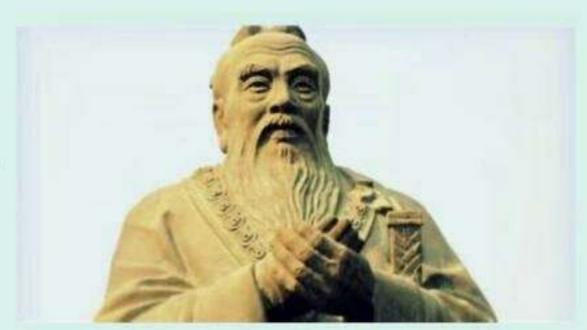
Hunner patches

Ulcerative (interstitial) cystitis





子路曰、衞君待子而為政、子將奚先、子曰、 必也正名乎、子路曰、有是哉、子之廷也、奚 其正、子曰、野哉由也、君子於其所不知、蓋 闕如也、名不正、則言不順、言不順、則事不 成、事不成、則禮樂不興、禮樂不興、則刑罰 不成、則禮樂不興、趙等足、故君子名 成中、刑罰不中、則民無所措手足、故君子名 之必可言也、言之必可行也、君子於其言、無 所苟而已矣。





The Analects of Confucius, Book 13, Verse 3 (James R. Ware, translated in 1980)

Tsze-lu said, "The ruler of Wei has been waiting for you, in order with you to administer the government. What will you consider the first thing to be done?"

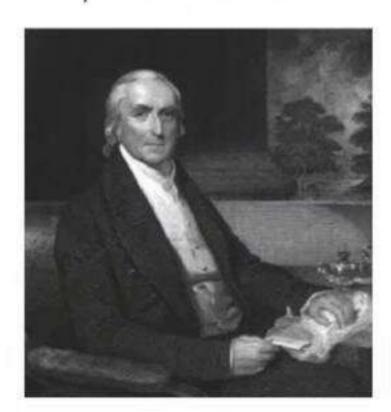
The Master replied, "What is necessary is to rectify names." "So! indeed!" said Tsze-lu. "You are wide of the mark! Why must there be such rectification?"

The Master said, "How uncultivated you are, Yul A superior man, in regard to what he does not know, shows a cautious reserve

"If names be not correct, language is not in accordance with the truth of things. If language be not in accordance with the truth of things, affairs cannot be carried on to success



1808 Philip Syng Physic (Philadelphia) - inflammatory bladder condition with "ulcer" with symptoms similar to bladder calculus



1836 Joseph Parrish (Philadelphia) — Tic douloureux of the bladder, "a nervous affliction characterized by severe suffering" 1836 Louis Mercier (Paris, inventor of coude catheter) — Ulcus simplex vesicae destroying each layer of bladder wall

Samuel D Gross: "Interstitial or parenchymatous cystitis, mucous cystitis if superficial

1876-1878

IC APPEARS:
A description, not a disease





Alexander JC Skene: "IC, interstitial cystitis" inflammatory process with ulcer

ENDOSCOPIC DEFINITION Hunner's definition of Interstitial Cystitis

"...a peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment" in patients with frequency and bladder symptoms (spasms)."

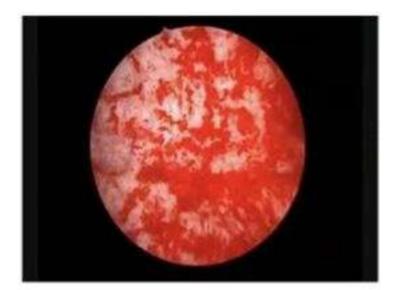


Hunner, GL, Boston Medical and Surgical Journal, 172:660, 1917

GLOMERULATIONS: 1949

JR Hand: "small, discrete, submucosal hemorrhages' and 'dotlike bleeding points"

Walsh: 1978 in Campbell's Urology coined the term "glomerulations"



1978: SYMPTOMS & ENDOSCOPIC APPEARANCE DEFINITION

Messing and Stamey: Nonspecific and highly subjective symptoms of around the clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia





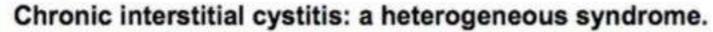
Urology, 12:381, 1978

Diagnosis of Exclusion





J Urol. 1987 Jan; 137(1):35-8.



Fall M, Johansson SL, Aldenborg F.

mast cells, unlike those in the muscular coat, are susceptible to aldehyde fixation, and require special fixation and staining techniques for proper demonstration. These cells were numerous in the epithelium and were recovered in bladder washings, consistent with the finding that they have a migratory capacity. In nonulcerative interstitial cystitis all signs of mast cell activation were absent, and the histopathological changes were few and fairly uncharacteristic. We also observed some marked clinical differences between ulcerative and nonulcerative interstitial cystitis. These 2 conditions appear to represent separate entities and should be evaluated separately in clinical studies.







Abstract -

J Urol. 1987 Jan; 137(1):35-8.

Ch Hunner lesion disease should not be Evaluated with non-Hunner disease In clinical studies

mast c echni washir staining s of

mast cell activation were absent, and the histopathological changes were few and fairly uncharacteristic. We also observed some marked clinical differences between ulcerative and nonulcerative interstitial cystitis. These 2 conditions appear to represent separate entities and should be evaluated separately in clinical studies.

2008

DEFINITION ESSIC, SUFU, AUA: IC/BPS

An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration (6 months in ESSIC), in the absence of infection or other identifiable causes

NO requirement Hunner lesion or glomerulation Purely a symptomatic diagnosis of exclusion







ETIOLOGY HAS PROVEN VERY CONFUSING

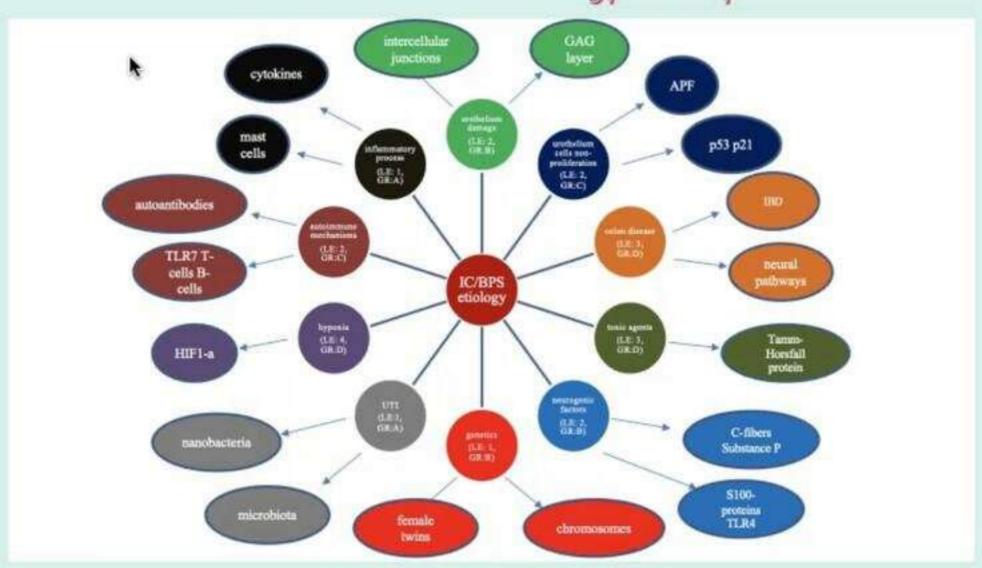
3 Gravity Sources

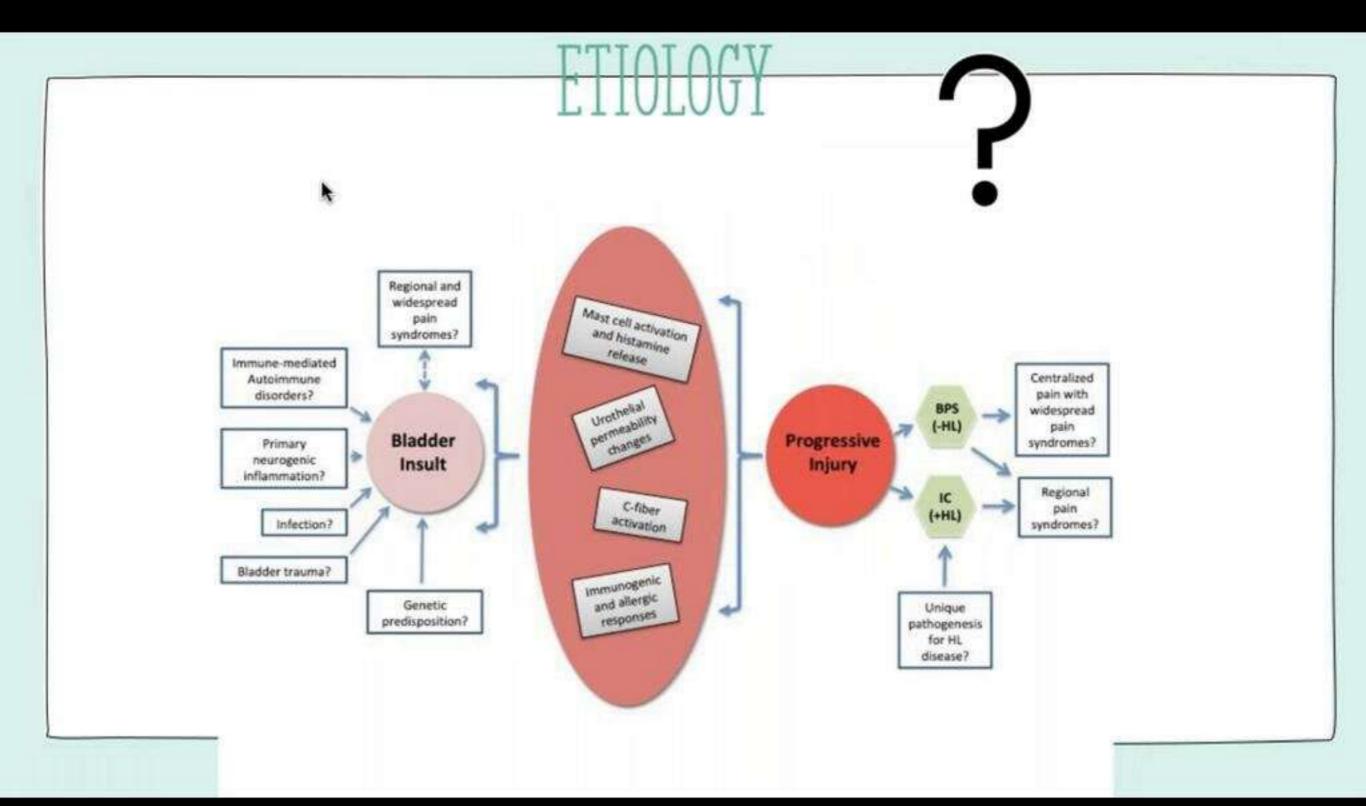
1 Space

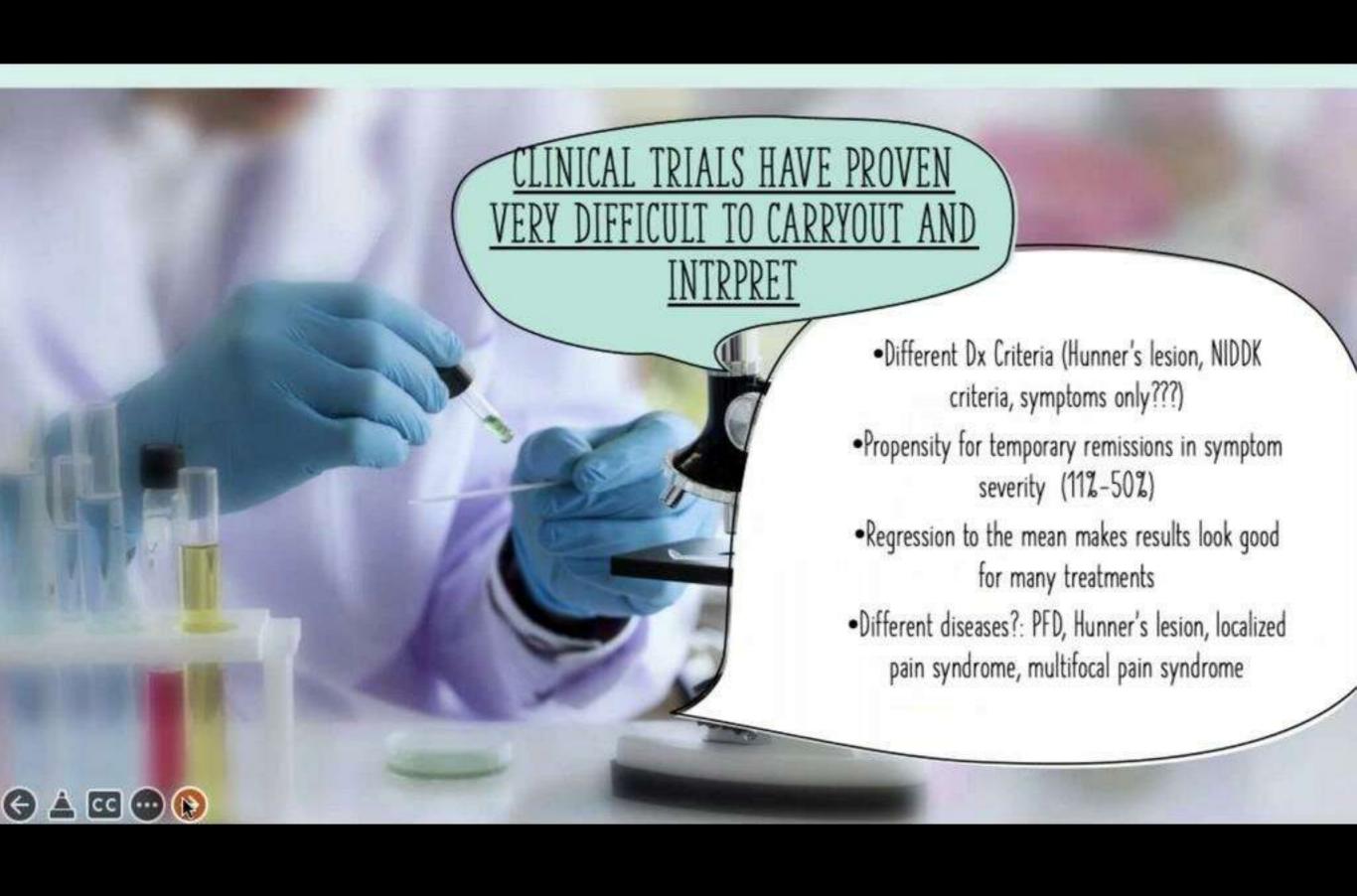


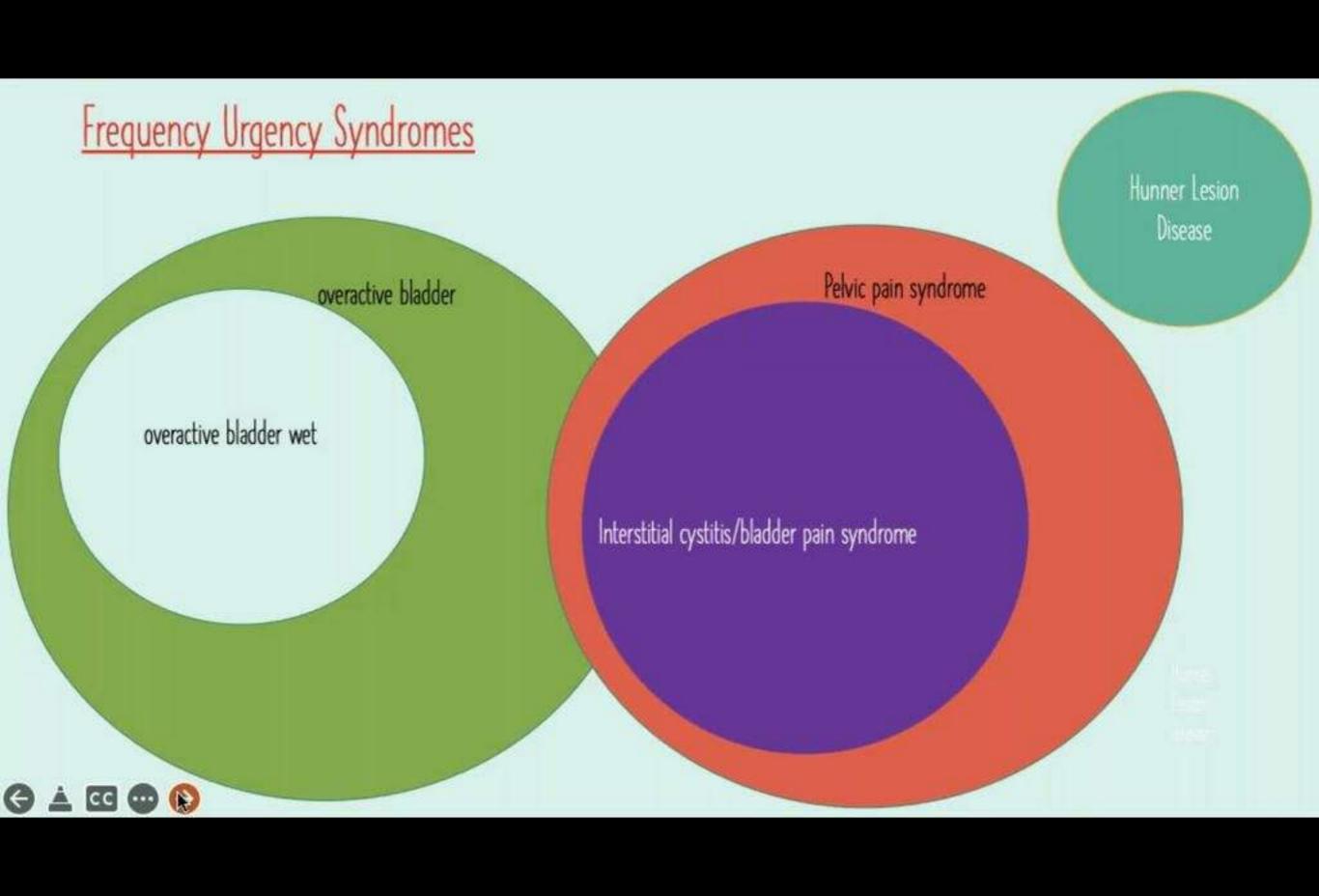
Relativity is a lithograph print by the Dutch artist M. C. Escher

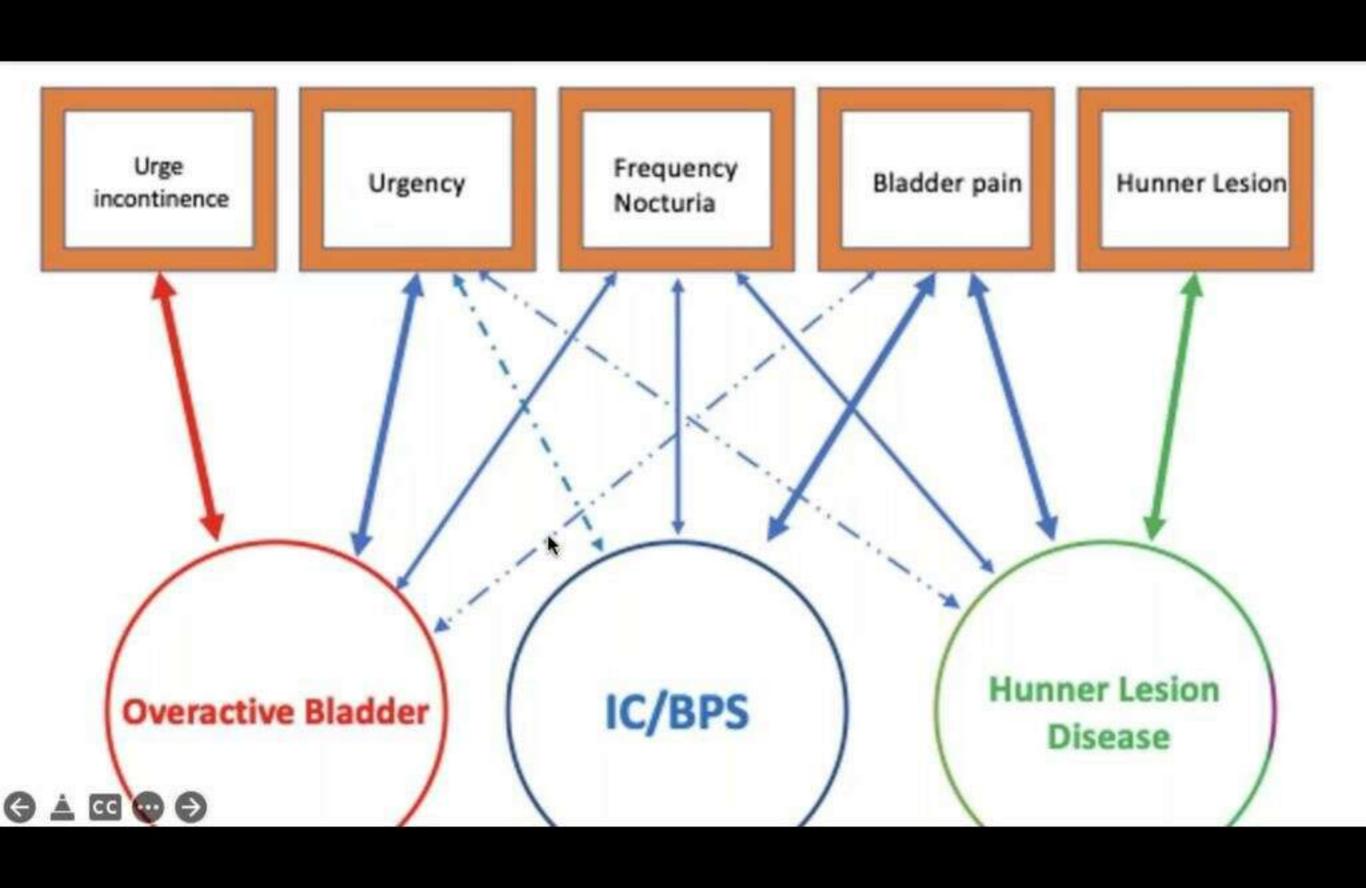
Multifactorial Etiology Likely





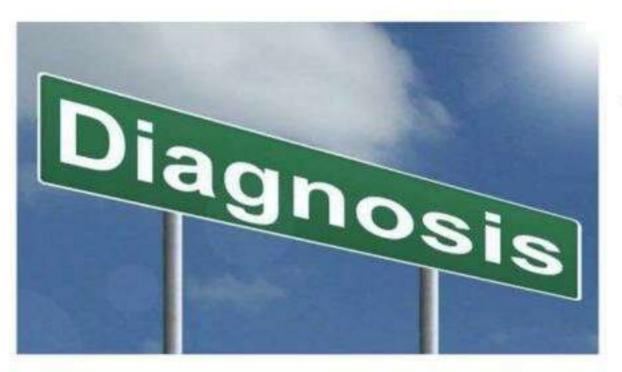






KEY: DIAGNOSIS IS ONE OF EXCLUSION IN PATIENTS WHO MEET THE DEFINITION. THIS CAN MAKE WHAT CAN APPEAR COMPLEX RELATIVELY STRAIGHT-FORWARD

- Confusable diseases as the cause of the symptoms must be excluded.
- Further documentation and classification of BPS might be performed according to findings at cystoscopy and morphological findings in bladder biopsies.
- The presence of other organ symptoms as well as cognitive, behavioral, emotional and sexual symptoms, should be addressed.



- IC/BPS diagnosis of exclusion based on symptoms and exclusion of confusable disorders
- HLD symptoms plus presence of Hunner lesion



Confusable Disorders

carcinoma
carcinoma in situ
infection with intestinal bacteria
infection with
Mycobacterium tuberculosis

Chlamydia trachomatis Ureaplasma urealyticum

Mycoplasma hominis

Mycoplasma genitalis

Corynebacterium urealyticum

Candida species

Herpes simplex

Human Papilloma Virus

radiation cystitis

chemotherapy-induced cystitis

cyclophosphamide-induced cystitis

ketamine induced cystitis

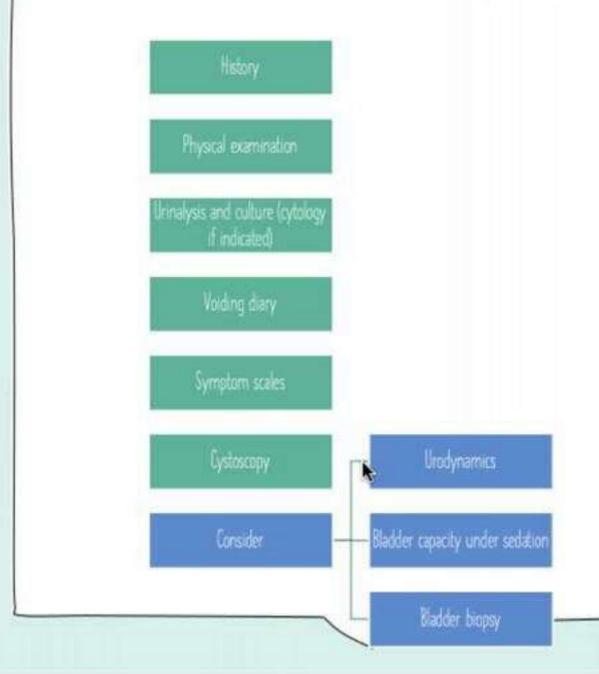
tiaprophenic acid induced cystitis bladder neck obstruction neurogenic outlet obstruction bladder stone lower ureteric stone urethral diverticulum urogenital prolaps endometriosis vaginal candidiasis cervical, uterine and ovarian cancer incomplete bladder emptying (retention) prostate cancer benign prostatic obstruction chronic bacterial prostatitis chronic non-bacterial prostatitis

pudendal nerve entrapment





DIAGNOSTIC STEPS



Goal to rule out common confusable conditions

pelvic floor dysfunction

overactive bladder

infection

pudendal neuropathy

endometriosis

vulvodynia

Goal to identify associated disorders

Confusable disorders

carcinoma
carcinoma in situ
infection with intestinal bacteria
infection with

Mycobacterium tuberculosis

Chlamydia trachomatis

Ureaplasma urealyticum

Mycoplasma hominis

Mycopla Corynebi Candida

Herpes :

Leaving IC/BPS as the diagnosis of exclusion

Human Fapmorna virus

radiation cystitis

chemotherapy-induced cystitis cyclophosphamide-induced cystitis ketamine induced cystitis tiaprophenic acid induced cystitis

bladder neck obstruction

neurogenic outlet obstruction

bladder stone

lower ureteric stone

urethral diverticulum

urogenital prolapse

endometriosis

an cancer

benign prostatic obstruction chronic bacterial prostatitis chronic non-bacterial prostatitis pudendal nerve entrapment

IT TURNS OUT ITS NOT QUITE SO EASY

Myofascial pelvic pain can be primary or secondary to perceived bladder pain

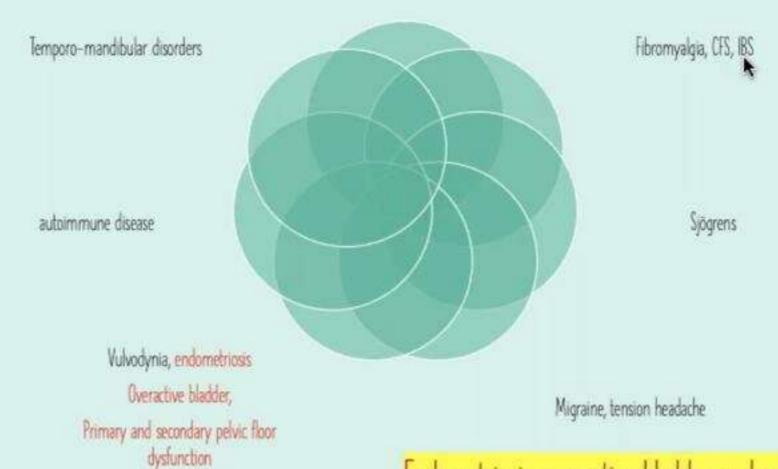
Overactive bladder can be difficult to differentiate

- A subset of OAB patients have pain in and/or outside the pelvis
- · Urodynamics may help in this situation
- Key history question: How would you feel if there were no toilet available
 Pain vs fear of incontinence?

Kowalik CG et.al.: J Urol 200:1332–1337, 2019 Siddiqui NY et.al.: J Urol 202:880–889, 2019 Petrikovets A et al. Urology 126:54-588, 2019 Ackerman AL et al. BJU Int. 123:682-693, 2019

Chronic overlapping pain conditions Associated Disorders / confusable disorders

IC/BPS





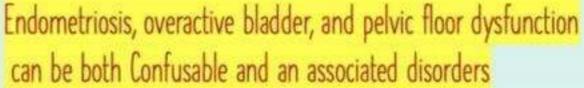


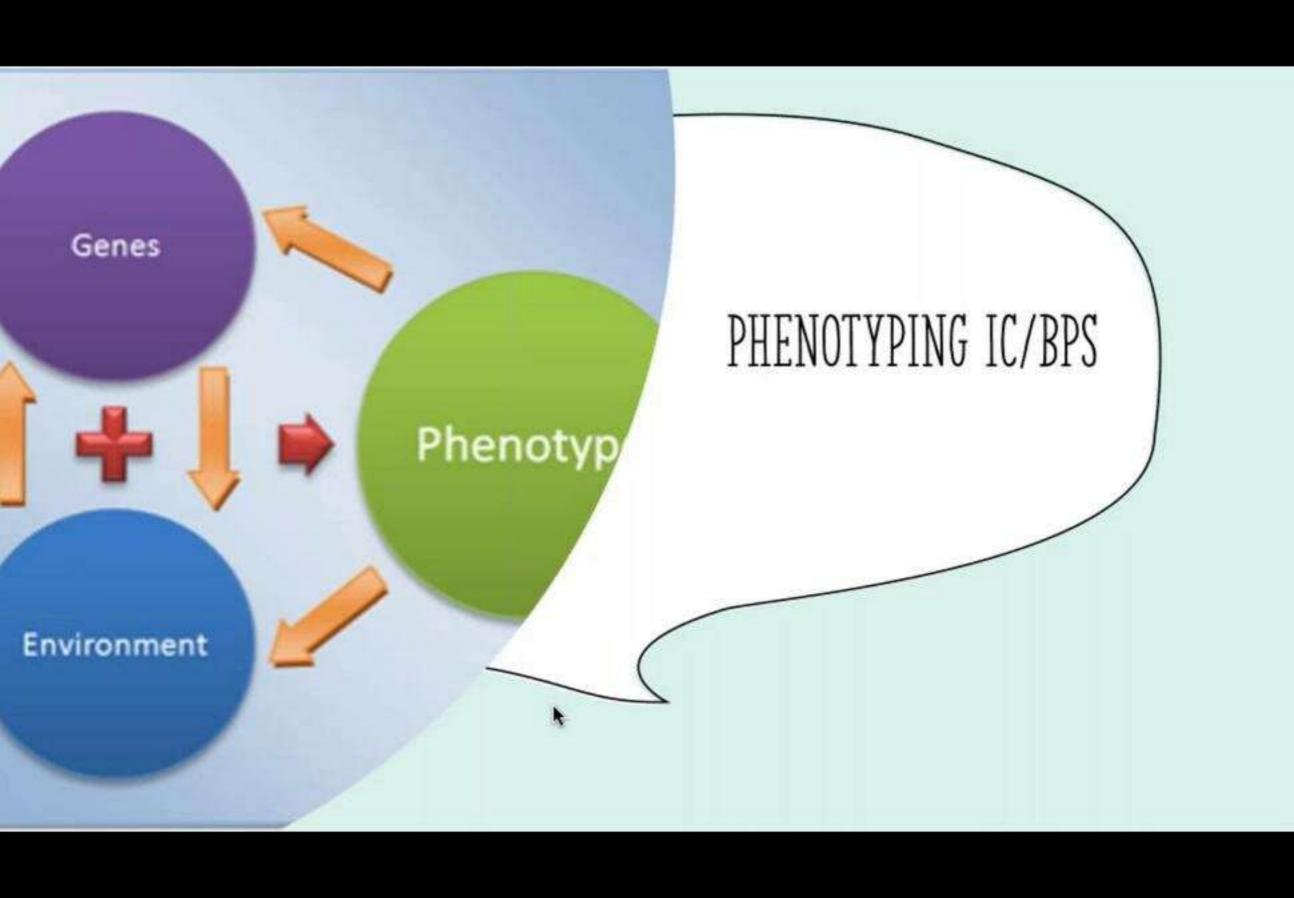












Phenetype

Regardless of what we call it or how we define it, phenotyping may hold the key to improving treatment outcomes and facilitating research

The only clinically important phenotype in 2022 is the Hunner lesion, which defined the disease 100 years ago.

- There are only a few anecdotal examples of a non-Hunner lesion patient assuming this phenotype
- The patient population seems to be different than non-Hunner patients

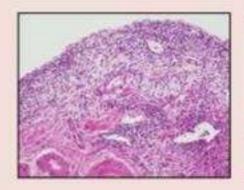
Histological distinction between the subtypes with and without Hunner lesions

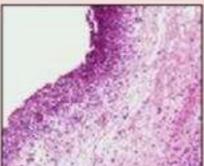
IC/BPS with Hunner lesions

Inflammatory disorder

Lesion

Non-lesion



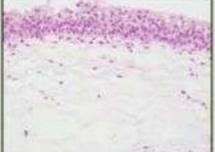




- Inflammation: Prominent
- Epithelial denudation
- **Pancystitis**

IC/BPS without Hunner lesions

Non-inflammatory disorder



- Inflammation: Scarce
- Preserved epithelium

Maeda D*, Akiyama Y* et al. PLoS One. 2015

Hunner

Non Hunner

Mean age at onset: 41–55 years

Response to cyclosporine 42-85%

Responds to fulguration/resection/steroid

Distinct pathology

Fewer comorbid conditions (Asters 2011)(Margar 2013)

Lower anatomic bladder capacity

Mean age at onset: 30–42 years

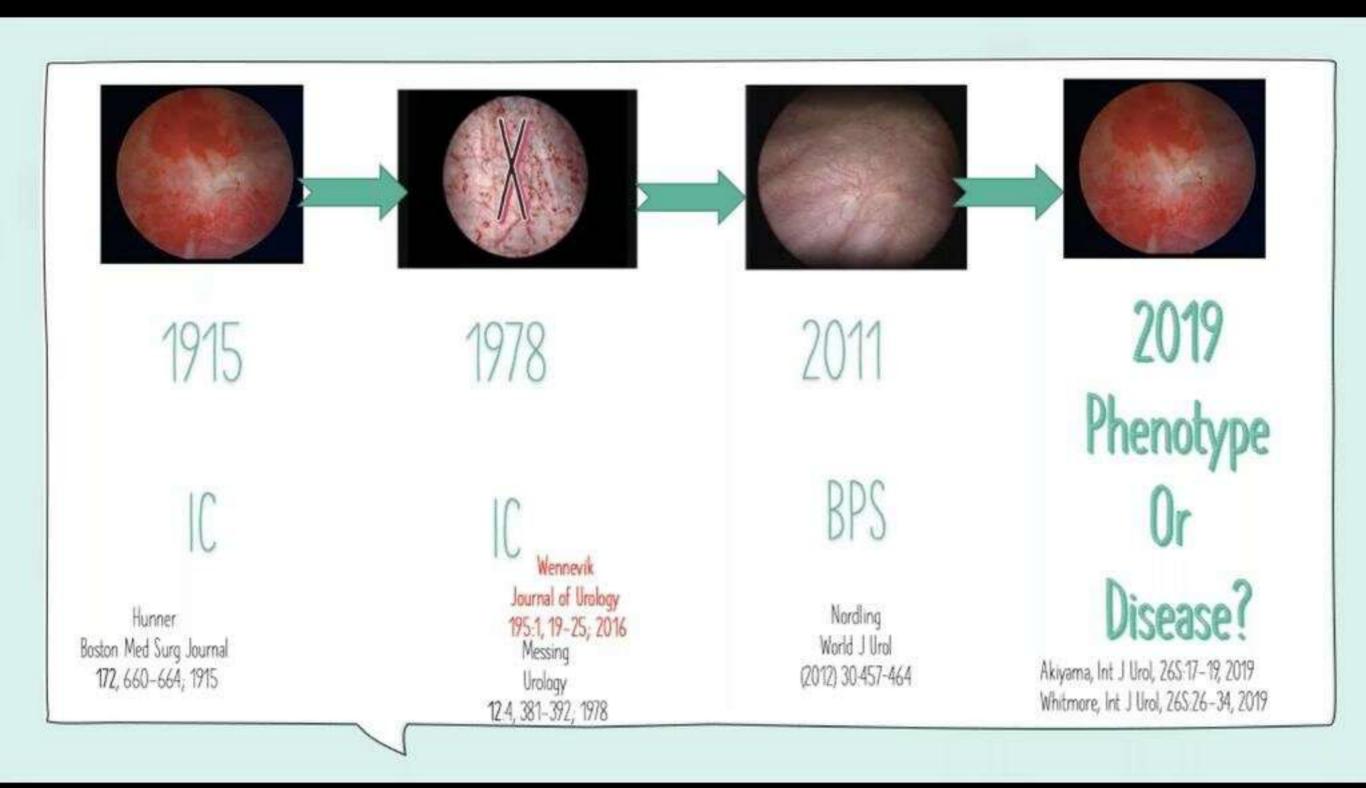
Response to cyclosporine: 11%-30%

Not responsive to fulguration/resection/steroid

Histology variable, may appear normal

More comorbid conditions

Larger anatomic bladder capacity



Changing Landscape

Changing Landscape

2017

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the nature Constitute or Undeptit Disease (CUS) Mendiput Collinson Barrey (CO)

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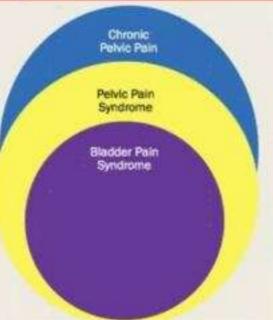
major international associations of unitage generatory and uniformists, and after marked associations. 6th International Consultation on Incontinence

> Recommendations of the International Scientific Committee:

OF URINARY INCONTINENCE, PELVIC ORGAN PROLAPSE AND FAECAL INCONTINENCE

P. Abrame, K.E. Andersson, A. Apustolidis, L. Birder, D. Biiss, L. Brutisker, L. Cardozo, D. Castro, P.R. O'Consell, A. Cottenden, N. Cotterill, D. de Ridder, R. Dmochowski, C. Dumcolin, M. Fader, C. Fry, H. Goldman, P. Hanno, Y. Homman, V. Khullar, C. Maher, I. Milsom, D. Newman, J.M. Nijman, K. Rademalars, D. Robinson, P. Rosier, E. Rovner, S. Salvatinre, M. Takesta, A. Wagg, T. Wagner, A. Wain

and the members of the committees



"New" Concept

Interstitial Cystitis as a distinct disease; circa 1915 and Hunner description

> Hunner lesion Diagnostic of Interstitial Cyntitis

Han E et.al. Ther Adv Urol, 10:197-211, 2018

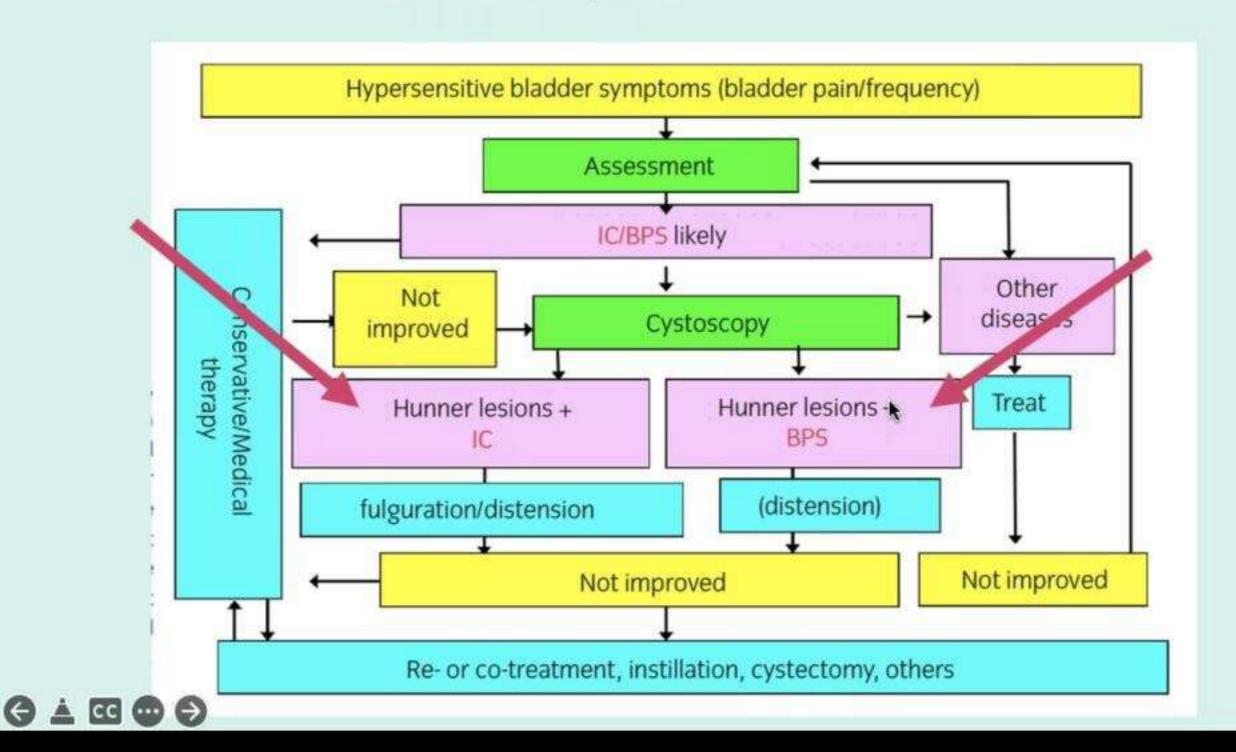
"We believe HL IC is a distinct disease and therapy should focus on the bladder"

Akiyama et.al. Histol Histopathol 34:25-32,2019

Terminology should be developed to refer separately to Hunner lesions

Fall M, Nordling J and ESSIC. Scand J Urol. 54:91–98, 2020

"It is time to accept that classic IC with Hunner lesions and BPS always should be evaluated separately in science as well as in clinical routine"



EPIDEMIOLOGY



Reasonable prevalence estimation 300/100,000 women based on O'leary Sant surveys in Europe and Asia

Prevalence of women and men with symptoms suggestive of IC/BPS could be 10X based on USA Rand Survey

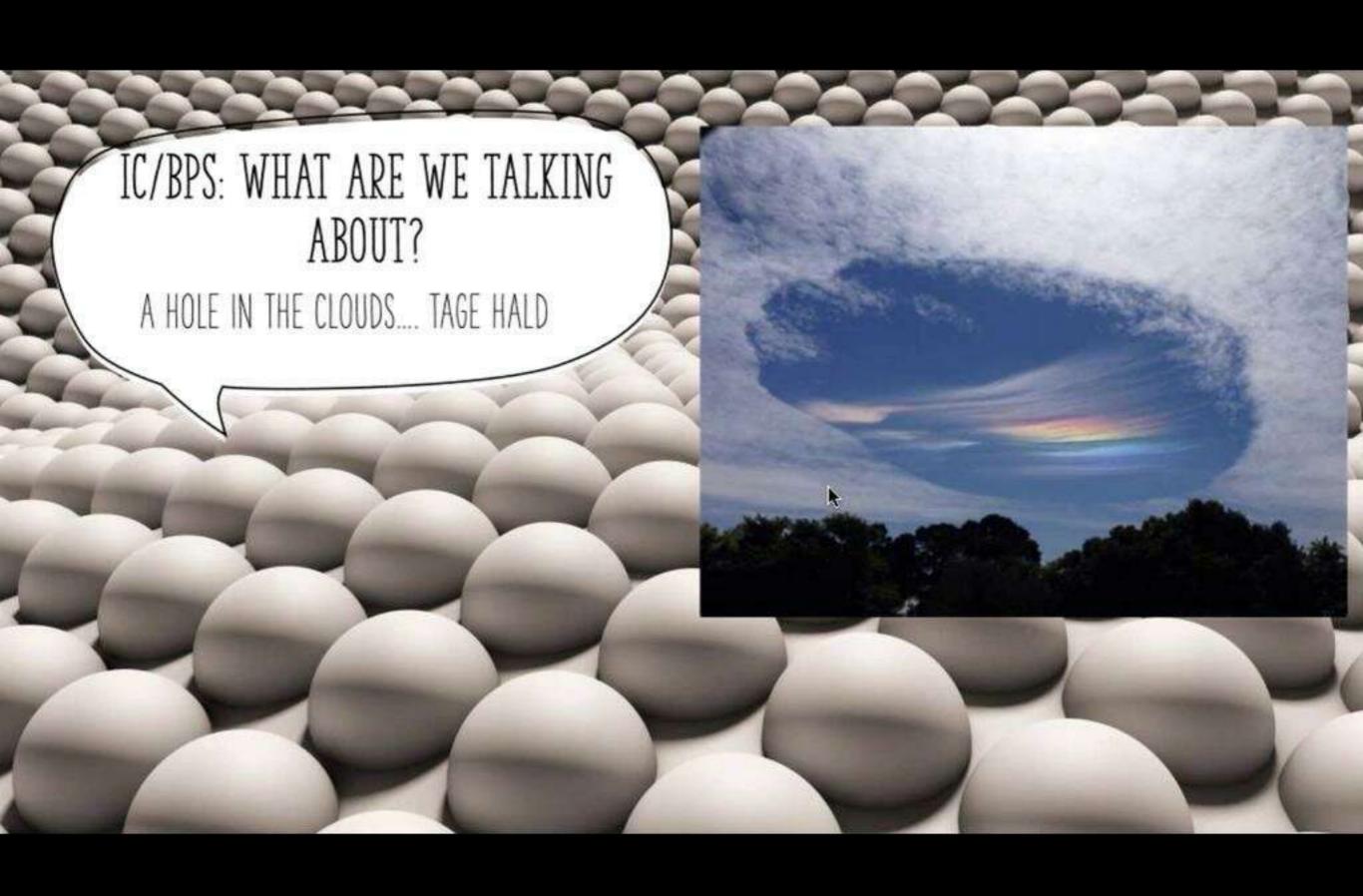
Male prevalence 10–20% of female estimate, potentially up to 60% based on Rand epidemiology survey

Epidemiological data required to describe long term progression patterns of IC/BPS is lacking

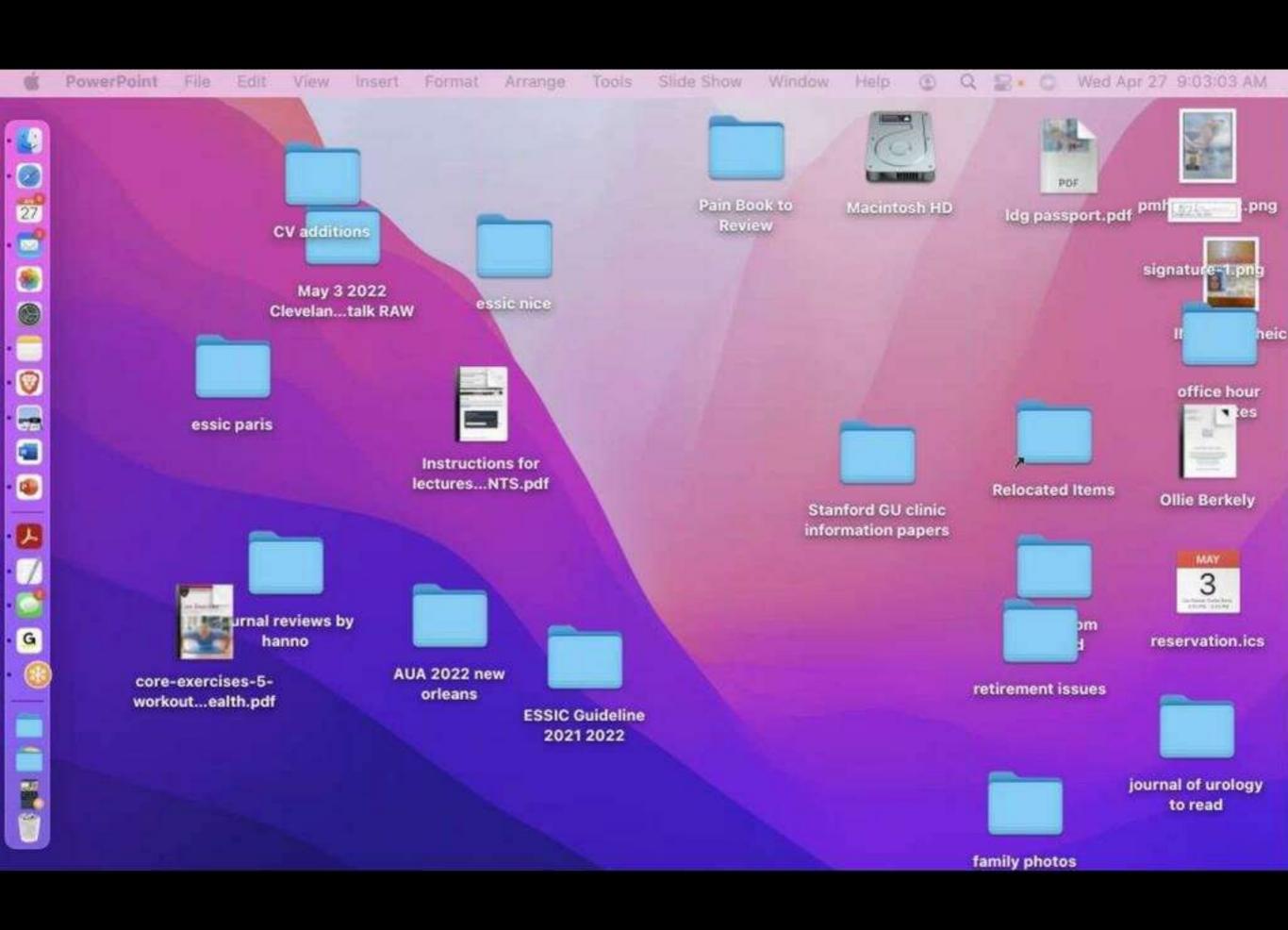
HOW COMMON IS HUNNER DISEASE REALLY??

MOLDWIN: 869/3408 34%

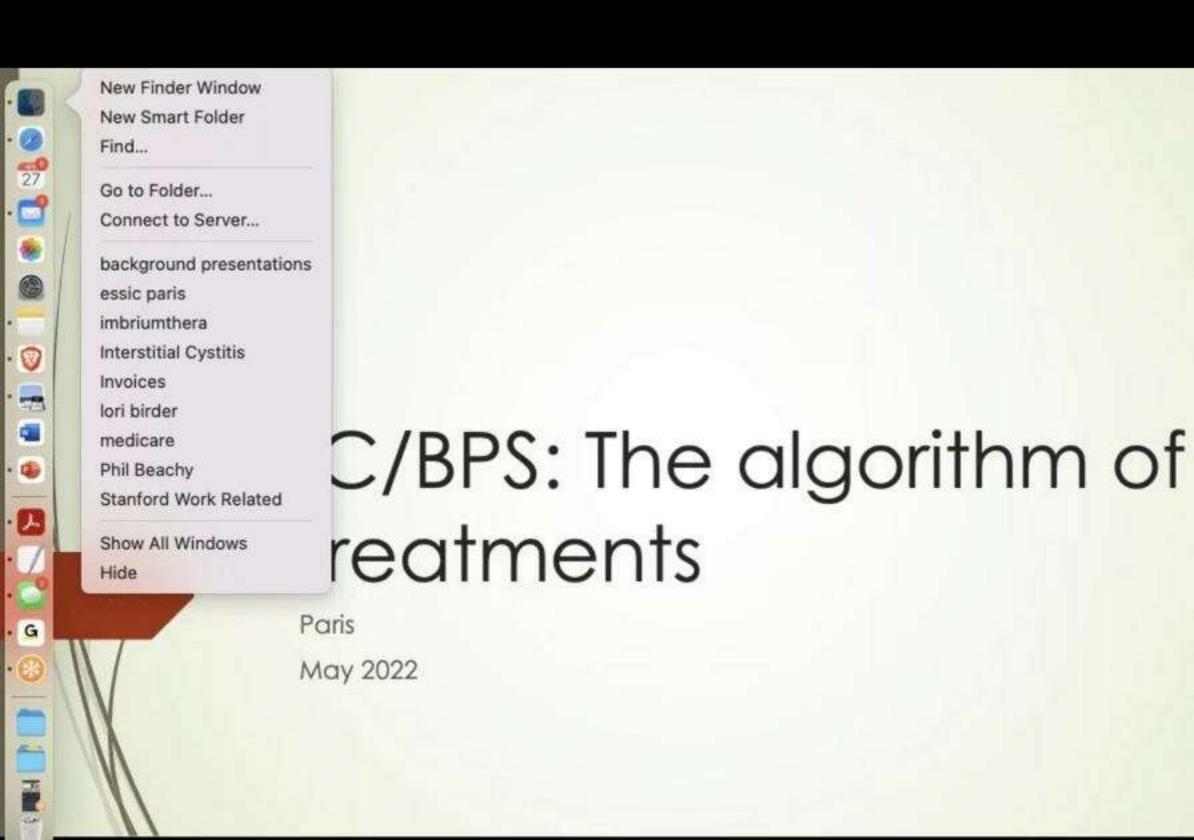
Year	Author	HL Prevalence/ Total No. IC/BPS patients
1949	Hand	13% / 223
1987a	Holm-Bentzen, et al	3.5%/115
1987	Parsons and Mulholland	28%/75
1993	Koziol, et al	20%/374
1996	Koziol, et al	19.6%/565
1997	Nigro, et al*	11.3%/113
1997	Simon, et al*	10.5%/190
1997	Messing, et al*	11.3%/150
2001	Forrest, et al **	10%/52
2002	Peeker and Pall	56%/231
2004	Forrest and Schmidt**	10%/92
2008	Braunstein, et al	39%/223
2011	Peters, et al	17%/214
2013	Logadottir, et al	55%/393
2013	Killinger, et al	17%/214



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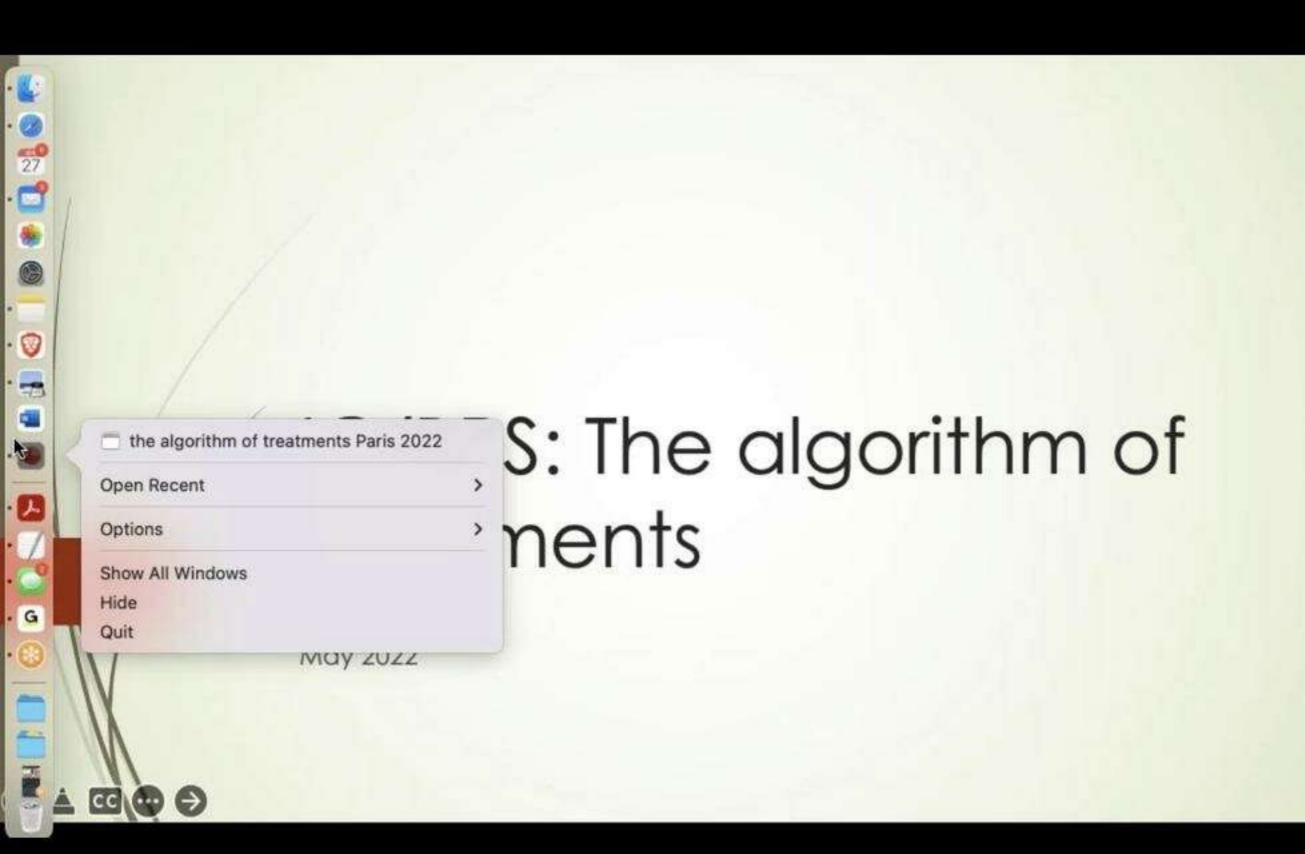
IC/BPS: The algorithm of treatments

Paris

May 2022









IC/BPS: The algorithm of treatments

Paris

May 2022



Natural history of IC/BPS is critical in understanding therapy choices

- Up to 50% patients improve regardless of treatment or follow up
- Symptom duration generally not associated with symptom severity
- Symptom duration not associated with risk for mental health comorbidity
- Symptom duration not associated with risk for overlapping pain comorbidities
- Catastrophizing increases morbidity

Allaire: J.Am J Obstet Gynecol 218:114e1-12, 2018 Rodriguez: <u>Urology</u>, 2019 Feb;124:14-22

Yeh: Neurourol Urodyn. 2019 Sep;38(7):1985-1993.

Oravisto: Ann Chir Gynaecol 1972 Fenn 64:2, 75-77.

Guiding principles



Base decisions on evidence as much as possible Patient driven outcomes are important Begin with less invasive and less potentially morbid therapeutic options

Early diagnosis of HLD by endoscopy

Time can be the great healer in many patients No single treatment works well over time for majority of patients

Consider a multidisciplinary approach

Add to initial therapy if necessary, substitute if ineffective



Tailor treatment to symptoms



Given natural history, consider an initial conservative treatment approach

Education: review normal bladder function, IC/BPS knowledge base, risks/burdens of available treatments, need to try multiple therapeutic approaches over time

Behavioral modifications that can improve symptoms

Stress management to improve coping and manage stress-induced symptom exacerbations

Effect of Comestibles

Shorter B, Moldwin R, et al, J Urol 191:1793-801, 2014 prospective survey

APPENDIX 2

Lenons

Oranges.

- statistical analysis of developed short form questionnaire
- abbreviated list including 35 most problematic comestibles
- high internal consistency (α=0.96), high reliability



IC/BPS Food Sensitivity Questionnaire Key Bothersome to XC/SPS Patients Cranberry Juice Foods Identified as Most Foods Identified as Least Bothersome to IC/BPS Patients. Bothersome to IC/BPS Patients Grapefruit juice. Orange juice Caffoinated coffee Pineapple juics Decaffeinated coffee Mik Torrato Caffeinated tea Tomato products Pass. Decaffernated to a Hot peggers. Cola reda Horseradish White potetoes Noncola soda Vinegar Diet sods Rice: Monosodium glutamate Boer Chicken Red wine NutraSweet®: White wine Sweet N Lowill-Turus Fish. Спатроспе Equal 8 Hard liquer and mixed drinks. Sacchann Prefet® Mexican food Turns% Grapefruit That food

Metamuch®/FiberCon®

Senekot®

Foods Identified as Most

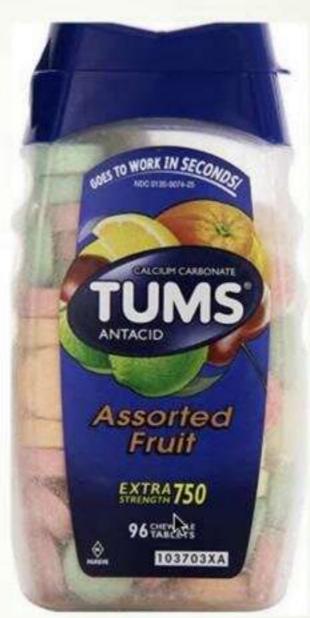
Indian food

Oili Burrios Foods Identified as Leant

Bothersome to IC/BPS Patie

Conservative suggestions based purely on anecdotal experience

- Management of fluid intake
- Dietary avoidance of YOUR food/beverage"symptom triggers"
- Consider over the counter sucrose / Calcium carbonate (TUMS)
- Consider over the counter calcium glycerophosphate (PRELIEF)





7:1, 44-46

- Quercetin, a plant pigment is a potent antioxidant flavonoid and more specifically a flavonol, found mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits. It is a versatile antioxidant known to possess protective abilities against tissue injury induced by various drug toxicities.
- ■500mg once or twice daily



Micronized
Palmitoylethanolamide
-Polydatin: OTC PEA



Protective role in a rat model of cyclophosphamide cystitis 400mg m-PEA plus 40mg polydatin twice daily for three months, then daily for 3 months



Polydatin 98%

Resveratrol analogue

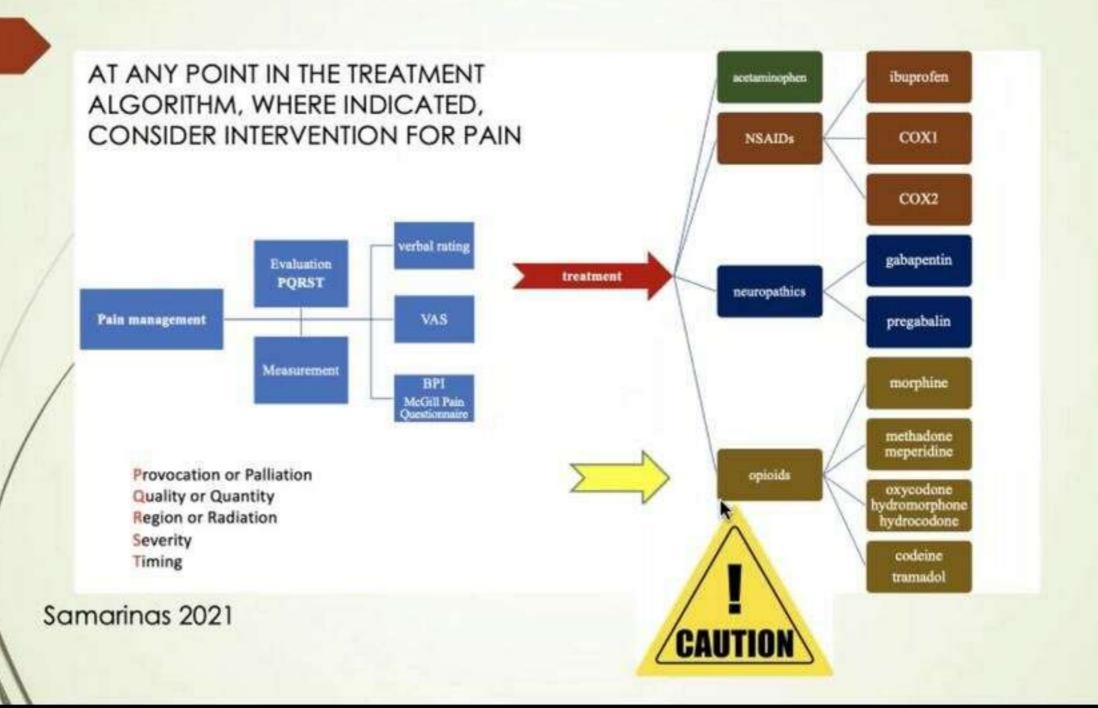
Resveratrol precursor

Better than resveratrol

Water soluble

Anti-coins anticodidant

Open label study of 32 patients reduced pain, OLS, PUF scores and urinary frequency and bladder capacity



Use of Narcotics

- Chronic opioids are best considered in patients not responsive to nonopioid analgesics or standard therapies.
- Consult a pain management expert and move this portion of care to a pain clinic where available that will be responsible for all prescribed analgesics and can institute a pain contract with patient.
- Educate patients and their families on the use of rescue medication in the event of overdose and have such medications available



Guideline Statements: First-Line Treatments

- STANDARD: Manual Physical Therapy if appropriately trained clinicians are available
 - Maneuvers that resolve pelvic, abdominal and/or hip muscular trigger points and connective tissue restrictions; avoid pelvic floor strengthening exercises
 - Thiele's massage is a particular method of massage to the posterior pelvic floor muscles including the coccygeus. ... The finger is then moved laterally, in contact with the soft tissues of the coccygeus, levator ani, and gluteus maximus muscles. The finger is moved with moderate pressure

Fitzgerald MP, Payne CK, Lukacz ES et al: J Urol 2012; 187: 2113 Publication May 2022

International Consultation on Incontinence

Interstitial cystitis/bladder pain syndrome committee

P Hanno (USA), M Cervigni (Italy), MS Choo (Korea), JQ Clemens (USA), MH Lee (Taiwan), S Malde (UK), J Meijlink (Netherlands), M Samarinas (Greece), T Ueda (Japan), D Gold (Austria) Algorithm for Diagnosis
IC/BPS and HLD symptom
complex: 2022 International
Consultation on
Incontinence.

Early cystoscopy is recommended to differentiate IC/BPS syndrome from HLD.

Diagnosis: Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS), Hunner Lesion Disease (HLD)

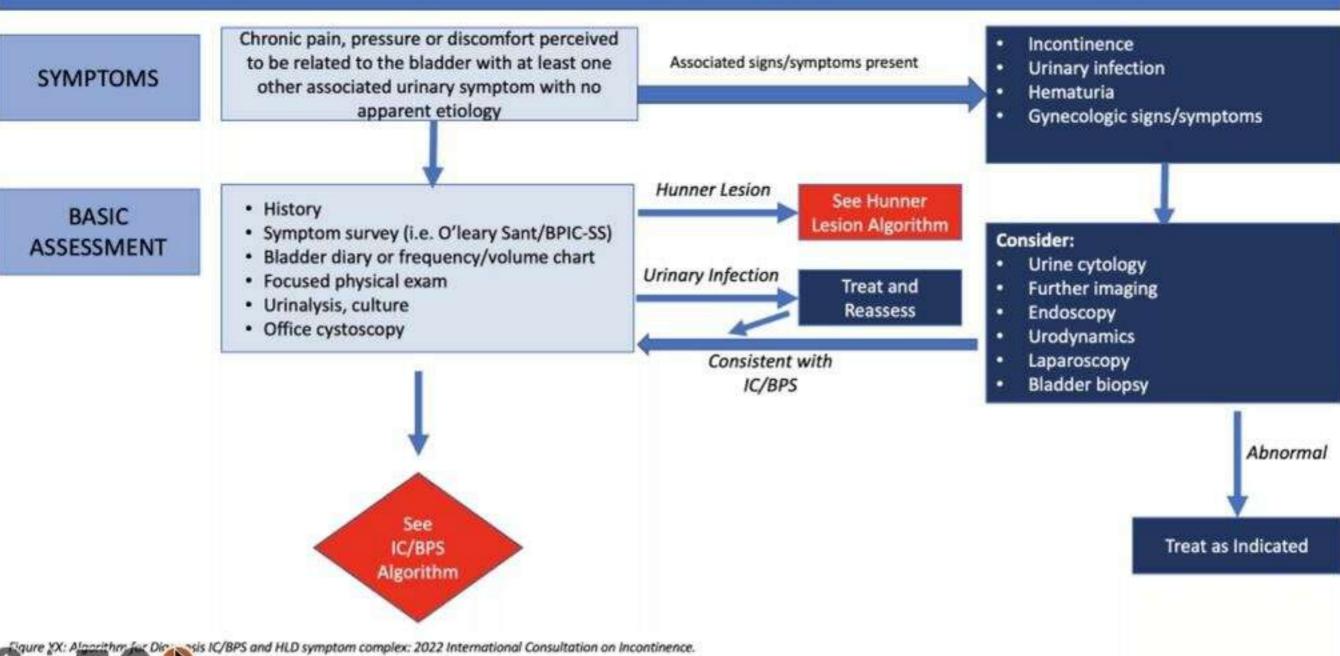
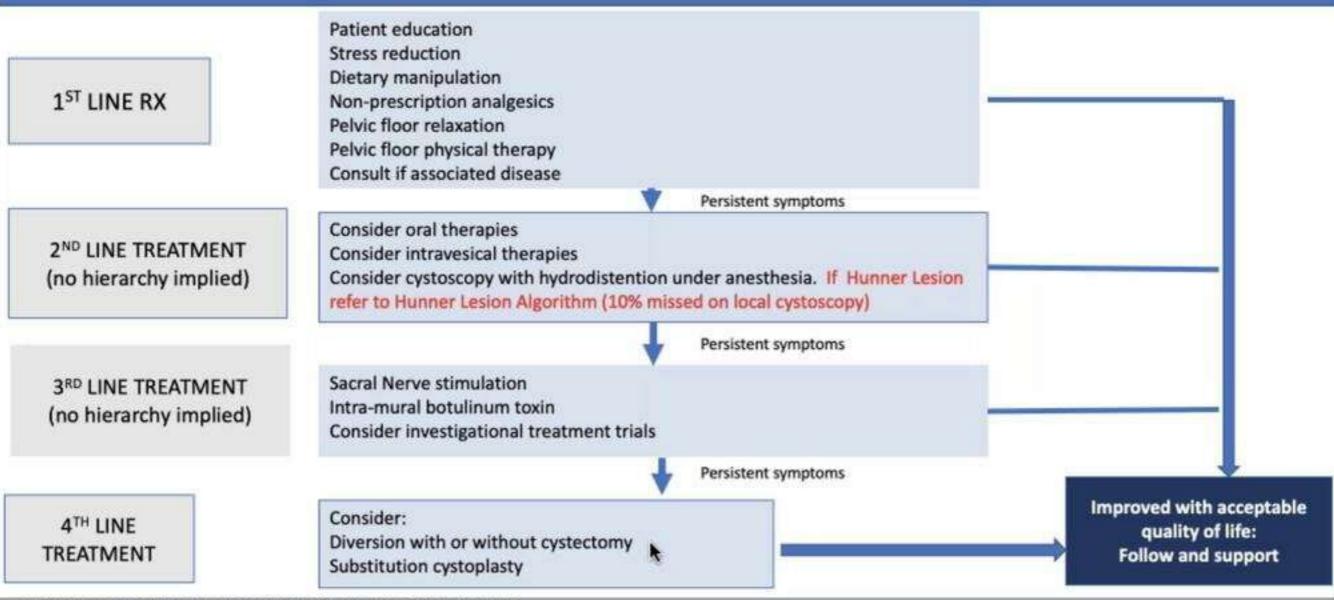


Figure YX: Algorithm for Discussis IC/BPS and HLD symptom complex: 2022 International Consultation on Incontinence.

Treatment: Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS)



- · Pain management is a primary consideration at every step of the algorithm
- Patient enrollment in an appropriate research trial is a reasonable option at any point.
- Consultation with a provider experienced in treating IC/BPS and Hunner lesion disease should be considered.
- Only DMSO and pentosan polysulfate are approved by FDA for IC/BPS indication



Hunner Lesion Disease

Diagnosis: Patient meeting IC/BPS definition. Cystoscopy local or under sedation -- circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. Rupture with increasing bladder distention with oozing of blood.

