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About Me

Associate Professor of Urology
Urology Residency Program Director
Board Certified in Urogynecology and Pelvic Reconstructive Surgery

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Outline

- Interstitial Cystitis/Bladder Pain Syndrome
  - Q&A
- Research and Improving Our Care
- Genitourinary Syndrome of Menopause
  - Q&A

3

1987

"Dear Ann Landers:
After 3 years of non-stop pain, 40-60 bathroom trips a day, little sleep, lots of tests, 12 doctors, hundreds of allergy shots, diets, antibiotics, and six unnecessary operations, I have finally been diagnosed as having interstitial cystitis, a 'rare' disease that doctors seldom look for and may turn out to be not so rare…"

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Definition and pathogenesis

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Terminology

Interstitial cystitis/ bladder pain syndrome (IC/BPS)
- Chronic bladder pain/ pressure/ discomfort
- Urinary frequency, nocturia
- Men or women

Chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS)
- Chronic pelvic pain in men (perineum, ejaculation)

Urologic chronic pelvic pain syndrome (UCPPS)
- Either of the above

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IC/BPS and UCPPS

- Diagnoses of exclusion
- Holistic and comprehensive approach
- Multi-disciplinary care often required

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Diagnostic Criteria for IC/BPS

1. Unpleasant bladder sensation (e.g., pain, pressure) and lower urinary tract symptoms
2. Lasting for more than 6 weeks duration
3. In the absence of infection or other identifiable causes

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Additional descriptors

Bladder "spasm"
Constant awareness of the bladder
Urinary urgency/frequency
Vaginal pain
Dysuria
Burning at tip of penis
Pain in the prostate/perineum

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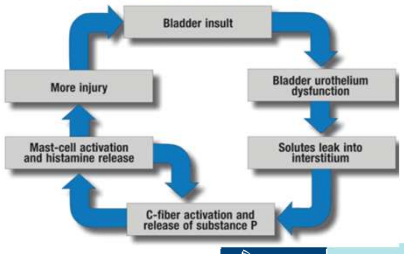
Old, bladder-centric view

Figure 1. Proposed mechanism for IC/PBS pathogenesis.



Evans, RJ. Rev Urol. 2002.

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Newer theories of etiology

1. Bladder epithelial dysfunction, which may lead to increased permeability and/or increased sensitivity, possibly via autocrine secretion of neurochemicals that effect bladder afferent function
2. Bladder inflammation
3. Neuropathic pain
   - pain related to dysfunction of one or more nerves, including peripheral, central, and/or failure of endogenous inhibitory pathways

Hanno P et al. J Urol 2014

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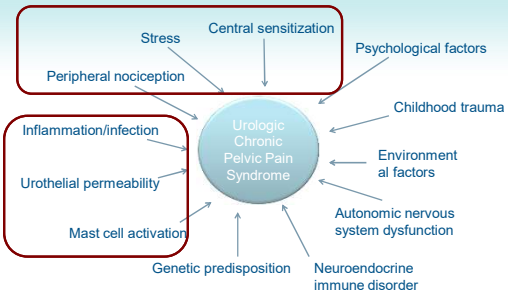

Modified from H. Lai, SUFU 2016

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Epidemiology

3.3-7.9 million women in the US
~2.7-6.5% of women in US
1-4 million men in the US
Unknown prevalence in pediatric/adolescents

4.5 years before diagnosis
5 physicians before diagnosis made
For every 1 diagnosis of IC
› 5 remain undiagnosed

Berry SH et al. J Urol 2011
Clemens JQ, et al. J Urol. 2007
Simon LJ, et al. Urology 1997
Ratner, V. Transl Androl Urol, 2015

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Clinical course

Spontaneous remission 11-50%
Waxing/waning clinical course (flares)
10% have Hunner's lesions – ulcers in bladder – most have normal cystoscopy
Most dx midlife (median age 40 y/o)

Berry SH et al. J Urol 2011
Simon LJ, et al. Urology 1997
Ratner V. Transl Androl Urol 2015
Peters K, et al. Urol 2009

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Why do we care?

QOL worse than someone on hemodialysis
Burden of health care utilization
› 4.1 million outpatient encounters in 2000
Economic impact of lost wages
› $1.7 billion per year

Hanno P, et al. J Urol 2011
Clemens JQ, et al. J Urol 2007
Ratner V. Transl Androl Urol 2015
Davis NF et al. Euro J Ob & Gyn and Repro Bio 2014

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Diagnosis

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American Urological Association

Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome

Published 2011; Amended 2014; Amended 2022

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; Norma Varela, PhD. H. Henry Lai

Hanno P et al. J Urol 2014

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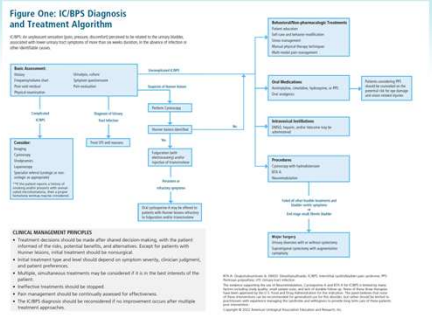
Figure One: IC/BPS Diagnosis and Treatment Algorithm



CLINICAL MANAGEMENT PRINCIPLES

- Treatment decisions should be made after shared decision-making, with the patient informed of the risks, potential benefits, and alternatives. Except for patients with Hunner lesions, initial treatment should be nonsurgical.
- Initial treatment type and level should depend on symptom severity, clinician judgment, and patient preferences.
- Multiple, simultaneous treatments may be considered if it is in the best interests of the patient.
- Ineffective treatments should be stopped.
- Pain management should be continually assessed for effectiveness.
- The IC/BPS diagnosis should be reconsidered if no improvement occurs after multiple treatment approaches.

Clemens et al, J Urol, 2022

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Clinical Symptoms

Pain, pressure, discomfort in the pelvic area >6 weeks
Daytime urinary frequency 10+
voids to relieve pain, pressure or discomfort, not fear of incontinence
Concern for acute bacterial cystitis/UTI, STI – testing negative
Symptoms did not resolve after treatment with antibiotics – no identifiable causes

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Definitions

Pain

- 'Unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage'
  - International Association for the Study of Pain, 1994

Urgency

- 'Sudden compelling desire to pass urine, which is difficult to defer'
  - International Continence Society, 2002
- 'I feel like my bladder is going to burst'!
- (Sounds a lot like 'pain' to me!)

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	Question
Q1	In the past 3 months, have you ever had a feeling of pain, pressure, or discomfort in your lower abdomen or pelvic area – that is, the part of your body that is above your legs and below your belly button?
Q2	In the past 3 months, have you had a feeling of a strong urge or feeling that you had to urinate or "pee" that made it difficult for you to wait to go to the bathroom?
Q3	Would you say this urge to urinate is mainly because of pain, pressure, or discomfort or mainly because you are afraid you will not make it to the toilet in time to avoid wetting?
Q4	In the past 3 months, before you urinate, as your bladder starts to fill, does your feeling of pain, pressure, or discomfort usually: (i) get worse, (ii) get better, or (iii) stay the same?

Lai, H et al. J Urol, Dec 2015

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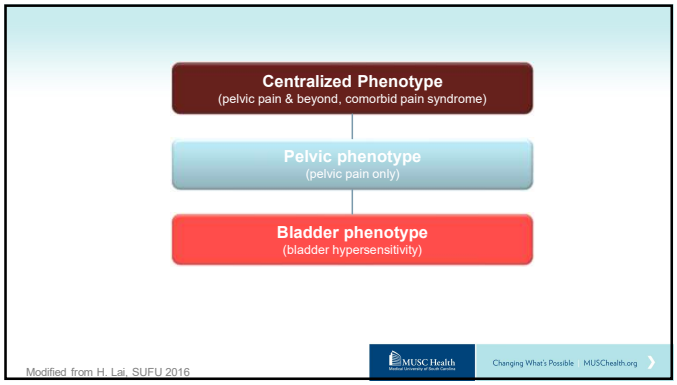
Centralized Phenotype
(pelvic pain & beyond, comorbid pain syndrome)
Pelvic phenotype
(pelvic pain only)
Bladder phenotype
(bladder hypersensitivity)
Modified from H. Lai, SUFU 2016
MUSC Health
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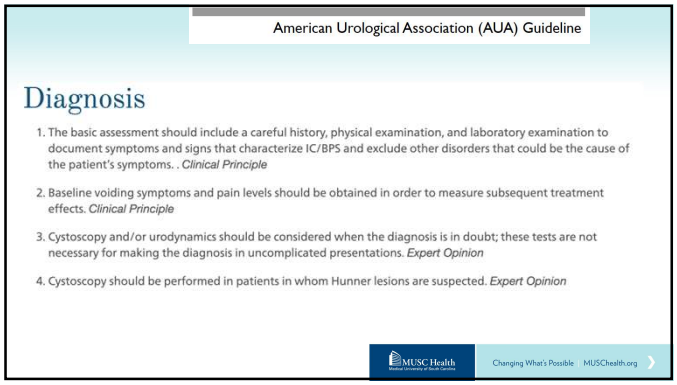
American Urological Association (AUA) Guideline
Diagnosis
1. The basic assessment should include a careful history, physical examination, and laboratory examination to document symptoms and signs that characterize IC/BPS and exclude other disorders that could be the cause of the patient's symptoms. . Clinical Principle
2. Baseline voiding symptoms and pain levels should be obtained in order to measure subsequent treatment effects. Clinical Principle
3. Cystoscopy and/or urodynamics should be considered when the diagnosis is in doubt; these tests are not necessary for making the diagnosis in uncomplicated presentations. Expert Opinion
4. Cystoscopy should be performed in patients in whom Hunner lesions are suspected. Expert Opinion
MUSC Health
Changing What's Possible MUSChealth.org

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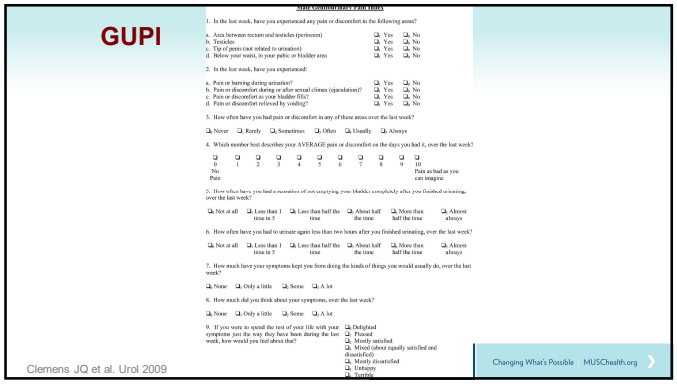
GUPI
Clemens JQ et al. Urol 2009
Changing What's Possible MUSChealth.org

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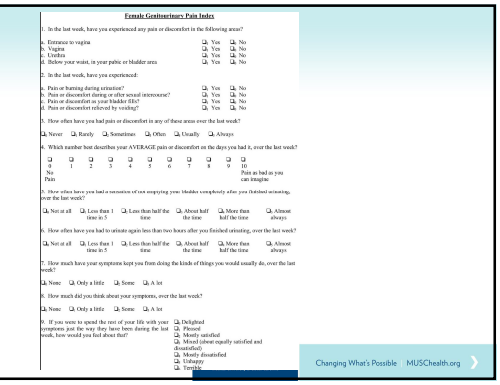
GUPI



Female Genitourinary Pain Index

1. In the last week, have you experienced any pain or discomfort in the following areas?

a. Entrance to vagina ❑ Yes ❑ No
b. Vagina ❑ Yes ❑ No
c. Urethra ❑ Yes ❑ No
d. Below your waist, in your pubic or bladder area ❑ Yes ❑ No

2. In the last week, have you experienced:

a. Pain or burning during urination? ❑ Yes ❑ No
b. Pain or discomfort during or after sexual intercourse? ❑ Yes ❑ No
c. Pain or discomfort in your bladder fills? ❑ Yes ❑ No
d. Pain or discomfort relieved by voiding? ❑ Yes ❑ No

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ Never ❑ Rarely ❑ Sometimes ❑ Often ❑ Usually ❑ Always

4. Which number best describes your AVERAGE pain or discomfort on the days you had it, over the last week?

❑ 0 No Pain ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Pain as bad as you can imagine

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑ Not at all ❑ Less than 1 time in 5 ❑ Less than half the time ❑ About half the time ❑ More than half the time ❑ Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑ Not at all ❑ Less than 1 time in 5 ❑ Less than half the time ❑ About half the time ❑ More than half the time ❑ Almost always

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑ None ❑ Only a little ❑ Some ❑ A lot

8. How much did you think about your symptoms, over the last week?

❑ None ❑ Only a little ❑ Some ❑ A lot

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑ Delighted
❑ Pleased
❑ Mostly satisfied
❑ Mixed (about equally satisfied and dissatisfied)
❑ Mostly dissatisfied
❑ Unhappy
❑ Terrible

Clemens JQ et al. Urol 2009

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PUF

		0	1	2	3	4
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+
2	**a.** How many times do you go to the bathroom at night?	0	1	2	3	4+
	b. If you get up at night to go to the bathroom, does it bother you?	Never	Mildly	Moderately	Severely	
3	Are you currently sexually active? **YES** ____ **NO** ____					
4	**a. IF YOU ARE SEXUALLY ACTIVE**, do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always	
	b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always	
5	Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, perineum, testes, or scrotum)? **If you do not have pain, please skip question 6.**	Never	Occasionally	Usually	Always	
6	**a.** If you have pain, is it usually...	No Pain	Mild	Moderate	Severe	
	b. Does your pain bother you?	Never	Occasionally	Usually	Always	
7	Do you have urgency after going to the bathroom? **If you do not have urgency, please skip final question.**	Never	Occasionally	Usually	Always	
8	**a.** If you have urgency, is it usually...	No Urgency	Mild	Moderate	Severe	
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always	
					Total Score	

© This is a modified version of the pelvic pain, urgency, and frequency (PUF) scale in the following article: (Parsons CL et al. *Urology.* 2002;60:573-578). 2000 C. Lowell Parsons, MD.

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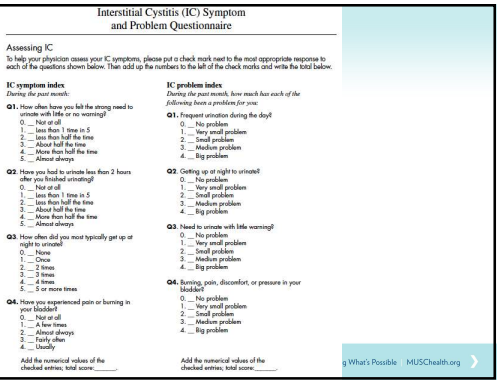
ICSI/PI



Interstitial Cystitis (IC) Symptom and Problem Questionnaire

Assessing IC

To help your physician assess your IC symptoms, please put a check mark next to the most appropriate response to each of the questions shown below. Then add up the numbers to the left of the check marks and write the total below.

IC symptom index
During the past month:

Q1. 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. 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. 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. Have you experienced pain or burning in your bladder?
0. __ Not at all
1. __ A few times
2. __ Almost always
3. __ Fairly often
4. __ Usually

Add the numerical values of the checked entries; total score_____.

IC problem index
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_____.

O'Leary MP et al. Urol 1997

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Common causes of flares

Perimenstrual/hormonal
Intercourse
Diet (multiple)
Stress
Cystitis/vaginitis
Allergies
Constipation

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Physical exam

Abdominal wall
Pelvic exam – chaperone, trauma informed
Pelvic floor dysfunction (high tone, tender)
- Check the levators, piriformis, obturator, perineal body

Vestibule
Vulvodynia
Bladder palpation (reproduces symptoms)
- trigone

Urethra palpation - masses
DRE for pelvic floor dysfunction and prostate tenderness

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Diagnostic tools

Cystoscopy in office
- If high suspicion for Hunner's lesion or hematuria

Urinalysis
PVR
[Urodynamics]
[K sensitivity test (PST)]
- Test for abnormal bladder epithelial permeability

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Therapeutic (diagnostic)

Cystoscopy with hydrodistention
- Many with IC, sx improve in 2-3 weeks after flare

Intravesical anesthetics
- Awareness of bladder, improvement

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American Urological Association (AUA) Guideline

Clinical Management Principles

Management Approach

5.Treatment decisions should typically be made after shared decision-making, with the patient informed of the risks, potential benefits, and alternatives. Except for patients with Hunner lesions (Statement 19), initial treatment should be nonsurgical. *Expert Opinion*

6.Efficacy of treatment should be periodically reassessed and ineffective treatments should be stopped. *Clinical Principle*

7.Multimodal pain management approaches (e.g., pharmacological, stress management, manual physical therapy if available) should be initiated. Pain management should be continually assessed for effectiveness because of its importance to quality of life. If pain management is inadequate, then consideration should be given to a multidisciplinary approach and the patient referred appropriately. *Clinical Principle*

8.The IC/BPS diagnosis should be reconsidered if no improvement occurs after multiple treatment approaches. *Clinical Principle*

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In practice….

Acknowledge their pain

IC is real! And we can help!

Assess psychosocial situation

Trauma informed

Clarify expectations (good/bad), chronic disease

Remission possible, cure rare

Put patient in charge
- Give them the IC guidelines
- Talk about the symptom questionnaire

Trustworthy resources - Address misinformation
- Send to www.ichelp.org

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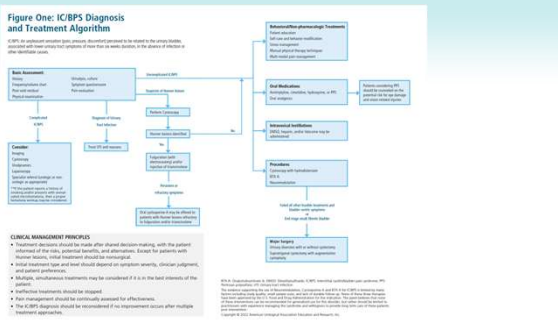

Clemens et al, J Urol, 2022

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IC diet

Perhaps 90% of IC/BPS are thought to be diet sensitive
No pathophysiologic connection identified

- ? Urinary solutes
- ? Organ cross-talk
- ? Neural up-regulation
  - Peripheral/central

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Dietary supplements for diet sensitive

sodium bicarbonate

calcium glycerophosphate

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Beverages
IC Friendly:
Water; whole, low-fat, nonfat, lactaid, rice, goat, and almond milk; blueberry and pear juice; vanilla, coconut, and caramel milk shakes; and chamomile, peppermint, and herbal teas
Avoid:
Alcoholic beverages, including beer and wine; carbonated drinks, such as soda; coffee and tea; citrus (grapefruit, orange), tomato, acai, and cranberry juices; and chocolate, coffee, and mocha milk shakes
Seasonings
IC Friendly:
Garlic and other seasonings (except those listed on the right)
Avoid:
Ketchup, spicy mustard, miso, soy sauce, vinegar, cayenne, hot curry powder, horseradish, and spicy foods (especially Mexican, Indian, and Thai foods)
Food Additives
Avoid:
Ascorbic acid; monosodium glutamate (MSG); aspartame (NutraSweet®); saccharin; and foods containing preservatives, artificial ingredients/colors
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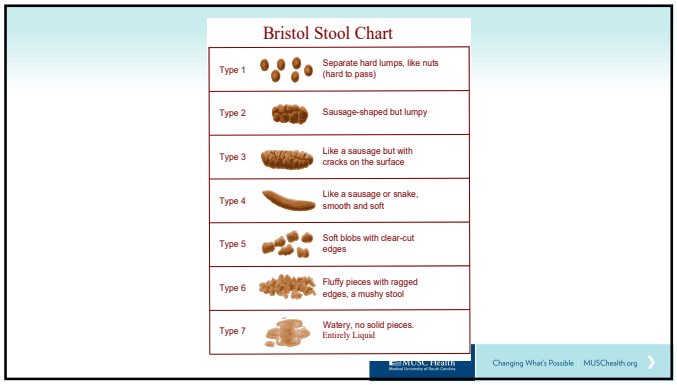
Bristol Stool Chart
Type 1
Separate hard lumps, like nuts (hard to pass)
Type 2
Sausage-shaped but lumpy
Type 3
Like a sausage but with cracks on the surface
Type 4
Like a sausage or snake, smooth and soft
Type 5
Soft blobs with clear-cut edges
Type 6
Fluffy pieces with ragged edges, a mushy stool
Type 7
Watery, no solid pieces. Entirely Liquid
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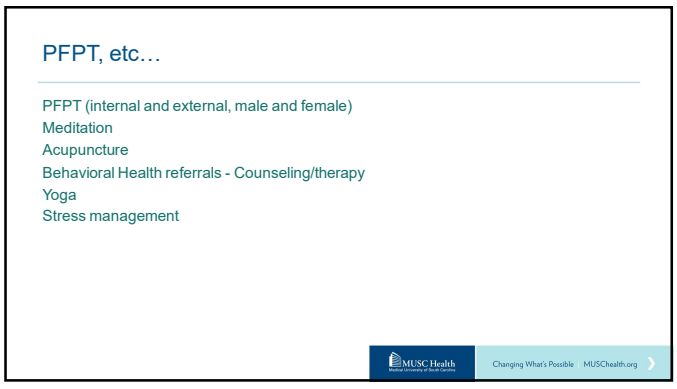
PFPT, etc…
PFPT (internal and external, male and female)
Meditation
Acupuncture
Behavioral Health referrals - Counseling/therapy
Yoga
Stress management
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American Urological Association (AUA) Guideline

Oral Medications

13. Clinicians may prescribe pharmacologic pain management agents (e.g., urinary analgesics, acetaminophen, NSAIDs, opioid/non-opioid medications) after counseling patients on the risks and benefits. Pharmacological pain management principles for IC/BPS should be similar to those for management of other chronic pain conditions. *Clinical Principle*
14. Amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate may be administered as oral medications (listed in alphabetical order; no hierarchy is implied) *Option (Evidence Strength: Grades B, B, C, and B)*
15. Clinicians should counsel patients who are considering pentosan polysulfate about the potential risk for macular damage and vision-related injuries. *Clinical Principle*
16. Oral cyclosporine A may be offered-particularly for patients with Hunner lesions refractory to fulguration and/or triamcinolone. *Option (Evidence Strength: Grade C)*

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Urinary Anesthetics

Phenazopyridine/Pyridium/Azo
- over the counter or prescription
- AE – methemoglobinemia – renal impairment/G6PD deficiency
- AE – hemolytic anemia – G6PD deficiency
- urine turns orange (stain)

Uribel/Urelle/Uro-MP (methenamine 118 mg, sodium phosphate monobasic 40.8 mg, phenyl salicylate 36 mg, methylene blue 10 mg, and hyoscyamine sulfate 0.12 mg)
- prescription only (Good Rx)
- AE – antimuscarinics
- AE – serotonin syndrome (MAOI)
- urine turns blue/green

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Amitriptyline

Tricyclic antidepressant (central mechanism)
Brand name: Elavil
Anticholinergic & antihistamine effect
Dosage 10mg titrated to 100mg qhs
Side-effects (79%!)
- Drowsiness, dry mouth, blurred vision, constipation, nausea
- Need to titrate up AND down

Significant central pain relief in ~60% of patients

Van Ophoven A et al. J Urol 2004
Hanno. Urol Clin North Am 1994

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Hydroxyzine

Antihistamine
Brand name: Atarax or Vistaril
Stabilize mast cell?
Start with 10mg qhs, uptitrate to 25 or 50mg
For responders – may increase to 50mg during allergy season
Side effect
- Drowsiness, cognition
- Need to titrate up and down

23-92% benefit… literature is poor

Sant GR et al. Urol 2003
Theoharis TC. Urol Clin North Am

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Cimetidine

H_2 receptor antagonist
Brand name: Tagamet
400mg daily (or 300mg BID)
Very limited literature on use
Side effect
- none but interacts with many other medications

Telegrah G et al. BJU Int 2001
Dasgupta J et al. BJU Int 2001

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Pentosan Polysulfate Sodium (PPS)

ELMIRON pentosan polysulfate sodium

Only FDA approved oral medication
100mg TID (practical?)
- 1-2 hours before food

Mechanism
- Rebuild the GAG layer (structurally related)? Antihistamine?

Side effects
- Hair loss, GI upset, elevated LFTs, headache
- Stop prior to surgery (blood thinning effect)
- !!!pigmentary maculopathy!!!

Takes 3-4 months to see benefit; use for at least 6 mo
Monitor LFTs

Graham E and T Chai. Cur Urol Rep 2006

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CystoProtek® Unique Dietary Supplement for Bladder Health

- **Chondroitin sulfate**
  - Repair the GAG layer
- **Sodium hyaluronate**
  - Repair the GAG layer
- **Quercetin**
  - antioxidant
- **Rutin**
  - Anti-inflammatory and assists quercetin absorption
- **Glucosamine Sulfate**
  - Repair the GAG layer and anti-inflammatory
- Does contain Shellfish

http://cysto-protek.com

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Intravesical Instillations

17. DMSO, heparin, and/or lidocaine may be administered as intravesical treatments (listed in alphabetical order; no hierarchy is implied). *Option (Evidence Strength: Grades C, C, and B)*

Procedures

18. Cystoscopy under anesthesia with short-duration, low-pressure hydrodistension may be undertaken as a treatment option. *Option (Evidence Strength: Grade C)*
19. If Hunner lesions are present, then fulguration (with ~~laser or~~ electrocautery) and/or injection of triamcinolone should be performed. Recommendation *(Evidence Strength: Grade C)*
20. Intradetrusor onabotulinumtoxin A may be administered if other treatments have not provided adequate improvement in symptoms and quality of life. Patients must be willing to accept the possibility that post-treatment intermittent self-catheterization may be necessary. *Option (Evidence Strength: Grade C)*
21. A trial of neuromodulation may be performed if other treatments have not provided adequate symptom control and quality of life improvement. If a trial of nerve stimulation is successful, then a permanent neurostimulation device may be implanted. Option *(Evidence Strength: Grade C)*

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Intravesical Instillation

Rescue Instillation
- 20cc of 2% lidocaine
- Hold for 20 min rotating 5 min L/R/back/front

DMSO Instillations
- Deplete substance P and reduce mast cell degranulation
- 6 weekly instillations x 15min each
- Side-effects: Garlic taste and odor on skin

Lidocaine/Heparin Instillations
- 6 weekly instillations x 20-60 min each
- 21-50% improvement
- Multiple regimens

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Hydrodistention

Technique
- General Anesthesia ONLY
- 80cmH_20 for 2 min dx
- Drain effluent and measure volume
- Refill & observe for 8 min tx

1. Diagnostic
   - evaluate for Hunner's lesions, tumors, stones
2. Therapeutic
   - Re-epithelialization?
   - Mast cell degranulation?
   - Neuropraxia?
3. Staging
   - Identify small fibrotic bladder/end stage

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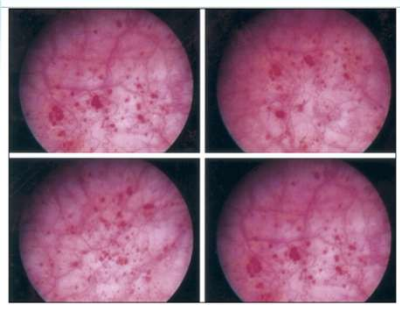

Glomerulations after hydrodistention

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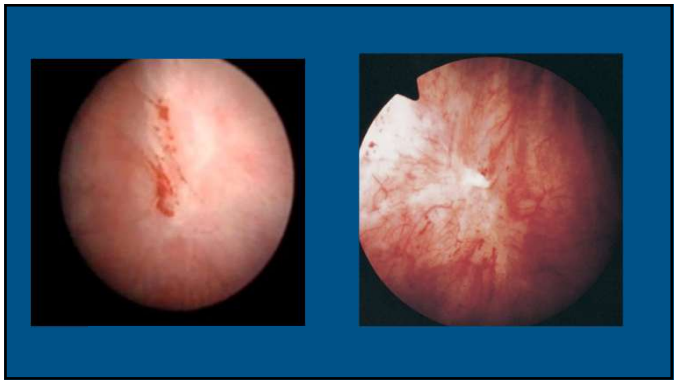

54

Triamcinolone injection of Hunner's lesions

Biopsy first time to demonstrate not cancer
Repeat injection in 3-6 months if not improved

55

Onabotulinum Toxin A

100U
Consideration of repeated procedures
Subset of patients may have relief of both LUTS and pain
Weigh adverse events

Kuo HC & MB Chancellor. BJU Int 2009
Chung SD et al. Pain Physician 2012

56

Sacral Neuromodulation (Interstim)

S3 placement (some institutions option pudendal nerve)
Bilateral lead placement option
If permanent device, 72-80% success rate
High revision/explant rate (21-50%)

Powell CR & KJ Kreder. Urol 2010
Marinkovic SP et al. Int Urogynecol J 2011
Peters KM et al. BJU Int 2007

57

Cyclosporine A

Immunosuppressant
Dosage 3mg/kg/day daily or divided BID
Use for only 3-6 mo if possible
Indication: Hunner Lesions refractory to triamcinolone - diffuse inflammed bladder that you would want to inject triamcinolone but too many lesions
Side effects
- HTN, gingival hyperplasia, alopecia, secondary cancers, mouth ulcers, nephrotoxic

Monitoring
- Serum creatinine
- CSA levels (trough)

Sairanen J, et al. J Urol 2005
Forrest JB, et al. J Urol 2012

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American Urological Association (AUA) Guideline

Major Surgery

22. Major surgery (e.g., substitution cystoplasty, urinary diversion with or without cystectomy) may be undertaken in carefully selected patients with bladder-centric symptoms, or in the rare instance when there is an end-stage small fibrotic bladder, for whom all other therapies have failed to provide adequate symptom control and quality of life improvement. *Option (Evidence Strength: Grade C)*

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American Urological Association (AUA) Guideline

Treatments that Should Not be Offered

The treatments below appear to lack efficacy and/or appear to be accompanied by unacceptable adverse event profiles. See body of guideline for study details and rationales.

23. Long-term oral antibiotic administration should not be offered. *Standard (Evidence Strength: Grade B)*
24. Intravesical instillation of bacillus Calmette-Guerin should not be offered outside of investigational study settings. *Standard (Evidence Strength: Grade B)*
25. High-pressure, long-duration hydrodistension should not be offered. *Recommendation (Evidence Strength: Grade C)*
26. Systemic (oral) long-term glucocorticoid administration should not be offered. *Recommendation (Evidence Strength: Grade C)*

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Treatment failure

Aiming towards the wrong pathophysiology for that patient
- i.e. the treatment is off target
- Beating a dead horse

Correct pathophysiology is being targeted, but the treatment is not ameliorating it
- i.e. the treatment is subtherapeutic

Pain management, PM&R, Behavioral Health, GI, Gyn

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Thank you. Questions?

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Improving our care

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The 1980's

- No large-scale studies of IC/BPS or CP/CPPS
- No consensus on:
  - Epidemiology
  - Terminology
  - Diagnosis
  - Treatment
  - Pathophysiology
  - Anything else

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Conquering IC. Changing Lives.
Interstitial Cystitis Association
www.ichelp.org

ICNetwork YOU ARE NOT ALONE
http://www.ic-network.com

Urology Care FOUNDATION
The Official Foundation of the American Urological Association

65

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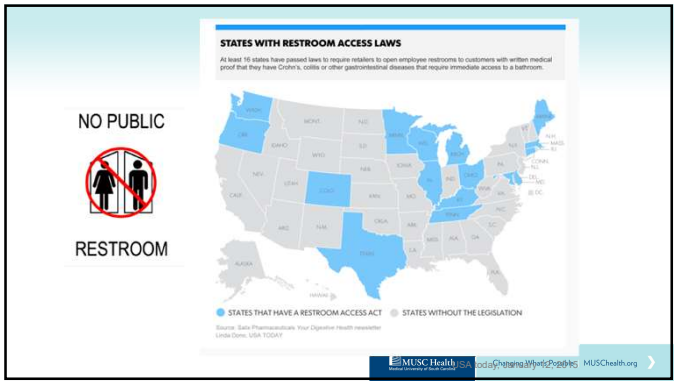
NO PUBLIC
RESTROOM
STATES WITH RESTROOM ACCESS LAWS
STATES THAT HAVE A RESTROOM ACCESS ACT
STATES WITHOUT THE LEGISLATION
MUSC Health
MUSCHealth.org

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MEDICAL ALERT
Restroom Access Required
The holder of this card has a medical condition (interstitial cystitis, prostatitis or pelvic pain syndrome) that requires frequent and urgent restroom access.
It is difficult, if not impossible, for this patient to 'hold it' without enduring severe pain and/or bladder spasms. Please provide restroom access to this patient. Your cooperation is greatly appreciated.
Medical Alert
PLEASE GIVE
IMMEDIATE RESTROOM ACCESS
TO THE PERSON
INTERSTITIAL CYSTITIS
Also known as IC, Painful Bladder Syndrome, Bladder Pain Syndrome
Interstitial Cystitis Association
www.ichelp.org
USChealth.org

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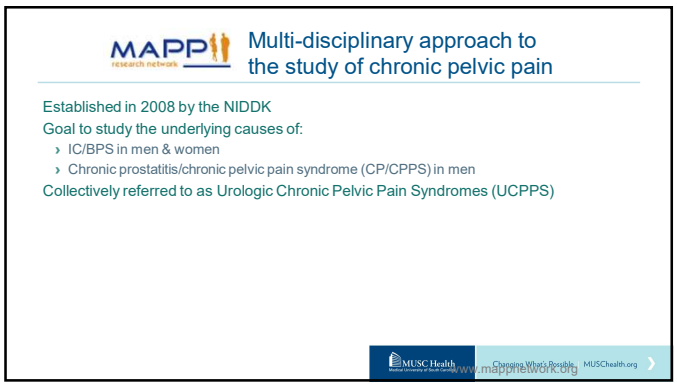
MAPP research network
Multi-disciplinary approach to the study of chronic pelvic pain
Established in 2008 by the NIDDK
Goal to study the underlying causes of:
› IC/BPS in men & women
› Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men
Collectively referred to as Urologic Chronic Pelvic Pain Syndromes (UCPPS)
MUSC Health
www.mappnetwork.org
MUSCHealth.org

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Unique clinical trial

Prior research looked at bladder-specific OR prostate-specific causes
Need to look more comprehensively and define the role of the CNS
Modeled after research protocols for other chronic pain conditions (e.g. fibromyalgia, chronic fatigue syndrome, IBS)
Other areas of the body, genes, environment, emotions

70

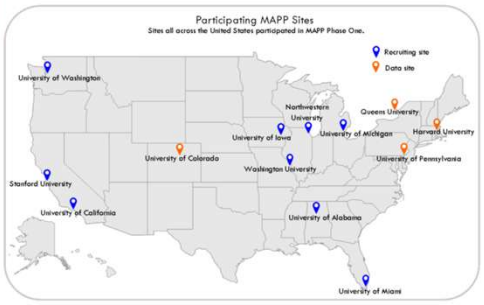

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Table 3 Baseline phenotyping battery for MAPP: urological self-report questionnaires

Instrument	Subscales
Symptom and Health Care Utilization Questionnaire (SYM-Q)	1. Pain, urgency, frequency
	2. Urologic/Pelvic Pain severity
	3. Non-urologic/Pelvic Pain severity
	4. Mood
	5. Most bothersome symptom
	6. Medical care seeking
	7. Menstrual information
	8. Flare status
Interstitial cystitis symptom and problem index	1. IC Symptom Index (ICSI)
	2. IC Problem Index (ICPI)
American Urological Association Symptom Index Score	1. AUASI total score
Rice case definition questionnaire	1. RICE total score
Brief flare risk factor questionnaire	1. Flare timing, symptoms, and symptom severity
	2. Cause attribution
	3. Foods
	4. Drinks
	5. Physical and sedentary activities
	6. Stress
	7. Sexual activity
	8. Infections
Genitourinary Pain Scale (GUPI)	1. Pain
Male version	2. Urinary symptoms
Female version	3. Quality of life
	4. Total
Female sexual function index	1. FSFI total score
International index of erectile function	1. IIEF total score
University of Washington male sexual function scale	1. Pain with ejaculation
	2. Premature ejaculation
	3. Difficulty reaching ejaculation
Self-esteem and relationship questionnaire	1. SEAR total score
Males	
Females	

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The FUTURE…

- Biomarkers
  - Help diagnosis and understand pathogenesis
  - Targets for treatment
  - Modulate a pathway
- Gene therapy
  - Aqx-1125-> SHIP1 pathway
- Different drug delivery modes
- Bladder MRI to detect areas of increased permeability
- Brain MRI to detect hyperactive areas

Brain, Behavior & Immunity. 2015

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How the MAPP Network Has Helped Us Understand Urologic Chronic Pelvic Pain Syndrome

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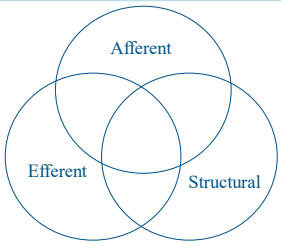
"Functional Urology" – Some Context



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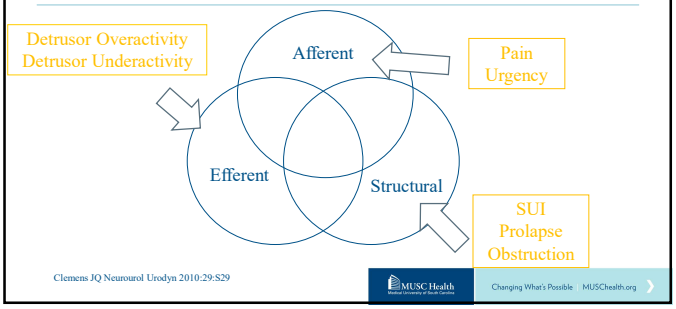
"Functional Urology" – Some Context



Clemens JQ Neurourol Urodyn 2010:29:S29

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IC/BPS

- NIDDK Consensus Definition 1987, 1990
- Cohort Study (ICDB) 1991-1996
- Validated Instrument (ICSI) 1997
- Clinical Trials (ICCRN1) 1998-2003
- More Clinical Trials (ICCRN2) 2003-2008
- Cohort Study (MAPP) 2008-2013 2014-2023

CP/CPPS

- NIDDK Consensus Definition 1995
- Cohort Study (CPC) plus Validated Instrument (CPSI) plus Clinical Trials (CPCRN1) 1997-2002
- More Clinical Trials (CPCRN2) 2003-2008

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NIDDK-Funded Clinical Trials

ICCRN	CPCRN
PPS vs Hydroxyzine factorial	Cipro vs tamsulosin factorial
Intravesical BCG vs placebo	Alfuzosin vs placebo
Amitriptyline vs placebo*	Pregabalin vs placebo*
Mycophenolate mofetil vs placebo	

Sant GR, et al. J Urol 170:810-15, 2003
Mayer R, et al. J Urol 173:1186-91, 2005
Foster HE Jr, et al. J Urol 183:1853-58, 2010
Yang CC, et al. J Urol 185:901-6, 2011

Alexander RB, et al. Ann Intern Med 141:581-6, 2004
Nickel JC, et al. N Eng J Med 359:263-73, 2008
Pontari MA, Arch Intern Med 170:1586-93, 2010

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UPPCRN

PT Trial

- Myofascial PT vs therapeutic massage
- Feasibility trial first
- Then full trial in women

Randomized Multicenter Clinical Trial of Myofascial Physical Therapy in Women With Interstitial Cystitis/Painful Bladder Syndrome and Pelvic Floor Tenderness

M. P. FitzGerald,* C. K. Payne,† E. S. Lukacz,‡ C. C. Yang, K. M. Peters,§ T. C. Chai,‖ J. C. Nickel,¶ P. M. Hanno,** K. J. Kreder,†† D. A. Burks,‡‡ R. Mayer,§§ R. Kotarinos, C. Fortman, T. M. Allen, L. Fraser, M. Mason-Cover, C. Furey, L. Odabachian, A. Sanfield, J. Chu, K. Huestis, G. E. Tata, N. Dugan, H. Sheth, K. Bewyer, A. Anaeme, K. Newton, W. Featherstone, R. Halle-Podell, L. Cen, J. R. Landis,‖‖ K. J. Propert, H. E. Foster, Jr., J. W. Kusek and L. M. Nyberg for the Interstitial Cystitis Collaborative Research Network

J Urol. 2012;187:2113-8

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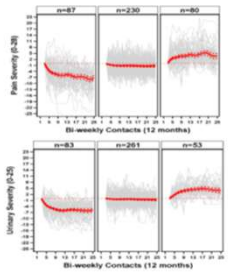
UCPPS Symptom Phenotypes



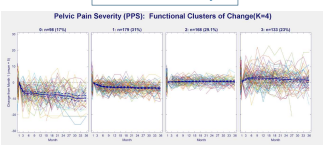
- Psychometrics => Two symptom patterns
  - Pain symptoms
  - Urinary symptoms
- MAPP Symptom Scales
  - Pain Symptom Severity (PSS)
  - Urinary Symptom Severity (USS)
- At 1 year:
  - 21% showed improvement in PPS
  - 22% showed improvement in USS

Griffith JW, et al. J Urol. 2016; 195:949-54.
Nalbhoff RD, et al. J Urol 2017;198:848

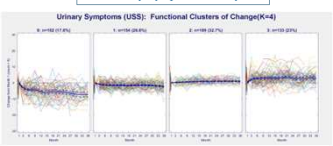
80

36-Month Symptom Trajectories

Pelvic Pain Severity



Urinary Symptom Severity



- 48% showed improvement in PPS, 44% showed improvement in USS
- 40% of those with PPS improvement also showed USS improvement
- 40% of those with USS improvement also showed PPS improvement

Bradley CS, submitted to J Urol

81

Clinical Message

Some IC/BPS patients report pain and some don't (pressure, discomfort) so pain scales may miss important symptoms

Assess frequency/ nocturia as well as pain

82

Clinical Message

Pervasive opinion is that nobody ever gets better

MAPP data show this is not true!

About 40% improve over time

- Not a statistical phenomenon

83

Who Does Worse?

More severe baseline symptom severity
Widespread pain
Poor sleep
Fatigue

Naliboff BD, et al. J Urol 2017;198:848.

84

Widespread Pain

Widespread pain (25%) was associated with:

- More severe UCPPS symptoms
- Worsened UCPPS symptoms over time
- Poorer QOL
- Different neuroimaging patterns
- More pain sensitivity
- Differential treatment response

Naliboff BD, et al. J Urol 2017;198:848.
Lai HH, et al. J Urol 2017;198:622.
Krieger JN, et al. J Urol 2015;193:1254.
Maixner W, et al. J Pain 2016;17:T93.

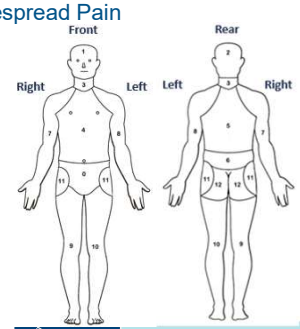
85

Measuring Widespread Pain

1 pelvic region
12 extra-pelvic regions

Categories:

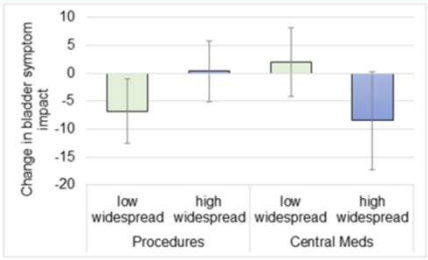
- Pelvic pain only (0)
- Widespread pain (3+ regions)
- Intermediate (1-2 regions)



Clemens JQ, et al. Neurourol Urodyn 2024 2024;43(3):727-37.

86

Symptom Improvement by Widespread Pain Status and Treatment Type



Schrepf A, et al. Neurourol Urodynam.

87

Re-Analysis of IC/BPS RCTs

Recall that there were multiple (negative) RCTs of IC/BPS therapies

Raw data were obtained from the NIDDK Repository

Some of these studies collected data on widespread pain
- Allowed retrospective stratification of all participants based on the degree of widespread pain

Farrar JT, et al. Pain 166(5):1179, 2025.

88

Clinical Message

Consider using the very simple MAPP body map to ask about widespread pain

Patients with widespread pain may respond more favorably to 'systemic' therapies
- We need more systemic therapies!

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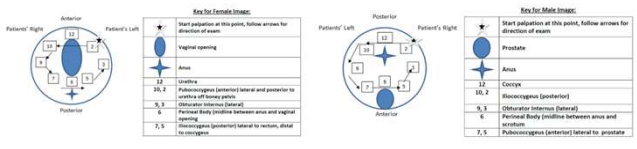
Pelvic Floor Muscle Tenderness Scoring System (0-6)



Low = 0-1 sites
Moderate = 2-5 sites
High/Severe = 6 sites

Gupta P, et al. J Urol 2022;208(2): 341-9.

90

Pelvic Floor Muscle Tenderness Scoring System (0-6)

Moderate/High tenderness
- 68% men, 87% women

High tenderness
- 21% men, 28% women
- Widespread pain
- Neuropathic pain

Gupta P, et al. J Urol 2022;208(2): 341-9.

91

Clinical Message

Simple standardized measurement system for pelvic floor muscle tenderness

(Those with PFM tenderness often benefit from PT)

Diffuse, severe PFM tenderness is associated with the presence of widespread pain
- Consider systemic therapies in addition to PT

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MAPP Biomarker Findings

There is no *H. pylori* for IC/BPS

Microbiome studies
- Bacteria - no differences observed between cases and controls
- Fungi - more species diversity in cases than controls

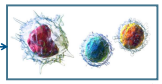
Urine biomarker studies
- None discriminated cases from controls
- Proteomics – differential expression of 9 proteins in UCPPS vs controls
  - Altered ECM
  - Immunomodulatory/ host defense

Serum biomarker studies
- systemic inflammation via-toll-like receptors may be important

Dagher A, et al. BJU Int. 2017;120:130-142 Nickel JC, et al. World J Urol. 2022
Nickel JC, et al. J Clin Med. 2019;8:415 Froelich JW, et al. Mol Cell Proteomics. 2022

93

Inflammatory Phenotype



+ LPS (TLR4)

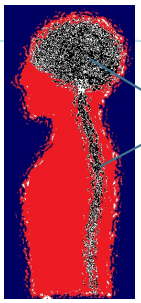
IL-6 IL-1β IL-8 IL-10 TNF-alpha MCP-1 MIP1alpha

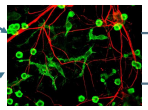
TLR4 composite score

Schrepf A, et al. Pain 2023 164(5):1148-1157

94

PAIN





IL-6

TNF-α

IL-1β

TLR4 activation

Schrepf A, et al. Pain 2023 164(5):1148-1157

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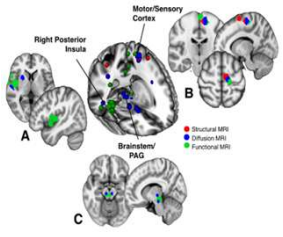
MAPP Neuroimaging

UCPPS =>

- Altered function (green)
- Altered gray matter (red) and white matter (blue) structure
- Findings associated with widespread pain

Implications:

- UCPPS dysfunction is not confined to the pelvis
- ? Predictor of treatment response/ disease course?

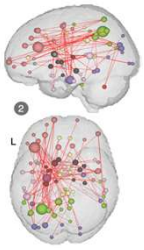


Clemens JQ, et al. Nature Rev Urol 2019;16:187

96

Patterns of Neural Activity (Functional Connectivity)

- Abnormal patterns in areas responsible for analgesic effects
- Increased functional connectivity in the frontoparietal brain network associated with reduced UCPPS symptoms at 3 months



Kutch JJ, et al. Pain 2017;158:1069.

MUSC Health | Changing What's Possible | MUSChealth.org

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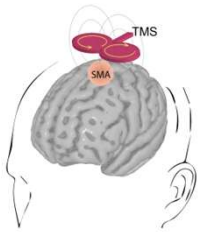
Exploring New Treatments Based On MAPP Neuroimaging

- R01DK121724 (2020-2025) PI: Jason Kutch. clinicaltrials.gov NCT04734847
- Study will provide an initial answer to the question of whether disturbances in SMA activity are causal for IC/BPS pain
- Neuroimaging can be used as a treatment response biomarker
- Enrichment of clinical trials



Johnson EV, et al. Trials. 2024;12;25(1):609

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MAPP Pain Testing

Pressure Pain Sensitivity
1. MAST
2. Suprapubic pressure
3. Forearm pressure
4. Trapezius pressure

Temporal Summation
1. Summation at suprapubic site
2. Summation at forearm

Harte SE, et al. Pain 2019 160(6):1270-80

MUSC Health | Changing What's Possible | MUSChealth.org

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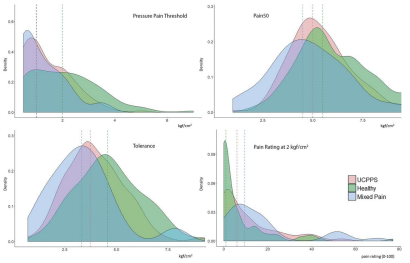
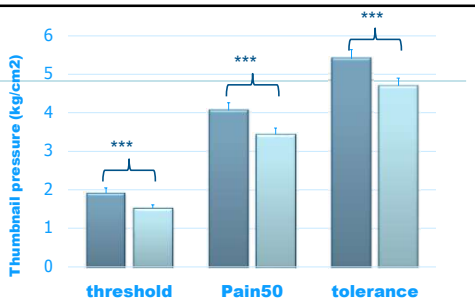
MAPP I Findings



- Patients reporting a "flare" at test showed greater pain sensitivity
- Greater pain sensitivity = more widespread pain
- Greater pain sensitivity = lower likelihood of improvement
- Centralized Phenotype (Nociplastic Pain)

Harte SE, Schrepf A, Gallop R, et al. Quantitative assessment of nonpelvic pressure pain sensitivity in urologic chronic pelvic pain syndrome: a MAPP Research Network study. Pain. 2019;160(6):1270-1280.

100



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MAPP

The Most Comprehensive Study of IC/BPS or CP/CPPS Ever Performed

- Extensive battery of questionnaires, PROs
  - Validated, longitudinal, urologic and non-urologic
- Standardized physical examination
- Treatment data
- Experimental pain testing
- Neuroimaging
- Biospecimens
- Animal Models

All data are now available at the NIDDK Repository!

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Genitourinary Syndrome of Menopause (GSM)

Guidelines 2025

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Genitourinary syndrome of menopause (GSM)

TRIGGER OF EVENTS

- Menopause
- Decrease in estrogens & androgens
- Vaginal & vulvar tissue atrophy
- Vaginal microbiome disruption…
  - Decreased lactobacilli
  - Decreased glycogen
  - Increased pH
  - Decreased defense against UTI

POSSIBLE ETIOLOGIES

- Menopause
- Premature ovarian failure
- Surgical induced menopause (bilateral oophorectomy)
- Breast feeding
- OCPs, spironolactone, antihistamines, anti-androgens
- Adjuvant hormone deprivation therapy
  - Breast cancer or gender-conforming therapy
- Thyroid disorders & pituitary tumors

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A Cost Savings Analysis of Topical Estrogen Therapy in Urinary Tract Infection Prevention Among Postmenopausal Women

Charlotte Goldman Houston*,[1] William S. Azar,[1] Sean Shenghsiu Huang,[2] Rachel Rubin,[1] C. Scott Dorris,[3] and Rachael D. Sussman[1]

UROLOGY PRACTICE
www.auajournals.org/journal/upr

Abstract

Introduction: UTIs are some of the most common infections in geriatric patients, with many women experiencing recurrent infections after menopause. In the US, annual UTI-related costs are $2 billion, with recurrent infections creating a significant economic burden. Given the data published on topical estrogen in reducing the number of infections for postmenopausal women with recurrent UTI, we sought to evaluate how this would translate to cost savings.

Methods: We performed a systematic literature review of UTI reduction secondary to topical estrogen utilization in postmenopausal female patients. The cost per UTI was determined based on published Medicare spending on UTI per beneficiary, weighted on reported likelihood of complicated and resistant infections. For a patient with recurrent infections, topical estrogen therapy reported on average can reduce infections from 5 to 0.5 to 2 times per person per year.

Results: At a calculated cost per UTI of $1222, the reduction in UTI spending can range between $3670 and $5499 per beneficiary per year. Per-beneficiary spending on topical estrogen therapies was $1013 on average ($578-$1445) in 2020. After including the cost of the therapy, overall cost savings for topical estrogen therapies were $1226 to $4888 annually per patient.

Conclusions: Topical estrogens are a cost-conscious way to improve the burden of UTI on postmenopausal women with the potential for billions of dollars in Medicare savings. System-wide efforts should be made to have these therapies available as prophylaxis for postmenopausal patients and to ensure they are affordable for patients.

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SHARED DECISION MAKING

1. Clinicians and patients should engage in shared decision-making, taking into consideration the best available evidence and the patient's expressed values, preferences, and goals of GSM care. *(Clinical Principle)*

SCREENING & DIAGNOSIS

2. Clinicians should screen patients at risk for, or presenting with signs of, GSM for genital, sexual, and/or urinary symptoms using a focused medical, sexual, and psychosocial history. *(Clinical Principle)*
3. Patients with symptoms of GSM should undergo a genitourinary examination. *(Clinical Principle)*
4. Clinicians should educate patients with GSM about genitourinary signs and symptoms that result from decreased sex steroid hormones. *(Clinical Principle)*
5. During evaluation of patients with GSM, clinicians should assess for coexisting genitourinary conditions, utilizing additional testing or referral when appropriate. *(Clinical Principle)*
6. In patients with GSM and psychosocial and/or sexual health concerns, clinicians may refer to a credentialed therapist. *(Expert Opinion)*
7. In patients with GSM and pelvic floor dysfunction, clinicians may refer to a physical therapist specializing in pelvic floor conditions. *(Expert Opinion)*

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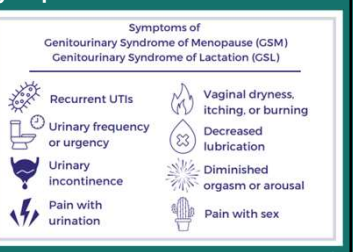
GSM Symptoms

- Genital dryness
- Decreased lubrication with sexual activity
- Discomfort or pain with sexual activity
- Discomfort with tight clothing/exercising
- Post-coital bleeding
- Irritation/burning/itching of vulva or vagina
- Dysuria
- Urinary frequency/urgency/nocturia
- Decreased arousal, orgasm, desire



AUA GSM Guidelines 2025

Rachel Rubin, MD, PLLC

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“trauma-informed” care

- Often women have not had an exam for 10-30+ years when they present for this evaluation
- May not be having intercourse
- Privacy, sheet or blanket
- Coach through exam, slowly
- External exam only, single digital exam, no speculum
- Consider offering a mirror

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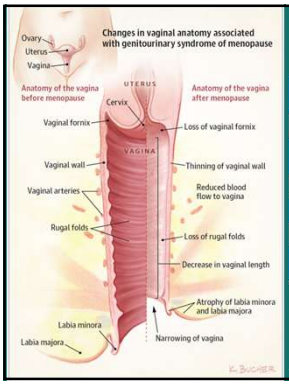

GSM Signs

Decreased moisture, loss of vaginal rugae, vaginal pallor/erythema
Decreased elasticity, decreased moisture, introital retraction
Decreased moisture/introital stenosis, loss of hymenal remnants
Vulvar erythema, vaginal pallor/erythema, introital retraction
Tissue fragility/fissures/petechiae
Vaginal fissures/petechiae/erythema
Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections

AUA GSM Guidelines 2025

Jin, Jill. Vaginal and Urinary Symptoms of Menopause. JAMA 2017

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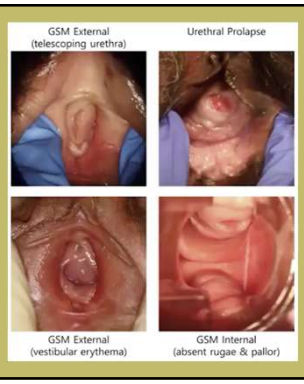
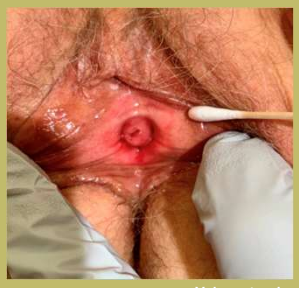


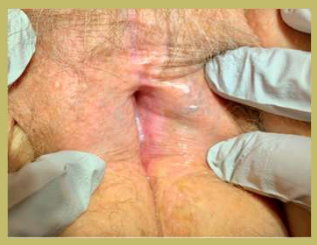
111

Labia Minora & introitus

Kelly JD Peters, DO. Vulvar Vestibulitis Syndrome. J Reprod Med. 2007;52(12):1083-1094.



Vulvar atrophy



Severe vulvar atrophy vs Lichen Sclerosis

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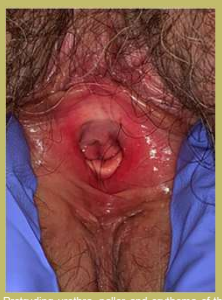
Labia Minora & introitus

partially resorbed and thin labia minora



Protruding urethra, pallor and erythema of the vestibule

Rachel Rubin, MD, PhD, DrMH, Howard University

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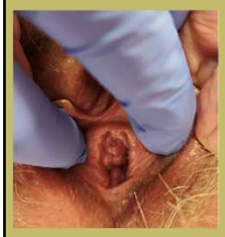
Urethra



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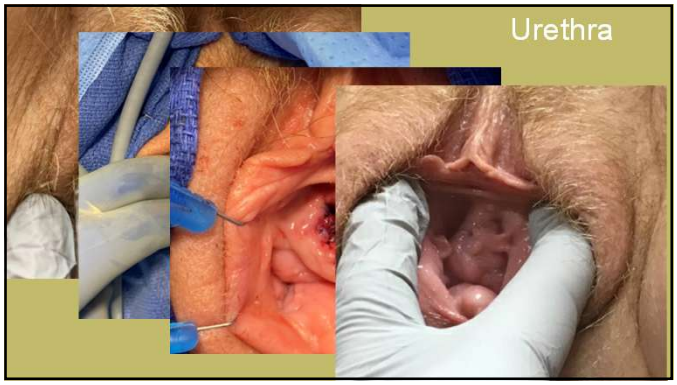

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GSM Symptoms & Signs

Genital dryness	Decreased moisture, loss of vaginal rugae, vaginal pallor/erythema
Decreased lubrication with sexual activity	Decreased elasticity, decreased moisture, introital retraction
Discomfort or pain with sexual activity	Decreased moisture/introital stenosis, loss of hymenal remnants
Discomfort with tight clothing/exercising	Vulvar erythema, vaginal pallor/erythema, introital retraction
Post-coital bleeding	Tissue fragility/fissures/petechiae
Irritation/burning/itching of vulva or vagina	Vaginal fissures/petechiae/erythema
Dysuria	Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections
Urinary frequency/urgency/nocturia	Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections
Decreased arousal, orgasm, desire	

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HORMONAL INTERVENTIONS

8. Clinicians should offer the option of local low-dose vaginal estrogen to patients with GSM to improve vulvovaginal discomfort/irritation, dryness, and/or dyspareunia. *(Strong Recommendation; Evidence Level: Grade C)*

9. Clinicians should offer the option of vaginal dehydroepiandrosterone (DHEA) to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Moderate Recommendation; Evidence Level: Grade C)*

10. Clinicians may offer the option of ospemifene to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Conditional Recommendation; Evidence Level: Grade C)*

11. In patients with GSM who are on systemic estrogen therapy, clinicians should offer the option of local low-dose vaginal estrogen or vaginal dehydroepiandrosterone (DHEA). *(Expert Opinion)*

12. In patients with GSM and comorbid genitourinary conditions (e.g., overactive bladder), clinicians may offer the option of local low-dose vaginal estrogen to improve genitourinary symptoms. *(Expert Opinion)*

13. In patients with GSM and recurrent urinary tract infections, clinicians should recommend local low-dose vaginal estrogen to reduce the risk for future urinary tract infections. *(Moderate Recommendation; Evidence Level: Grade B)*

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TABLE 4: FDA Approved treatments for GSM

Category	Composition	Commonly used starting dose	Commonly used maintenance dose	Typical serum estradiol level (pg/mL)
Vaginal creams	17β-estradiol 0.01% (0.1 mg active ingredient/g)	0.5-1 grams daily for 2 weeks	0.5 -1 gram 1-3 times per week	Variable, 3-5a
	Conjugated estrogen (0.625 mg active ingredient/g)	0.5 -1 grams daily for 2 weeks	0.5 grams 1-3 times/week	Variable
Vaginal inserts	17β-estradiol inserts	4 or 10 μg/d for 2 weeks	1 insert twice/week	3.6 (4 μg) 4.6 (10 μg)
	Estradiol hemihydrate tablets	4 or 10 μg/d for 2 weeks	1 insert twice/week	5.5
	Prasterone (DHEA) inserts	6.5 mg/day	1 insert/day	5
Vaginal rings	Silicone polymer with a core containing 2mg estradiol	7.5 mcg/day for 3 months	1 ring/three months	8
Oral tablet	Ospemifene	60 mg/day	1 tablet by mouth/day	N/A

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Prescription Options

	FORM	GENERIC	BRAND (* if generic exists)	INSTRUCTIONS
	Cream	Estradiol 0.01% Conjugated estrogens 0.625mg	Estrace* Premarin	1 gram vaginally nightly for 2 weeks, then 1 gram 2x/week thereafter. Use topically around urethra and vestibule. Rub into vaginal walls for less mess.
	Vaginal Estradiol Insert	Estradiol 10mcg	Yuvafem* Vagifem* Imvexxy	1 insert vaginally nightly for 2 weeks, then 2x/week thereafter.
	Vaginal DHEA Insert	DHEA/Prasterone 6.5mg	Intrarosa	1 insert vaginally nightly. DHEA converts to estrogen and testosterone, helps vestibular pain.
	Vaginal Ring	Estradiol 2mg ring	E-String	Insert ring vaginally. Replace every 3 months.

Rachel Rubin, MD, PLLC

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Estrace black box warning

ESTRACE® CREAM
(estradiol vaginal cream, USP, 0.01%)

Rx only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer*.**)

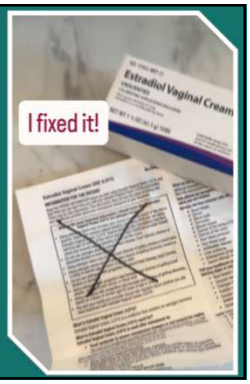
CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders**.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins have not been adequately studied for the above risks. In the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.



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ESTRADIOL 0.01% CREAM

Rx

MEDICATION: Estradiol 0.1 mg/gm (0.01%) Vaginal Cream

DOSE: 1 gm of 0.1 mg/gm (0.01%) cream

INSTRUCTIONS: Insert 1 gm vaginally nightly for 2 weeks and rub in. Use 1 gm twice weekly thereafter.

DISPENSE: 42.5 gm (1 tube)

DAYS SUPPLY: 90 days

Brand is Estrace vaginal cream (NOT the same as Estrace estradiol tablets)
- Generic available

Rub in to decrease mess.

Applicator is reused.

Cash pricing:
- GoodRx coupon: $30/tube ($10/mo)
- Cost Plus Drugs: $13/tube ($4/mo)

Rachel Rubin, MD
Urologist & Sexual Medicine Specialist

Rachel Rubin, MD, PLLC

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HORMONAL INTERVENTIONS

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9. Clinicians should offer the option of vaginal dehydroepiandrosterone (DHEA) to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Moderate Recommendation; Evidence Level: Grade C)*

10. Clinicians may offer the option of ospemifene to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Conditional Recommendation; Evidence Level: Grade C)*

11. In patients with GSM who are on systemic estrogen therapy, clinicians should offer the option of local low-dose vaginal estrogen or vaginal dehydroepiandrosterone (DHEA). *(Expert Opinion)*

12. In patients with GSM and comorbid genitourinary conditions (e.g., overactive bladder), clinicians may offer the option of local low-dose vaginal estrogen to improve genitourinary symptoms. *(Expert Opinion)*

13. In patients with GSM and recurrent urinary tract infections, clinicians should recommend local low-dose vaginal estrogen to reduce the risk for future urinary tract infections. *(Moderate Recommendation; Evidence Level: Grade B)*

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TABLE 3: GSM symptoms and signs[1]

Symptoms	Signs
Genital dryness	Decreased moisture, loss of vaginal rugae, vaginal pallor/erythema
Decreased lubrication with sexual activity	Decreased elasticity, decreased moisture, introital retraction
Discomfort or pain with sexual activity	Decreased moisture/introital stenosis, loss of hymenal remnants
Discomfort with tight clothing/exercising	Vulvar erythema, vaginal pallor/erythema, introital retraction
Post-coital bleeding	Tissue fragility/fissures/petechiae
Irritation/burning/itching of vulva or vagina	Vaginal fissures/petechiae/erythema
Dysuria	Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections
Urinary frequency/urgency/nocturia	Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections
Decreased arousal, orgasm, desire	

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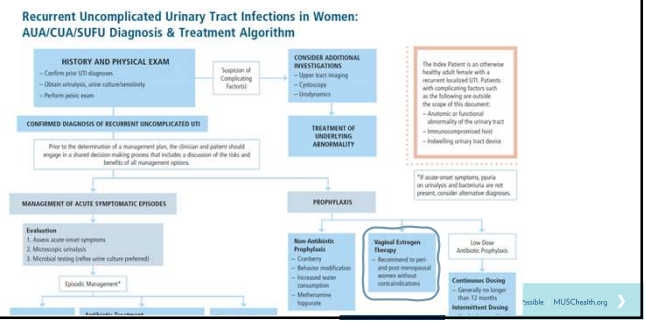
Overlap with many other guidelines



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NON-HORMONAL INTERVENTIONS

14. Clinicians should recommend the use of vaginal moisturizers and/or lubricants, either alone or in combination with other therapies, to improve vaginal dryness and/or dyspareunia in patients with GSM. *(Moderate Recommendation; Evidence Level: Grade C)*

15. Clinicians should counsel patients that the evidence does not support the use of alternative supplements in the treatment of GSM. *(Expert Opinion)*

16. Clinicians should counsel patients to avoid vulvovaginal irritants and/or cleansers which may exacerbate the signs and symptoms of GSM. *(Expert Opinion)*

ENERGY-BASED INTERVENTIONS

17. Clinicians should counsel patients that the evidence does not support the use of CO_2 laser, ER:YAG laser, or radiofrequency in the treatment of GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, quality of life, change in bothersome symptoms, satisfaction with treatment, or dyspareunia. *(Moderate Recommendation, Evidence Level: Grade C)*

18. In the context of shared decision-making, and with the disclosure that these therapies are considered experimental outside of clinical trials, clinicians may consider CO_2 laser treatment in patients who are not candidates for, or prefer alternatives to, FDA-approved treatments for GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, and/or dyspareunia. *(Expert Opinion)*

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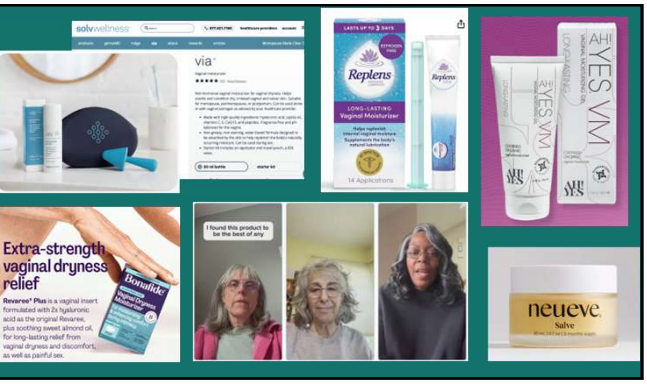

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- **Alma Lasers** (FemiLift)
- **BTL Industries** (Exilis/Ultra Femme 360)
- **Cynosure** (DEKA SmartXide2/MonaLisa Touch)
- **InMode** (FormaV and FractoraV)
- **Sciton** (JOULE Multi-Platform System/DiVa Laser Vaginal Therapy)
- **Thermigen** (THERMIva)
- **Venus Concept, Ltd.** (Venus Fiore System)

- **Safety Concerns:** The FDA has received numerous reports of adverse events associated with the unapproved use of these devices, including:
  - Vaginal burns
  - Scarring
  - Chronic, recurring, or long-term pain
  - Pain during sexual intercourse (dyspareunia)

ENERGY-BASED INTERVENTIONS

17. Clinicians should counsel patients that the evidence does not support the use of CO_2 laser, ER:YAG laser, or radiofrequency in the treatment of GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, quality of life, change in bothersome symptoms, satisfaction with treatment, or dyspareunia. *(Moderate Recommendation, Evidence Level: Grade C)*

18. In the context of shared decision-making, and with the disclosure that these therapies are considered experimental outside of clinical trials, clinicians may consider CO_2 laser treatment in patients who are not candidates for, or prefer alternatives to, FDA-approved treatments for GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, and/or dyspareunia. *(Expert Opinion)*

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BREAST AND ENDOMETRIAL CANCER

19. Clinicians should inform patients of the absence of evidence linking local low-dose vaginal estrogen to the development of breast cancer. *(Expert Opinion)*

20. For patients with GSM who have a personal history of breast cancer, clinicians may recommend local low-dose vaginal estrogen in the context of multi-disciplinary shared decision-making. *(Expert Opinion)*

21. Clinicians should counsel patients with GSM that neither vaginal dehydroepiandrosterone (DHEA) nor ospemifene increase the risk for breast cancer. *(Expert Opinion)*

22. Clinicians should counsel patients with GSM that local low-dose vaginal estrogen, does not increase the risk for endometrial hyperplasia with atypia or endometrial cancer. *(Moderate Recommendation; Evidence Level: Grade C)*

23. Clinicians should counsel patients with GSM that neither vaginal dehydroepiandrosterone (DHEA) nor ospemifene increase the risk for endometrial hyperplasia with atypia or endometrial cancer. *(Moderate Recommendation; Evidence Level: Grade C)*

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JAMA Oncology | Brief Report

Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer

Lauren McVicker, PhD; Alexander M. Labeit, PhD; Carol A. C. Coupland, PhD; Blánaid Hicks, PhD; Carmel Hughes, PhD; Una McMenamin, PhD; Stuart A. McIntosh, PhD; Peter Murchie, MD; Chris R. Cardwell, PhD

- >49,000 women with breast cancer
- 5% used vaginal estrogen after diagnosis
- no evidence of increased breast cancer-specific mortality
- small decrease in mortality with vaginal estrogen
- reassurance regarding safety of treatment

JAMA Oncol. 2024;10(1):103-108. doi:10.1001/jamaoncol.2023.4508
Published online November 2, 2023.

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ENDOMETRIAL SURVEILLANCE

24. Clinicians should not perform endometrial surveillance in patients with GSM solely due to their use of local low-dose vaginal estrogen, vaginal dehydroepiandrosterone (DHEA), or ospemifene. *(Expert Opinion)*

FOLLOW-UP

25. After initiation of treatment, clinicians should reassess patients with GSM to monitor response. *(Clinical Principle)*

26. Clinicians should counsel patients receiving therapy for GSM that long-term treatment and follow-up may be required to manage signs and symptoms. *(Clinical Principle)*

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Summary

HIGHLIGHTS

- Be suspicious & screen all post-menopausal women
- Examination… carefully!
- Shared-decision making
- Offer vaginal estrogen therapy often
- Part of multimodal care
  - OAB, rUTI, POP, (IC)
- Okay with systemic therapy
- Plan until “death do she part”…

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Summary

- Be suspicious & screen all post-menopausal women (some peri)
- Examination… carefully!
- Shared-decision making
- Offer vaginal estrogen therapy often
- Part of multimodal care
  - OAB, rUTI, POP, (IC)
- Okay/not always redundant with systemic therapy
- Plan until “death do she part”…

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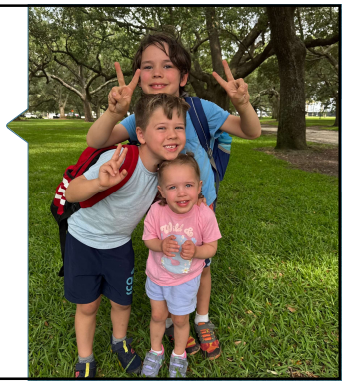
Questions?

Please help **EDUCATE** about vaginal estrogen



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email

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MUSC Health

Changing What's Possible MUSChealth.org

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