When a bladder infection is not an infection; What to do next

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we have all seen this patient...

- **55-year-old woman who reports that she was treated for another bladder infection at urgent care but she still has symptoms**
- often this is simply an issue related to antibiotic resistance and is a simple problem to take care of...
- but sometimes it is not that simple, so what is going on?

objectives for today

- I would like to review how to diagnose and treat a bladder infection with special emphasis on the pitfalls of this diagnosis and treatment of urinary tract infections
- I would like to discuss the problem of asymptomatic bacteriuria
- I will review the differential diagnosis involved in helping patients who think their symptoms are caused by a bladder infection but the culture is negative
- I will briefly review management of patients with recurrent bladder infections

Disclosures…

- Research supported by Uroshape, LLC (SoLa Pelvic Therapy®)
  - Unrelated
- Consultant for Axonics Inc (sacral neuromodulation device)
  - Unrelated

background

- most common bacterial infection in the world, infecting 150 million people each year-11 million office visits (3% of all visits) and 2-3 million ER visits each year in US
- more than 50% of all women will experience at least 1 UTI in their life and 20-30% we will experience a recurrent UTI within 4 months
- cost that exceeds $3.5 billion annually

*_Open Forum Infectious Diseases_, Volume 8, Issue Supplement_1, November 2021,

Diagnosis of UTI
AUA, IDSA, AGA Guidelines:

- UTI diagnosis should be based on clinical symptomatology of urinary symptoms to include dysuria in the absence of vaginal symptoms. Plus at least one other symptom: hematuria, urinary frequency, new incontinence associated with culture proven bacteriuria with a bacterial uropathogen

Pearls in the Diagnosis of a UTI

- clinical symptoms
  - dysuria with increase in urgency frequency and typically with odor
  - **but** clarify that dysuria represents burning and discomfort during urination typically located in the bladder or the urethra
  - **dysuria** is not burning discomfort before or after urination located externally around the vaginal opening or the labia-
- **External dysuria requires an exam and evaluation to rule out yeast infection, significant urogenital atrophy and is extremely common in patients with lichen sclerosus**

Diagnosis of UTI

- clean-catch, midstream urine sample is appropriate for most patients but not all
- chemical (dipstick) urinalysis
  - leukocyte esterase 63-90% specific but false positives with poor sample
  - nitrites very specific for gram-negative bacteriuria and if positive with symptoms consider treatment
  - if negative plus symptoms consider culture prior to AB therapy
- microscopic UA
  - if significant epithelial cells are present then poor sample provided
  - greater than equal to 10 WBC's per HPF is considered significant

Pitfalls to avoid when obtaining a urine culture

- Ask about voiding dysfunction if present the MS CC sample will be questionable
- never allow a sample to be at room temperature for more than 30 minutes unless in a special transport media tube
- a sample collected at home and brought to the office will be suspect with a high false positive
- never collect a sample using a “toilet hat”
- a catheterized urine sample will always be better and cut-off should be lowered to 10^2
- if a positive culture is found you must always consider if the symptoms you are treating are truly caused by a urinary tract infection

urine cultures

- the gold standard UTI dx includes new onset dysuria with frequency, urgency, odor **and a positive culture** but new data is challenging this "gold standard"
- 10^5 CFU/Ml has been the arbitrary cut-off for >60yrs and the agar and growth techniques are unchanged since the 19th century and when compared to enhanced techniques 3x the number of uropathogens are found
- standard urine culture technique commonly misses polymicrobial infection and significant infection by organisms not cultured by standard techniques*
- Urine is not sterile and when enhanced quantitative techniques are used we see a whole new microbial community that is not yet fully understood in healthy and diseased urinary tracts

*Price,et al, The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. J Clin Microbiol. 2016 May;54(5):1216-22

But here is what we do know…

Key Points about Female Urinary Microbiota

Mueller ER, Wolfe AJ, Brubaker L. Female urinary microbiota. Curr Opin Urol. 2017 May;27(3):282-286

1. Standard urine culture does not detect most members of the existing female urinary microbiota (FUM), including many uropathogens.

2. Microbial detection using **enhanced urine culture** techniques correlates with **DNA sequencing**, a culture-independent method.

3. Similar to other human microbial niches, there is no one "normal" state, but rather variable between individuals.

4. Characteristics of the FUM, such as microbial diversity and predominance, vary based on hormonal status, body mass index and certain clinical conditions, especially urinary urgency incontinence.

5. Differences exist in the FUM of women with urinary urgency incontinence compared to unaffected women.

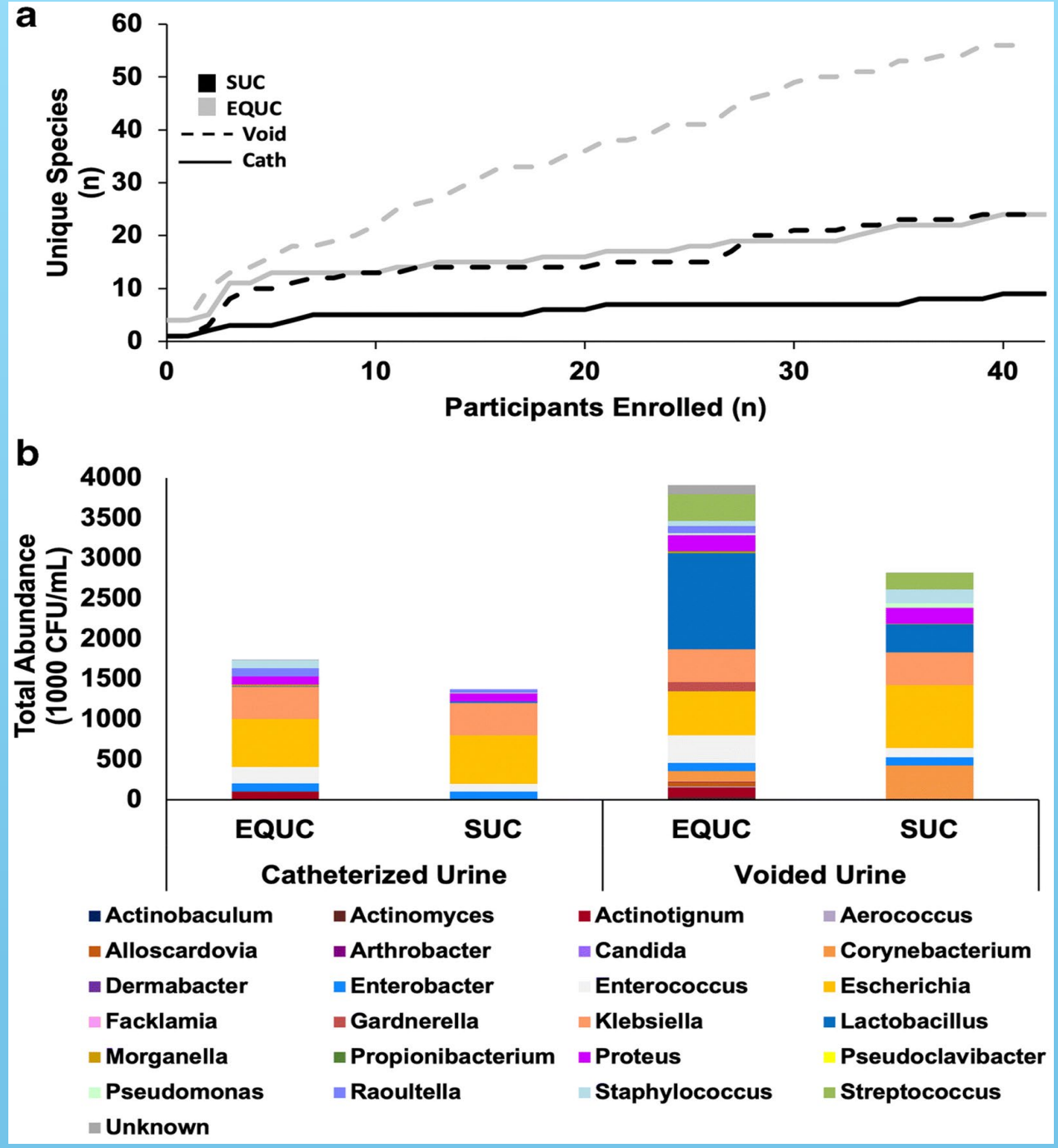
enhanced urine culture techniques versus standard urine culture

the potential to over diagnosis of symptomatic UTIs must always be considered

antibiotic sensitivity testing should be a part of this advanced evaluation.

Enhanced quantitative techniques are ideally suited for patients with negative cultures yet UTI symptoms and the presence of WBCs / leukocyte esterace

abnormal microbiome associated with various urologic disorders such as overactive bladder and some forms of IC /BPS



Bottom line…

- Urine is never “sterile”
- “Normal flora” in the urine changes with multiple factors
- If standard cultures are negative and pyuria or nitrites are present there still might be a true uropathogen in the urine (false negative)
  - Diff DX: HIV, Stone disease, Lupus, DM, Kawasaki disease
- Enhanced quantitative urine cultures collected by cath sample in selected patients will be helpful **in the future**
  - **Especially in patients with rUTI’s, IC/BPS and OAB syndromes**

Treatment of Uncomplicated UTIs

- 3 day therapy associated with fewer side-affects but higher failure
- 5 to 7 day therapy typically best
- Full 7 days best for pts w/ DM, >65 yrs old, hx of pyelonephritis or symptoms for >3 days prior to starting ABs
- Prolonged therapy (10 to 14 days) should be avoided

Remember, complicated UTI's include:

UTI in men, pregnancy, pts with abnormal GU anatomy or function (prolapse, obstruction, stone disease) neurogenic bladder dysfunction, immunosuppressed

Antibiotic Treatment Options

- Nitrofurantoin / Macrobid 88-93% cure
- TMP-SMX 90-100% cure
- Fosfomycin- Single 3 gram dose 83-91% cure

Fluroquinalones should be avoided for empiric therapy of uncomplicated UTIs **2016 FDA advisory and black box warning**

WARNING

Fluoroquinolones, including FLOXIN® (ofloxacin) , are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

Fluoroquinolones, including FLOXIN® (ofloxacin) , may exacerbate muscle weakness in persons with myasthenia gravis. Avoid FLOXIN® (ofloxacin) in patients with a known history of myasthenia gravis

What is a Black Box Warning?
-Black Box warning is the strictest warning put in the labeling of prescription drugs by the FDA

antibiotic overprescription for UTIs

neurourology and urodynamics 2024, Murrary et al

- 909 patients diagnosed with a UTI, 85% were female
- 64% were treated with antibiotics despite only 28% having symptoms of a UTI, 40% had positive UA or culture
- in patients with no urinary tract symptoms 95% were given antibiotics based upon the urinalysis in ER setting
- patient's presenting with mental status change are more likely to be diagnosed with a UTI even though data does not support the relationship between mental status changes and bacteriuria
- AGS and IDSA recommend against testing patients with mental status changes and no urinary tract symptoms, despite these recommendations 100% of patients in this study received antibiotics yet only 7% had urinary tract symptoms

UTIs and acute mental status change

- 2019 update by the infectious diseases Society of America

- a causal relationship between asymptomatic bacteriuria and delirium (acute mental status change with fluctuating level of confusion and orientation) has not been established.
- treatment of ABU in patients with episodes of delirium has not shown to have any beneficial effect on clinical outcomes compared to no treatment.

In patients diagnosed to have urosepsis based upon hospitalization with positive blood cultures and the presence of a urinary tract infection as the only source for that bacteria I will initiate non-antibiotic based suppressive therapy (EVC, Ellura, D-mannose, Methenamine Hippurate)

What happens when we treat asymptomatic UTIs in patients with mental status change admitted to the hospital?

- 92 of 365 pts with new onset delirium treated with antibiotics with no symptoms of a UTI but positive laboratory tests*
- worse functional recovery versus those not treated; RR 1.3
- 7.5% developed C. difficile

Stall et al 2024, J of American Geriatric Society; … a Systematic Review

Our systematic review found no evidence that treatment with antibiotics is associated with improved delirium outcomes in older adults with pyuria or bacteriuria and without systemic signs of infection or genitourinary symptoms.

BUT remember symptoms of a UTI in the elderly can be more subtle and history difficult to obtain:

-increased frequency, urgency and worse incontinence

-expect to see >10 WBC's on cath UA

* Dasgupta et al, Arch Gerento. Gari; 2017

how to interpret a positive urine culture

- **Does the patient has urologic symptoms? And was the UA positive?**
- is the organism a uropathogen?
  - E coli, Klebsiella, Enterobacter, Proteus, Citrobacter
  - Pseudomonas a., Enterococcus, Staph saprophyticus
  - Staph aureus, Streptococcus A (group B)
  - Candida
- If the patient has a positive culture and no UTI-like symptoms- especially if she has <10 WBC / neg leukocyte esterase- then she has **asymptomatic bacteriuria and should not be treated**

Prevalence of Asymptomatic Bacteriuria

- healthy premenopausal women: 1 to 5%
- healthy postmenopausal women: 2.8 to 8.6%
- women with diabetes mellitus: 10.8 to 16%
- women in long-term care facilities: 25 to 50%
- neurogenic bladder with intermittent catheter use: 23 to 69%
- patients with chronic indwelling catheter: 100%
  - Short term use: increase prevalence 4% per day the catheter is present

Do not screen asymptomatic patients with urine cultures

Treatment ASB causes harm: Antibiotic side effects, antibiotic resistance and opportunistic infections

but what about the patient with urinary tract symptoms and a **negative urine culture**

what are the possibilities and what do we do next?

because of persistent symptoms the next step is an office visit to establish a differential diagnosis

- carefully reevaluate the history
  - do they have urinary tract symptoms or not
  - do they have odor to the urine and is it cloudy, then recheck a culture (enhanced?)
  - if they have dysuria (and this is a classic symptom of a UTI) then clarify the characteristics (*where is the burning coming from?*)
- recheck a urine sample-ideally a catheterized sample
- if symptoms have been triggered after a new sexual partner then consider evaluation for Mycoplasma and Ureaplasma as well as other STDs
  - these organisms live in the vagina and intermittently will populate the urinary tract, are not able to be identified on the routine urine culture but a DNA probe of the vaginal secretions in the posterior fornix should be obtained in high risk patients
  - in the past this was felt to be a benign organism but we now realize significant symptoms and complications arise from this organism even though approximately 20% of sexually active women will be found to have this organism without symptoms

if dysuria is the chief complaint obtain a more detailed history

- where is the dysuria?
  - **External** burning especially when occurring after urination is almost always a vulvar pain disorder
    - Lichen sclerosus
    - Vulvovaginal yeast
    - Postmenopausal genitourinary syndrome
    - Vulvodynia

Lichen Sclerosus Therapy

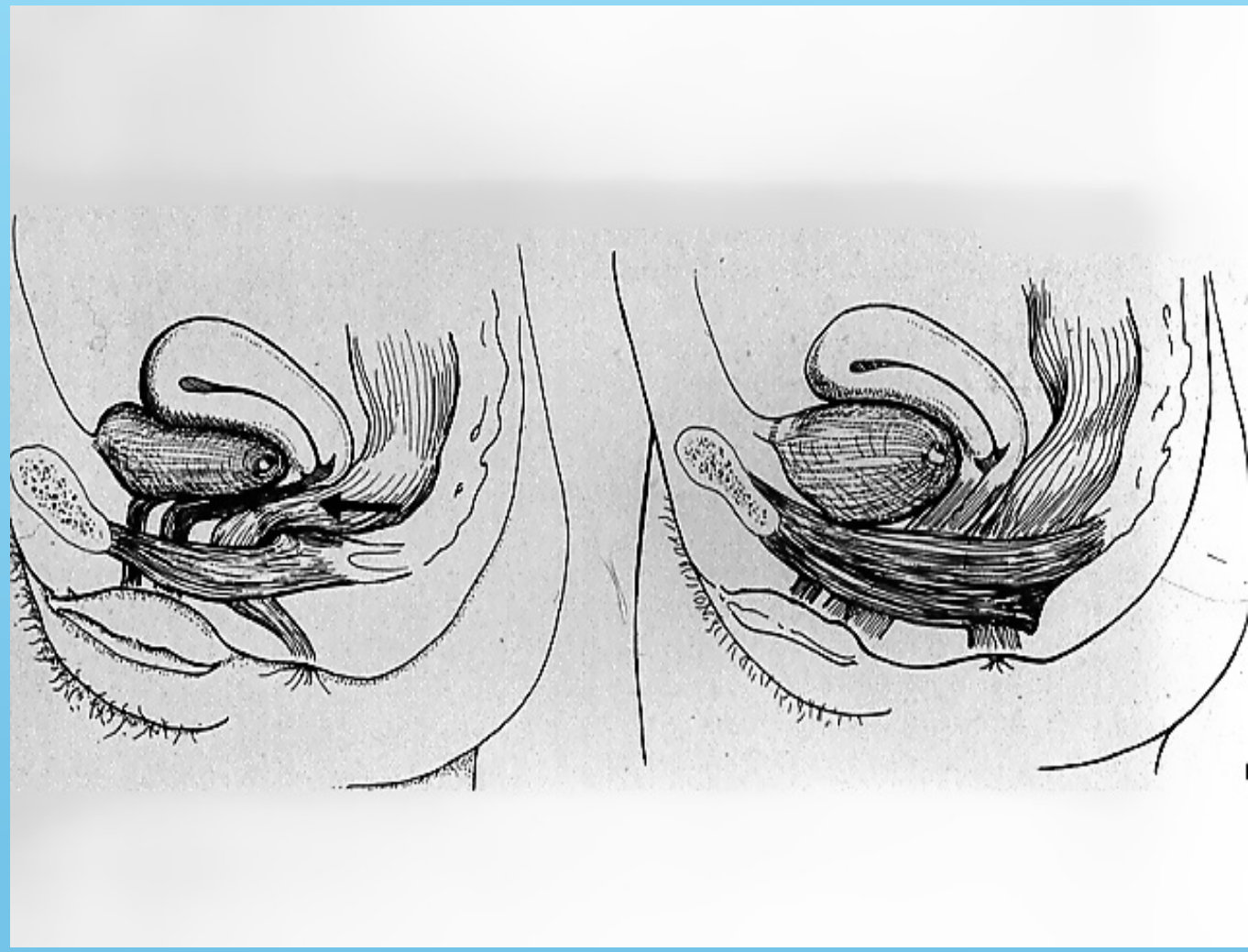
- Topical High potency steroids
  - Clobetasol .05%, BID x 4 weeks then Q HS x4 wks
  - Triamcinolone 0.1% ointment
  - Must then re-evaluate and determine maintaince dose of low dose or combo therapy (clobetasol 2x / week & hydrocortisone 5 x/ week
  - Avoid steroid dermatitis (rare)
- Asymptomatic patients (40%) need therapy to avoid scarring, agglutination and vulvar cancer (2-6% risk)

If Dysuria is reported; where is it coming from?

- symptom “mapping” during a pelvic exam will often help clarify the location of dysuria. If you obtain a catheterized urine sample then, during this procedure, ask if while passing the catheter “is this the location of the burning?”
- Continuous Urethral Burning
- burning prior to voiding or pain after voiding that is located in the urethra or the bladder (“higher up”) are both classic findings of urethral syndrome: a pain disorder caused by hypertonic pelvic floor muscles

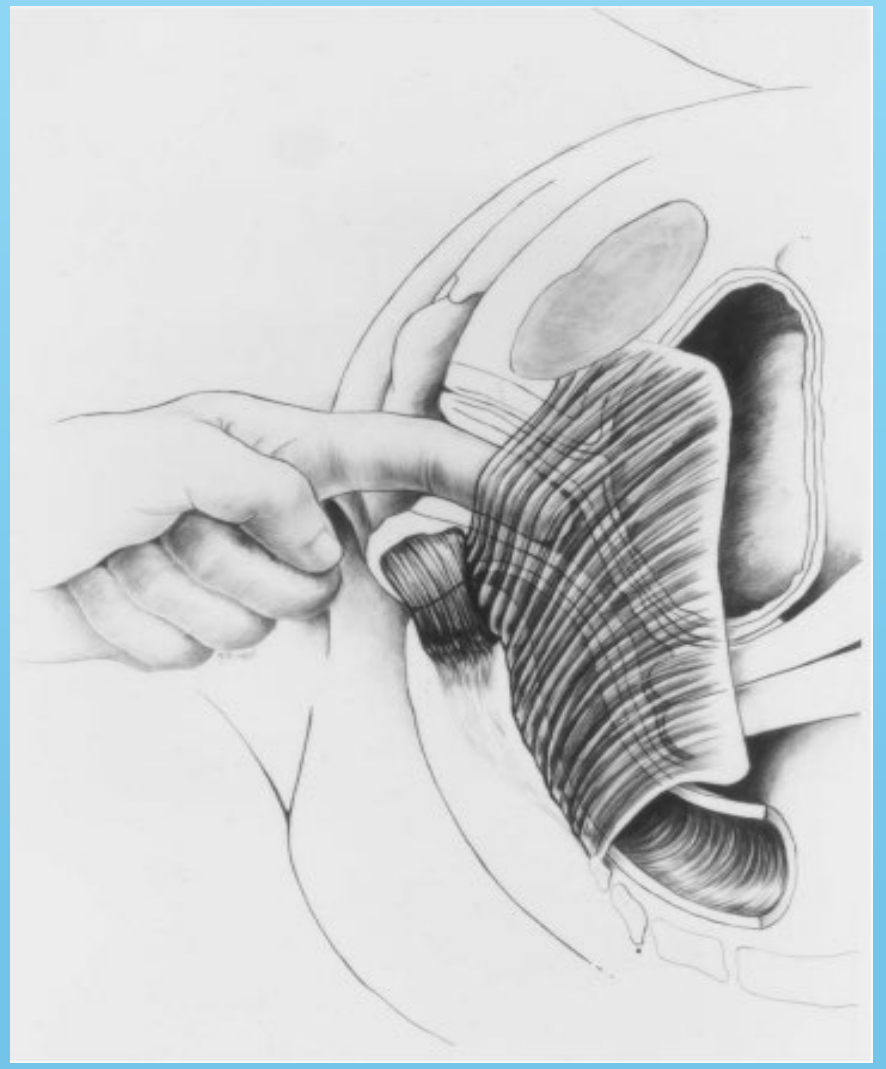
hypertonic pelvic floor muscle dysfunction

- in the past this was thought to be very unusual but now multiple articles demonstrate a prevalence of 25% in the general population and up to 85% in patients with various bladder problems including incontinence, voiding dysfunction, overactive bladder, interstitial cystitis, recurrent bladder infections and prolapse.
- any patient with a chronic pain disorder have a high likelihood of hypertonic pelvic floor dysfunction
- **classic symptoms** include urinary frequency, pressure or achy discomfort often associated with urinary hesitancy, obstructed defecation and dyspareunia (esp pain after sex)



Pelvic examination with Single digit

- Visualize PF awareness
  - Squeeze and relax, stay relaxed?
- Palpation of levator muscles
  - Tenderness that reproduces pain
  - Trigger points
  - Taut bands of fibromuscular tissue
- Obturator muscle tenderness
  - May reproduce “ovarian pain”
- “Other pain”
  - Hip, groin, SIJ Pain
  - Pain with sitting
  - Sudden stabbing pain
  - Constant urge to void (pressure)



The Evolution of IC…

A Bladder disorder that is rare and

DX is based on cystoscopy

VS

A common pain disorder that is a symptom-based diagnosis, that involves at least 2 phenotypes.

The most common involves dysregulation of sensory processing with both

peripheral sensitization and central sensitization called BPS and a distinct bladder disorder with inflammatory bladder lesions (Hunner lesions) called IC

Rand IC Epidemiology Study

Berry et al J Urol 2010; 183:1848

**Suprapubic pain related to bladder filling,
accompanied by
other symptoms such as frequency in the absence of
infection or other pathology. "Pain" is to be broadened to
include "pressure" and "discomfort".**

- **2.7% to 6.53% of all US females (3.3 to 7.9 million women>18 yo)**

Confusable Disorders*

Infection : UTI, mycoplasma, ureaplasma, candidiasis, HSV
Bladder Cancer / CIS
Radiation injury
Cyclophosphamide
Stone Disease
Urethral diverticulum
Bladder neck obstruction (anatomic and functional)
Retention
Bladder endometriosis

Overlap with treatment resistant OAB

*Whitmore Intern J Urol 2019

the key is phenotyping all patients with chronic pain, esp IC/BPS

- pelvic floor dysfunction is the most common type (85% with at least a component of PFD and / or pain)
  - high-tone dysfunction results then voiding dysfunction and voiding dysfunction up regulate c-fibers causing bladder allodynia
  - primary pelvic floor dysfunction typically starts with pelvic floor symptoms in childhood
  - secondary pelvic floor dysfunction starts after an insult to the pelvic floor such as surgery or trauma **OR** is secondary to other pain disorders

- Other types include infectious with cycles of culture positive and culture negative episodes
- Part of a diffuse centralized pain disorder
- Autoimmune disorders often associated with ulcerative type of IC

Phenotyping IC/BPS

Clinical DX
IC/BPS

Hunner Lesion +
IC

These patients have a unique bladder disorder and often develop secondary centralized pain with other pain generators

25%*
Hunner Lesion Neg
BPS
Bladder Centric
Assoc w/ reduced bladder volume w GA

75%* w 1/3 >3 sites (Widespread P)
Women > Men
Hunner lesion Neg
BPS
Beyond Bladder

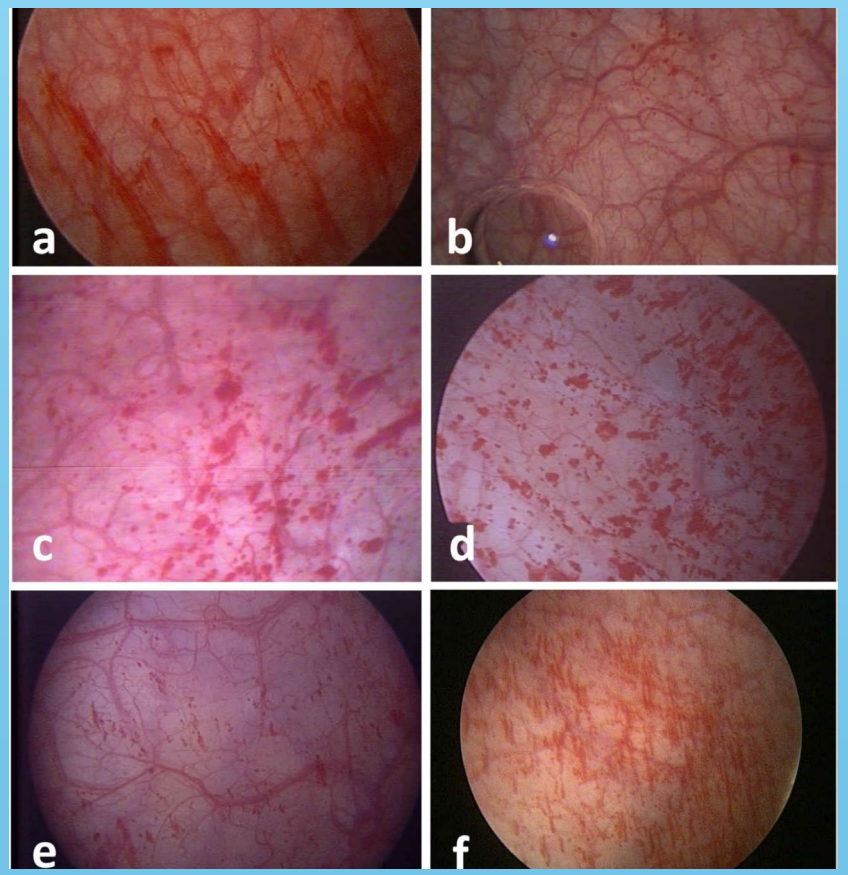
These patients had an event and /or a predisposition for the development of a centralized pain disorder with bladder related symptoms. The management of their symptoms requires the treatment of their BPS and all other pain generators: local vs diffuse pain

* H Lai, et al: J of Urol; 2017

Phenotyping allows a better understanding and targeted therapy

IC/PBS in 2025

- we now understand why patients have interstitial cystitis/bladder pain syndrome
- There are many different types of this pain disorder and phenotyping is the key to targeted therapies
- individualizing therapy based upon the phenotype provides marked improvement or resolution of symptoms in greater than 50% of patients
- the key is identifying every pain generator and treating each one-not just the bladder!
- advanced therapies include: pelvic floor physical therapy, sacral neuromodulation, intra-detrusor Botox® injections, transvaginal photobiomodulation (SoLa® Tx)



The Role of Cystoscopy?

- It is **not** used to r/out or r/in IC/BPS*
  - Glomerulations w/ HD should be noted but not used for diagnostic or therapeutic decision-making# and because of high prevalence of false negatives and false positives
- Office cystoscopy is part of a work-up for hematuria in high-risk patients (>50, >15 RBC's / HPF, >20 pack-yr hx smoker), remember to eval upper tracts also
- Office cystoscopy should be used to r/out confusable disorders and to determine if Hunner lesions are present if symptoms do not improve with initial therapy
- Cystoscopy with HD under GA /Regional may be therapeutic
  - **But benefit is short lived^**
    - 2-3 month: 18-56% benefit
    - 5-6 months 0-7% benefit
  - **Flare in 10% i.e. worse after HD**
- Treat Hunner lesion if found, BX to verify and r/out CIS

*Erickson, J of Urol: 2005 ^ AUA guidelines IC # Akiyama, Hanno et al Urology 2021

recurrent urinary tract infections

- definition: 3 culture positive episodes in 12 months or 2 in 6 months (remember, 20% of patients will develop a recurrent urinary tract infection after initial therapy but this is considered the same episode)
- the most common etiology is voiding dysfunction (a slow stream, urinary hesitancy, intermittent flow are classic symptoms, voiding dysfunction can certainly be identified with a normal postvoid residual). This is identified in at least 42% of all patients with rUTIs
- simple pelvic exam indicated to rule out extrinsic causes for voiding dysfunction such as prolapse

do not treat asymptomatic bacteriuria

- many patients sent for evaluation report repeated urine cultures that are positive but she has no symptoms of a urinary tract infection or symptoms are unrelated to an UTI.
- do not do urine cultures simply as a “test of cure”
- as noted earlier mental status changes are rarely caused by a urinary tract infection unless sepsis with positive blood cultures caused by the same organism as is found in the urine

Pearls rUTI's*

- Wiping in the wrong direction is not a cause
- Increasing fluids prevents (only helps if drinking less than 1.5 liters/day)
- Hot tubs use does not cause
- Tampon use does not cause
- Not using Pre and post-coital voiding habits not a trigger
- Douching not a trigger
- Probiotics might help prevent rUTIs#

*Scholes DM, Hooton TM, Roberts RL et al: Risk factors for recurrent urinary tract infection in young women. J Infec Dis 2000; **182**: 1177.

#Turk J Urol. 2018 Sep 1;44(5):377–383

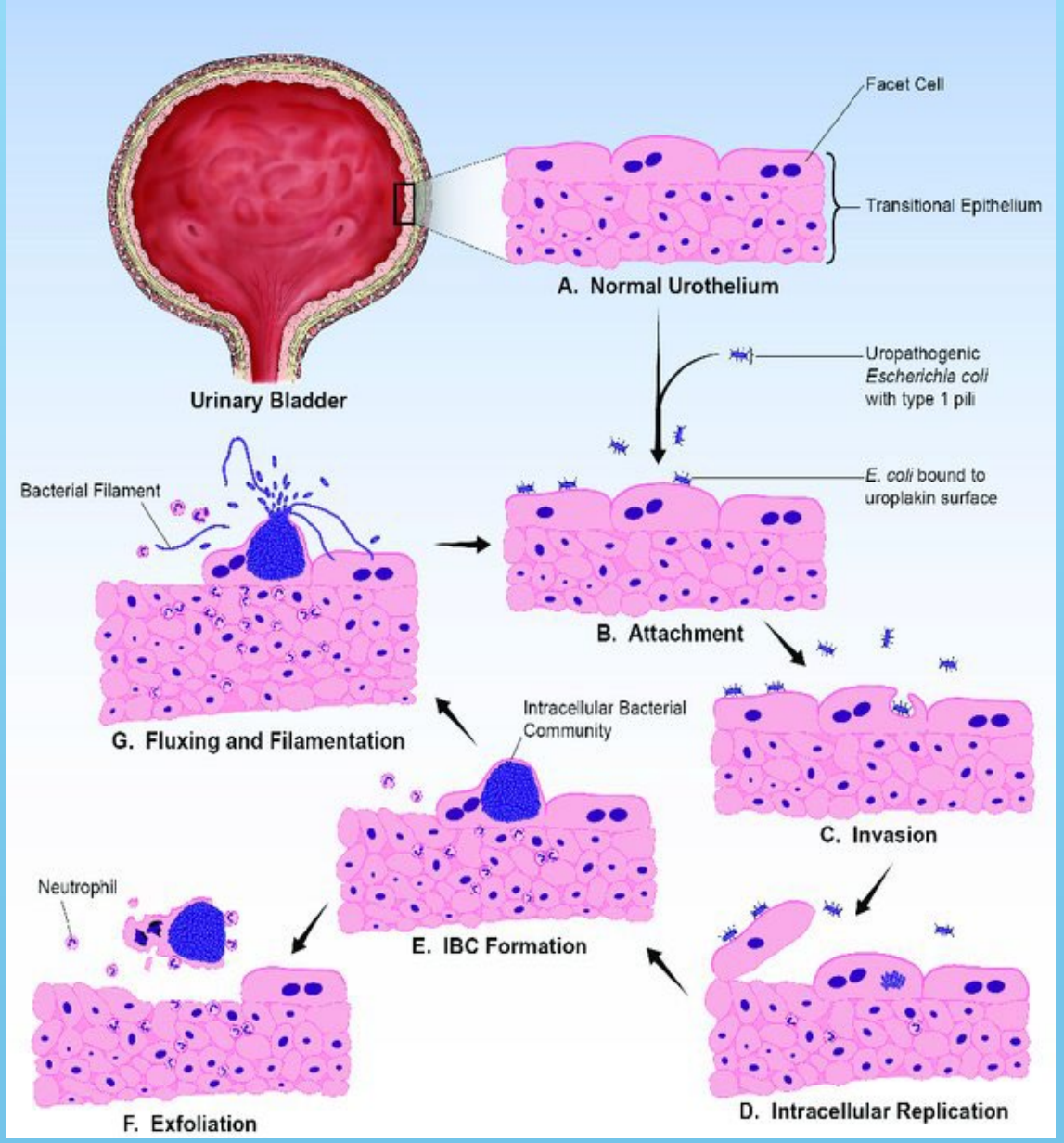
management options for rUTIs

- high-dose cranberry pill supplements such as Ellura® or Utivia®
  - $90,000,000 spent in US in 2019 on cranberry supplements
  - Proanthocyanidins (PCA) responsible for anti adhesion of Pili of E. coli
  - Cochrane review in 2012: “no evidence to support or refute use” but dose of PACs not reported- most OTC contain very little
  - Ellura® shows better anti-adhesion than D-Mannose
  - Ellura® shows reduction in rUTI in select populations 36mg PAC
- Estrogen Vaginal cream (not systemic) to correct vaginal pH and vaginal flora
- D-mannose
  - Cochrane review in 2022: “no evidence to support or refute use”
- Methenamine Hippurate (1G every 12 hours):
  - almost as good as AB suppression (.9 vs 1.4 UTI per women-year) Non-inferior to AB suppression*
  - 44% of women had no episodes of symptomatic UTIs during this 12 month study
  - Adverse event rate similar (2.8% vs 2.4%; AB vs MH)
- If UTI related to coitus then post-coital AB suppression
- 6 to 12 months of suppressive antibiotics if not coital related but associated with development of resistant organisms
  - Macrobid Q HS
  - Septra DS Qhs
  - Keflex 250 Q HS

* Harding BMJ 2022;376

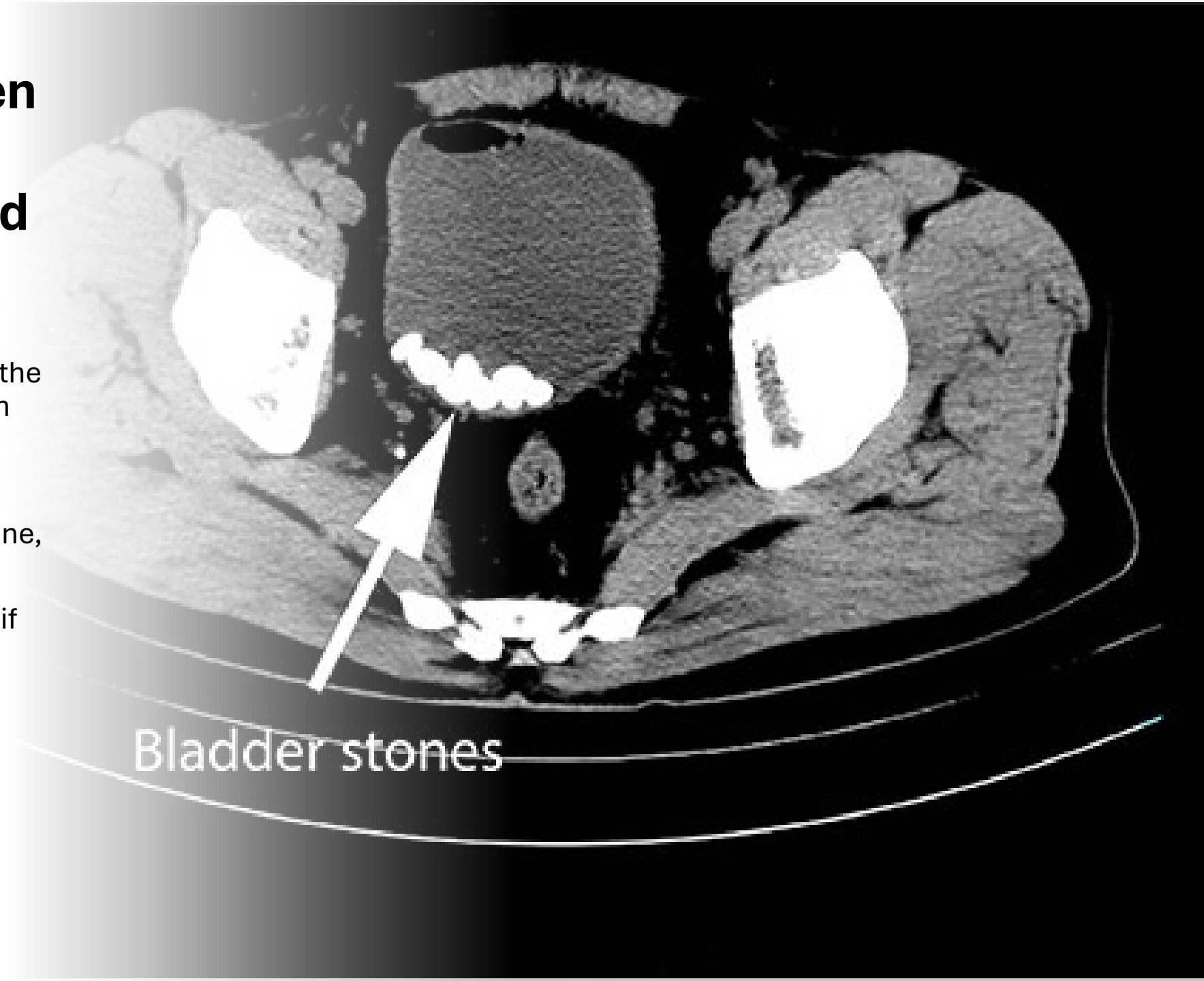
Pathology of rUTIs

- Risk factors for UTI's
- Development of clusters of bacteria in the submucosa of the bladder, exfoliation for **up to 6 months**
- Development of abnormal immunologic environment
- Neuropathic changes causing sensory nerve activation
- These changes result in an increasing risk for continued rUTI's and BPS/IC pain syndromes



if rUTIs continue then referral for further evaluation is indicated

- urodynamics
  - Evaluate, Identify and treat the voiding dysfunction found in 47% of pts
- office cystoscopy
  - Rule out bladder lesion, stone, foreign body, fistula, etc
- CT urogram or renal sonogram (if low risk for upper tract disease)
  - Low rate of identifying unexpected lesion



Vaccine for rUTI’s

- Uromune® and MV140 approved in other counties (26) with special access programs (under review in Canada with MV140), FDA will require other studies for approval
- Inactivated uropathogens to boost patient’s immune system:
  - Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris and Enterococcus Faecalis
- UTI-free rates reported to be 35% to 90%
- Uromune original 9 year study showed excellent results with 50% having no infections in 9 years
- Still a few years away for us in USA

So we now have a better idea about the differential diagnosis as well as the pitfalls in diagnosing a bladder infection…

obtain an accurate history looking for dysuria, increase in urinary frequency and malodorous urine

obtain a urine sample appropriately and perform at least a dipstick and a culture

if history and UA is compatible with a UTI then initiate therapy now

Macrobid or Bactrim or Monurol

if symptoms present for more than 3 days then a 7-day treatment is preferred

avoid quinolones for empiric therapy*

*** Black Box Warning**

if symptoms are persistent and urine culture is negative then
review the symptoms and examine the patient to consider other causes for those symptoms.
Consider an enhanced urine culture if + Leuk

treat the new symptom generator if one is identified & consider bladder analgesics such as Pyridium as a diagnostic as well as therapeutic step

if symptom improvement is noted with bladder analgesic than the **bladder** represents a significant component of her pain but if no / little improvement then patient education and **management of other symptom generators**

In Summary…

- Most of the time a UTI is easy to diagnosis and treat…
- But not always…
  - Think about the symptoms and **are they really related to the findings on the UA and culture**
  - Remember to consider other symptom generators
  - Educate patients about asymptomatic “UTIs” ie ASB
- Many different problems can mimic a UTI so be aware of the differential for symptoms like dysuria, frequent urination and pelvic pain

Thank you for your time and your attention