Dysuria and Bladder Spasms in the Palliative Care population

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UVA health
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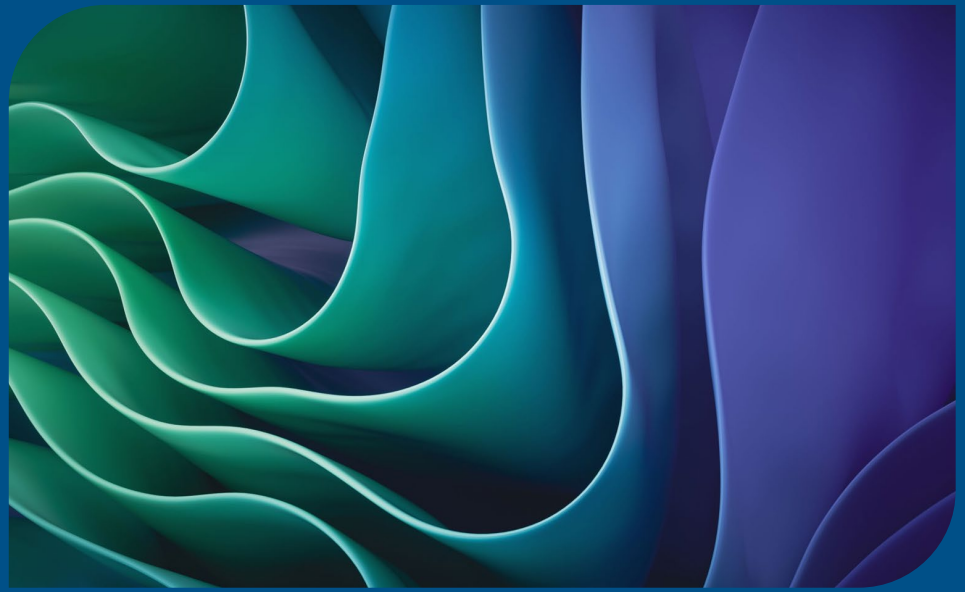

OBJECTIVES

1. **Identify common causes of dysuria and bladder spasms in the palliative care population**

2. **Describe how the cause effects treatment and identify best treatment depending on the etiology**

3. **Explore medications, procedures and treatments used to palliate dysuria. Discuss the risks and side effects for each**

Starting with a case…

- A 77 year old man with high-grade urothelial bladder carcinoma invading the deep muscularis propria was admitted to the hospital on day 9 of palliative radiotherapy for intractable dysuria and suprapain pain
  - Notes a 3 month history of “bladder spasms” that have become progressively more severe with radiotherapy
  - He has tried multiple oral agents in an attempt to control his symptoms but they have had little to no effect

- The patient is admitted for pain control and you are the palliative care physician consulted to help the primary team

- What other history would you like to know?
- What is the primary cause of the patient’s dysuria?
- Are there any agents that you would consider?

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2. Describe how the cause effects treatment and identify best treatment depending on the etiology

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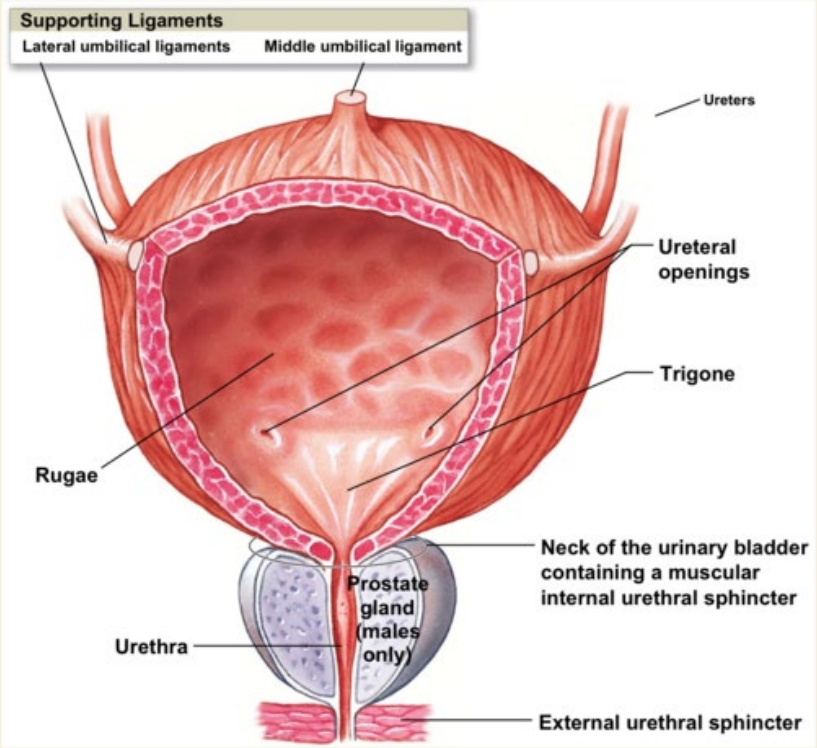
What is Dysuria?

- Burning, tingling, or stinging of the urethra and meatus associated with voiding
  - occurs when urine comes in contact with the inflamed or irritated urethral mucosal lining
  - This is exacerbated by and associated with detrusor muscle contractions and urethral peristalsis
  - stimulates the submucosal pain and sensory receptors, resulting in pain, itching, or a burning sensation during urination.

- Difficult to distinguish from suprapubic pain and discomfort
  - This is associated with high bladder volume which can help differentiate the two



Causes of Dysuria

- Many causes but in palliative care most common causes are
  - Infectious
    - UTI
    - Prostatitis
  - Obstructive
    - Constipation
    - Blood clots
  - Direct Irritation of the detrusor muscle
    - Radiation
    - Tumor
    - Blood
    - Catheter
  - Idiopathic
    - Interstitial cystitis

Table 2. Differential Diagnosis of Dysuria in Adults

Category	*Sex*	*Causes**
Inflammatory		
Dermatologic	Both	Irritant or contact dermatitis, lichen sclerosus, lichen planus, psoriasis, Stevens-Johnson syndrome, Behçet syndrome
Infectious	Both	Cystitis, urethritis, pyelonephritis, other sexually transmitted infections
	Women	Vulvovaginitis, cervicitis
	Men	Prostatitis, epididymo-orchitis
Noninfectious	Both	Foreign body (e.g., stent, stone), urethritis (e.g., reactive arthritis)
Noninflammatory		
Anatomic	Both	Urethral stricture or diverticulum
	Men	Benign prostatic hyperplasia
Drug- or food-related	Both	Spermacides, topical deodorants, cyclophosphamide, opioids, ketamine (Ketalar), nifedipine, and others; bladder-irritating foods
Endocrine	Women	Atrophic vaginitis, endometriosis
Idiopathic	Both	Interstitial cystitis/bladder pain syndrome
Neoplastic	Both	Bladder or renal cancer, lymphoma, metastatic cancer†
	Women	Vaginal or vulvar cancer, paraurethral leiomyoma
	Men	Prostate or penile cancer
Trauma/iatrogenic	Both	Genitourinary instrumentation or surgery, pelvic irradiation, foreign body presence, horseback or bicycle riding

**—Infectious causes, particularly acute cystitis, are the most common. There are few data to rank other diagnoses by prevalence; specific causes are listed by estimated prevalence.*

†—Some cancers (e.g., renal cell) present with dysuria primarily by causing hematuria, and others by bladder-wall irritation, which may be difficult to distinguish from true dysuria.

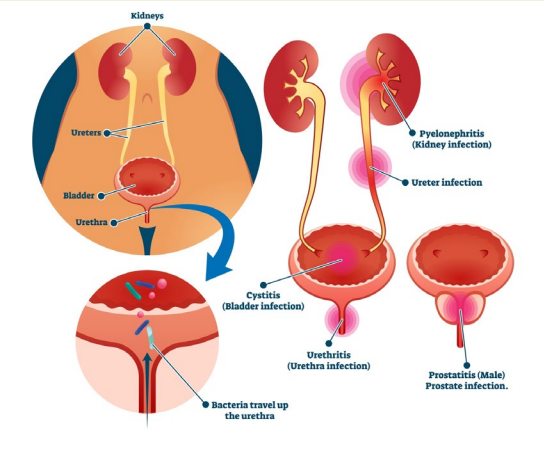
Information from references 2, 4, 8, and 11 through 19.

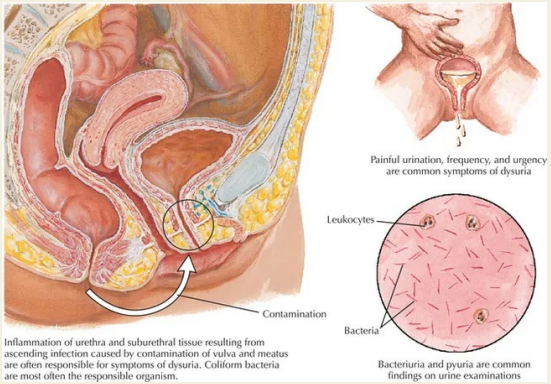
Am Fam Physician. 2015;92(9):778-788

Infectious

- Most common cause of dysuria in the general population
  - Responsible for nearly 7 million OP visits per year
- Underlying cause is inflammation caused by bacteria leading to detrusor muscle spasms

- Considerations:
  - Catheters
    - Approximately **74%** of hospice patients require a Foley catheter before death
    - Infection rate about 5% per day





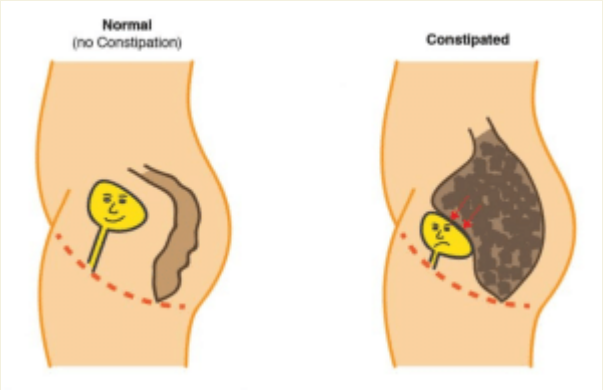
The Use of Urinary Catheters In Terminally Ill Cancer Patients.
Fainsinger RL, MacEachern T, Hanson J, Bruera E.

Journal of Pain and Symptom Management. 1992;7(6):333-8. doi:10.1016/0885-3924(92)90085-v.
Nicolle LE. Catheter-related urinary tract infection. Drugs Aging. 2005;22(8):627-39. doi: 10.2165/00002512-200522080-00001. PMID: 16060714.

Obstruction

- Usually associated with suprapubic pain and discomfort
  - However, this CAN lead to dysuria

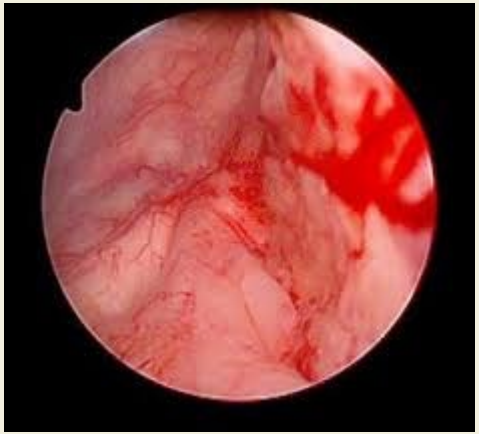
- High stool burden can cause irritation and inflammation of bladder from the outside
- Obstruction from blood clots in severe bleeding can also have a similar effect



Direct Irritation- Hemorrhagic cystitis

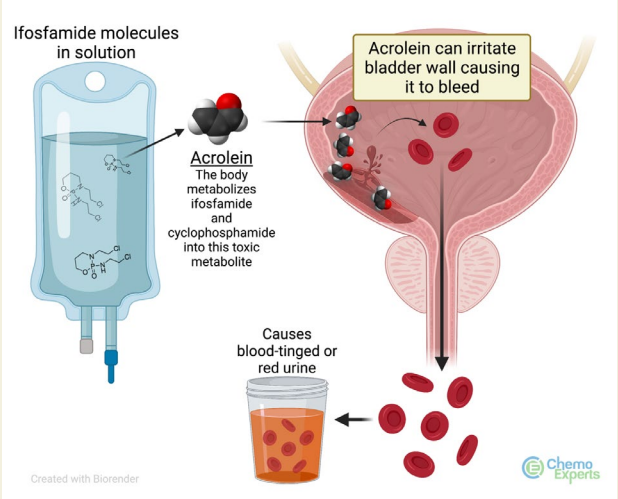
- What is hemorrhagic cystitis?
  - Diffuse inflammatory condition of the bladder that leads to bleeding of the mucosal lining

- Causes
  - Drug-induced
  - Radiation
  - Infection (usually in immunocompromised hosts)
    - BK virus
    - JC Virus
    - CMV
  - Other systemic conditions
    - Lupus
    - Amyloidosis



Direct Irritation- Hemorrhagic cystitis

- Most common cause in palliative care population is from ifosfamide and cyclophosphamide
  - Used in many chemotherapeutic regimens
    - Allogeneic Stem Cell Transplant
    - Lymphoma (RCHOP)



Drugs	Ifosfamide
	Cyclophosphamide
	Busulphan
	Thiotepa
	Temozolomide
	9-nitrocamptothecin
	Pencillin and its derivatives like methicillin, carbenicillin, ticarcillin, piperacillin
	Danazol
	Tiaprofenic acid
	Allopurinol
	Methaqualone
	Methenamine mandelate
	Gentian violet
	Acetic acid

Hemorrhagic cystitis: A challenge to the urologist - PMC

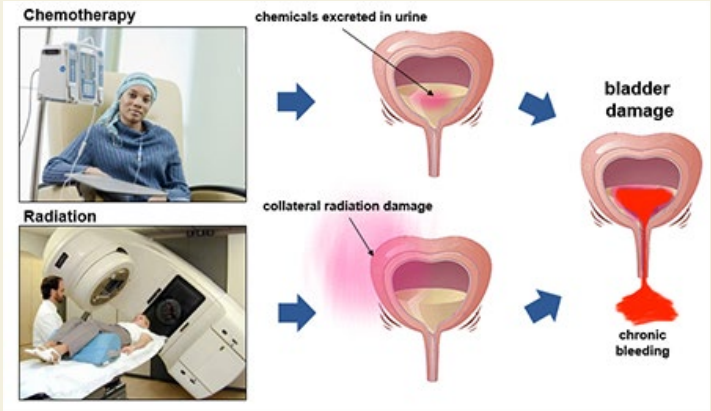
Direct Irritation- Radiation cystitis

- side effect of inflammation and subsequent destruction to the normal anatomy of the urinary bladder at the cellular level after the use of radiation by causing
  - urothelial edema
  - Perivascular fibrosis
  - Detrusor muscle ischemia

- Can be acute or delayed
  - 6 month cut off

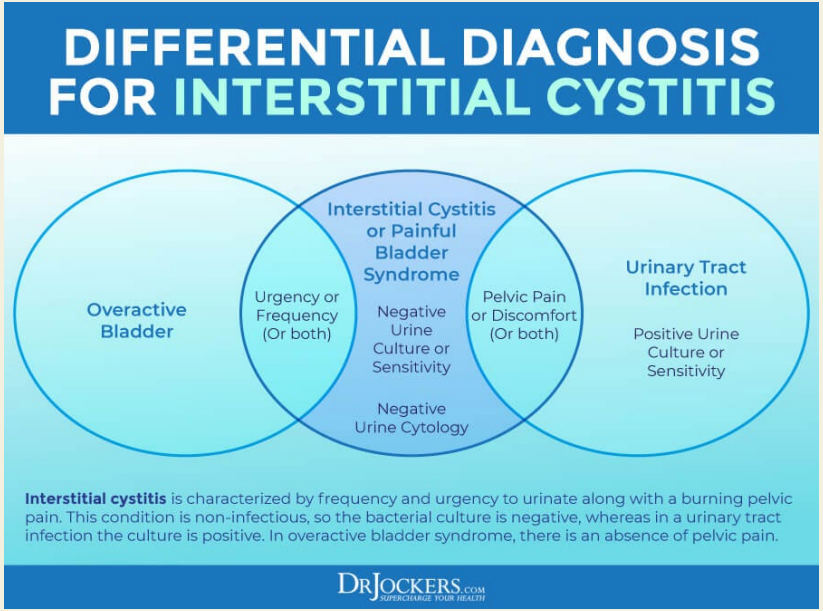
- Course unpredictable and varied
  - Fistula formation
  - Spontaneous resolution
  - Graded in severity
    - Grade 1 - any evidence of epithelial damage or atrophy, telangiectasia, microscopic hematuria
    - Grade 2 - any moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria, intermittent urinary incontinence
    - Grade 3 - any severe frequency or urgency, severe telangiectasia, persistent incontinence, reduced bladder capacity < 150 mL, frequent hematuria
    - Grade 4 - any necrosis, fistula, hemorrhagic cystitis, reduced bladder capacity < 100 mL, refractory incontinence requiring either catheter or surgical intervention

Radiation Cystitis and Hyperbaric Management - StatPearls - NCBI Bookshelf



Idiopathic- Interstitial cystitis

- Now called Bladder Pain Syndrome (BPS)
  - Defined as a noninfectious inflammatory cystitis of unknown etiology
- Often a diagnosis of exclusion
- Very difficult to treat



Interstitial Cystitis/Bladder Pain Syndrome - StatPearls - NCBI Bookshelf

1. Identify common causes of dysuria and bladder spasms in the palliative care population

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General Approach in Palliative population

- Accurate history taking!
  - Hx of radiation
  - Up to date list of medications
  - “Does it feel like you have a UTI?”

- In the inpatient setting
  - Ultrasound for PVR (help differentiate bladder fullness from spasms)
  - Urinalysis

- Home hospice setting
  - Evaluate for suprapubic fullness via physical exam

- Start by treating easily reversible causes!
  - Stop offending agents
  - Treat constipation
  - Antibx for infx?

Treatment- Infectious

- Growing concern over antibiotic resistance has led to studies on use of antibiotics in hospice
  - A study by Reinbolt et al. demonstrated that antimicrobial treatment improved infection-related symptoms in 79% of hospice patients with UTIs

- A retrospective case review of 200 terminally ill patients w/ fever found the strongest correlation between use of antibiotics and (subjective) patient comfort in patients exhibiting dysuria
  - Minimal improvement in comfort for patients experiencing abdominal pain and dyspnea

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.
Barlam TF, Cosgrove SE, Abbo LM, et al.

Antibiotic Stewardship Program (ASP) in Palliative Care: Antibiotics, to Give or Not to Give.

Hung KC, Lee LW, Liew YX, et al.

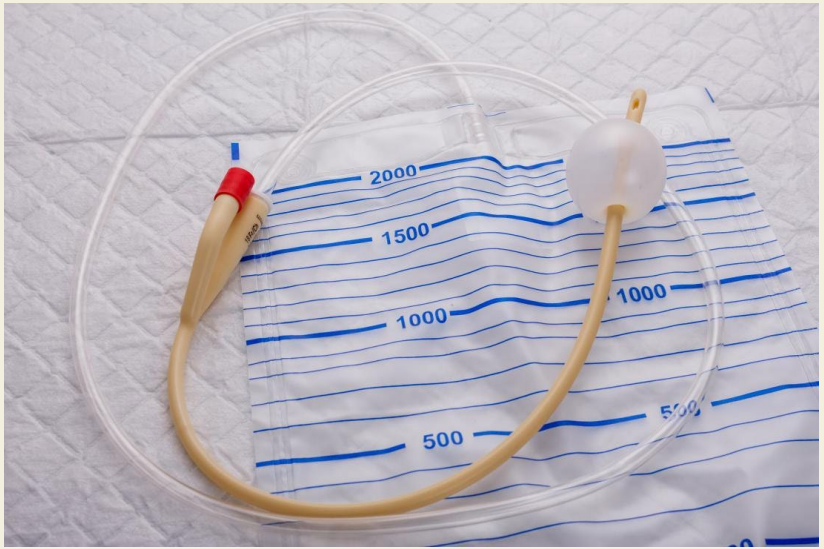
European Journal of Clinical Microbiology & Infectious Diseases : Official Publication of the European Society of Clinical Microbiology. 2022;41(1):29-36. doi:10.1007/s10096-021-04325-z.
Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America. 2016;62(10):e51-77. doi:10.1093/cid/ciw118.

Treatment- Obstructive

- Treat constipation and obtain PVR and consider catheterization

- If catheter already present
  - Pull gently on the tubing so the tip is not pushing against the bladder wall.
  - Ensure appropriate catheter drainage by irrigating with saline, elevating and dropping the tubing to minimize airlocks, and avoiding large uphill loops which may impede drainage by gravity.
  - Consider upsizing catheter to improve drainage.
  - Palpate the catheter for hardness and consider changing to a softer catheter with a shorter tip.
  - Use securing devices or tape to prevent pulling of the tubing against the bladder neck

Keep in mind catheters themselves can cause bladder spasms and dysuria- may need UA to differentiate this from infection



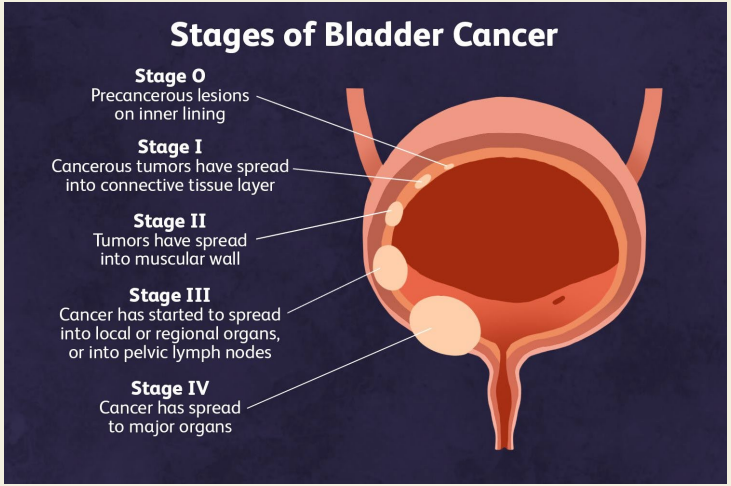
Treatment-Radiation Cystitis

- Hyperbaric oxygen therapy
  - For Symptom relief AND treatment of the underlying cause
- Promotes angiogenesis
  - Reestablishes blood flow to the areas in danger of necrosis
  - Helps maintain bladder functionality
- Early intervention may be key
  - patients treated within six months of hematuria onset had 96% complete or partial symptomatic resolution whereas those treated after six months had but a 66% response rate
- Overall
  - Studies have shown a complete response rate ranging from 27% to 100% of patients studied according to meta-analysis data

1Chong KT, Hampson NB, Corman JM. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. Urology. 2005 Apr;65(4):649-53.
2.Ribeiro de Oliveira TM, Carmelo Romão AJ, Gamito Guerreiro FM, Matos Lopes TM. Hyperbaric oxygen therapy for refractory radiation-induced hemorrhagic cystitis. Int J Urol. 2015 Oct;22(10):962-6.

Back to the case…

- Urinalysis is grossly unrevealing
- CT abdomen and pelvis shows no new masses or metastasis. Patient is not constipated
- PVR's reveal urinary retention and catheter is inserted
  - No resolution in the patient's symptoms
- You feel that the patient's dysuria is likely due to irritation and invasion of the cancer on the bladder mucosa
  - Patient is already s/p 2 resections
  - Only option is complete cystectomy which patient does not wish to undergo
- Patient wishes to enroll in hospice but is worried that his dysuria will never be controlled



How can we help if we cannot treat the underlying cause?

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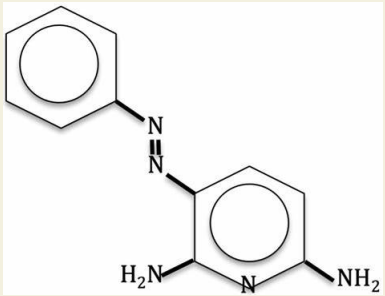
Medications

Medication Class	Examples	Side effects
Bladder Muscle Relaxants		
Oral anticholinergics *1st line pharmacologic agent* (9,10)	• Oxybutynin 5-15 mg TID or ER qday • Tolterodine 2-4 mg IR BID • Solifenacin 5-10 mg daily • Dicyclomine 20 mg up to QID	• Dry mouth • Dry eyes • Constipation • Delirium
Beta-3 agonist (10)	• Mirabegron 25 to 50 mg daily	• Hypertension • Potentiation of metoprolol
Bladder Emptying Agents		
Oral Alpha blockers	• Tamsulosin 0.4 mg daily • Terazosin 2-10 mg daily	• Orthostatic hypotension • Terazosin requires titration
Medications that Calm Surface Irritation		
Phenazopyridine *1st line; often used in conjunction with anticholinergics* (11)	• 100 to 200 mg PO TID as needed (may stain clothing)	• Check UA and culture before initiating • Methemoglobinemia • Skin pigmentation changes with prolonged use
Rectal Opioids	• Belladonna extract 16.2 mg daily • Opium 60mg suppository daily	• Opioid side effect profile
Benzodiazepines	• Diazepam 5-10 mg via rectum or intravaginally q8 hours prn	• Few systemic side effects
Other	• Anti-inflammatories (NSAIDS/steroids) • Systemic opioids • Cannabinoids (12)	• Anecdotal and emerging evidence only

FF #337 Palliation of Bladder Spasms | Palliative Care Network of Wisconsin

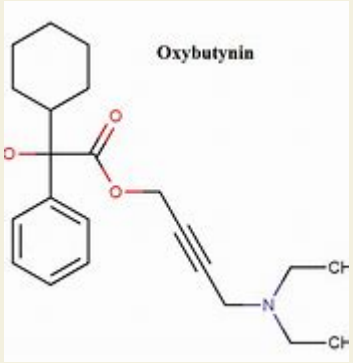
Medications-Phenazopyridine

- Mechanism of action
  - Not well understood
  - Hypothesis: Local analgesic effect on bladder mucosa
    - Has been shown to inhibit nerve fibers in bladder that respond to mechanical stimuli
- Pearls
  - May use for long term
    - Was used safely for up to 2 months to treat radiation cystitis[1]
  - Phenazopyridine should not used in patients with a glomerular filtration rate of less than 50 mL/min
- Side effects
  - Hemolytic anemia and methemoglobinemia
  - Discoloration of bodily fluids
  - Interstitial nephritis



Phenazopyridine - StatPearls - NCBI Bookshelf

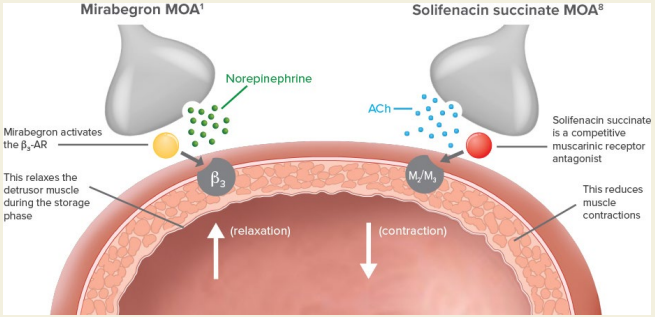
Medications-Oral anticholinergics



- Drugs in Class
  - Oxybutynin, dicyclomine,solifenacin
- Mechanism of Action
  - Antispasmodic against smooth muscle
- Pearls
  - Should be avoided in geriatric population due to anticholinergic and neurocognitive side effects
  - CYP3A4 primarily metabolizes oxybutynin. Caution should be exercised when using potent CYP3A4 inhibitors, such as ketoconazole
- Side effects
  - Dry mouth
  - Constipation
  - Nausea
  - Urinary retention
- Ineffective?
  - Data is mixed
  - A randomized controlled trial specifically evaluated the use of oxybutynin for urinary symptoms during intravesical Bacillus Calmette-Guérin (BCG) treatment and found that oxybutynin actually increased urinary frequency and burning on urination compared to placebo, suggesting it may exacerbate rather than alleviate dysuria

Medications-B3 agonists

- Drugs in Class
  - Mirabegron, Vibegron,
- Mechanism of Action
  - Causes detrusor muscle relaxation
- Pearls
  - Growing evidence to support its use in radiation cystitis
    - 2022 study showed mirabegron, in combination with tamsulosin, improved symptoms of urinary frequency dysuria and overactive bladder following radiation therapy for prostate cancer
  - Vibegron has also been studied and shown to have high selectivity and potent agonist activity for beta-3 adrenergic receptors
- Side effects
  - Very well tolerated
  - HTN most common



Mirabegron - StatPearls - NCBI Bookshelf

Mirabegron Reduces Urinary Frequency and Improves Overactive Bladder Symptoms at 3 Months After 125I-Brachytherapy for Prostate Cancer: An Open-Labeled, Randomized, Non-Placebo-Controlled Study.
Nakai Y, Tanaka N, Asakawa I, et al.
Urology. 2022;161:87-92. doi:10.1016/j.urology.2021.12.018.

Medications–Rectal Therapies

- limited evidence on its use
  - Most evidence for Belladonna and Opium suppositories
    - Belladonna contains antimuscarinics atropine and scopolamine
    - Data is mixed and mostly for procedural pain
      - 2017 study looked at preoperative use before ureteral stent placement to stop urologic spasms[1]
        - Found that it improved QOL measure including dysuria
      - A study of nearly 3000 patients undergoing OP cystoscopy were treated with perioperative B&O suppository
        - Found no difference in post procedural symptoms including dysuria

Preoperative Belladonna and Opium Suppository for Ureteral Stent Pain: A Randomized, Double-Blinded, Placebo-Controlled Study.
Lee FC, Holt SK, Hsi RS, Haynes BM, Harper JD.

Urology. 2017;100:27-32. doi:10.1016/j.urology.2016.07.035.

Medications-Intravesical Therapies

- Most data on its use comes from BPS/IC and Bladder cancer
  - Topical anesthetics
    - Lidocaine and bupivicaine
    - Done multiple times per day, requires foley catheter
  - Botulinum toxin A
    - Strongest evidence for resolution of symptoms in BPS/IC
      - 2016 meta-analysis of 16 studies showed that botulinum toxin had the highest probability (81.6%) of being the most effective treatment in the study
  - Heparin
    - Believe to work by restoring aminoglycoside layer on bladder wall
    - Weekly administration
- Little to no data on its use in radiation cystitis or hemorrhagic cystitis

Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome.
Clemens JQ, Erickson DR, Varela NP, Lai HH.

The Journal of Urology. 2022;208(1):34-42. doi:10.1097/JU.0000000000002756.
Intravesical Treatment for Interstitial Cystitis/Painful Bladder Syndrome: A Network Meta-Analysis.
Zhang W, Deng X, Liu C, Wang X.

International Urogynecology Journal. 2017;28(4):515-525. doi:10.1007/s00192-016-3079-4.

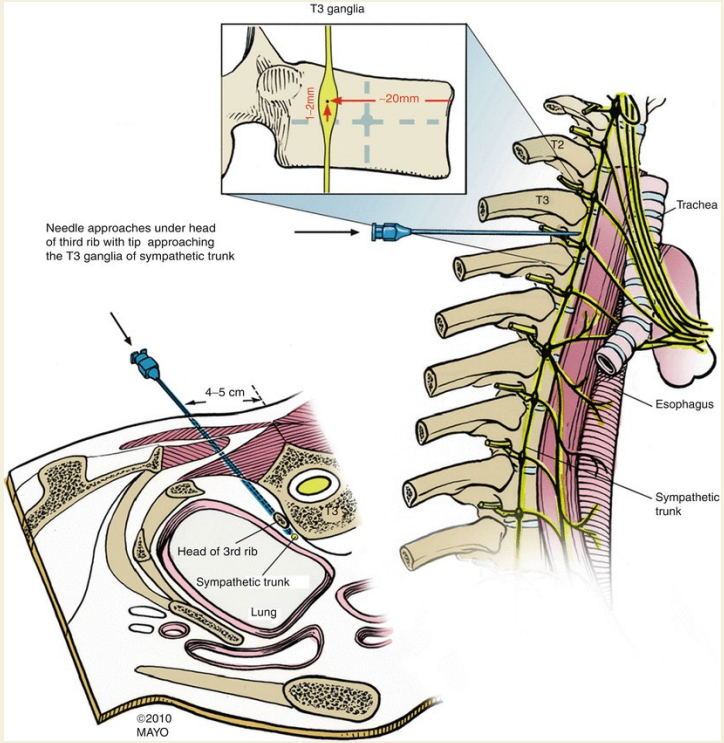
Back to the case again…

- To review:
  - 77 year old man with necrotic high grade urothelial cell carcinoma admitted to hospital for symptom control
    - Endorses severe dysuria near constantly for past 2 weeks, but started at diagnosis
      - believed to be related to direct tumor invasion of detrusor muscle
        - Already s/p 2 tumor resections without benefit in symptoms
        - Does not wish to undergo palliative cystectomy
    - Current therapies at home
      - Anti muscarinic (tolterodine)
      - Anti inflammatory (diclofenac)

Medications- Other therapies, practical application

- Therapies tried in hospital:
  - Insertion of Foley catheter - ineffective
  - Morphine PCA - helpful but began to lead to sedation concerns
  - Intravesical Bupivacaine - helpful but fleeting
    - Using TID and helpful for approx 1-2 hours after use
- Due to severe debilitating symptoms new methods were tried
  - (1) intravesical baclofen - positive effect longer lasting than bupivicaine (reported 3-4 hours of relief)
  - (2) lumbar sympathetic nerve block- caused complete resolution of pain and patient was discharged 48 hours after
- Side effects unable to be reported
  - Patient unfortunately died 2 weeks after discharge due to MI

- Area of further research?



Intravesical Baclofen, Bupivacaine, and Oxycodone for the relief of Bladder Spasm - Elaine Wallace, Marie Twomey, Ray Victory, Maeve O'Reilly, 2013

Questions?

THANK YOU!