HealthCare

Management of the Big Three

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Financial Disclosures

- Nothing to disclose

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Objectives

- Discuss PSA and factors that alter PSA
- Define the role of PSA in prostate cancer screening
- Review current guidelines for PSA screening
- Explain evaluation and treatment of BPH
- Identify evaluation of microhematuria based on risk categories

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Prostate Cancer Screening

Epidemiology

- Lifetime risk of prostate cancer is 1 in 8
  - Mean age at diagnosis: 67
- Approximately 35,000 men will die of prostate cancer per year
- Risk factors: increasing age, family history, history of genetic syndromes (BRCA2, Lynch syndrome)

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PSA-Based Screening

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- Prostate specific antigen (PSA)
  - Reproductive protein involved in seminal fluid liquefaction.
  - Disruption of the glandular architecture increases levels in the blood stream (trauma, infection, inflammation, and prostate cancer)
  - PSA may rise in prostate cancer; but up to 15% of men with a PSA <4.0 harbor prostate cancer.

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PSA-Screening Trials

- Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial
  - ~80,000 men randomized to PSA screening versus standard of care
    - No difference in prostate cancer mortality at 17 years of follow-up
    - PSA screening contamination in the standard of care arm is estimated at ~90%

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PSA-Screening Trials

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- European Randomized Study of Screening for Prostate Cancer (ERPSC)
  - ~180,000 men randomized to PSA screening versus no screening
    - 20% reduction in prostate cancer mortality with PSA-screening
    - Number needed to screen to prevent 1 death from prostate cancer: 570 at 16 years of follow-up
      - Longest and largest arm (Goteborg): 46% reduction in mortality with a number needed to treat of 5.

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PSA-Screening Trials

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- Current U.S. Preventative Task Force grade: C
  - Shared-decision making
- AUA Guidelines:
  - High risk (family history/genetic syndromes): 40-54
  - Average risk: Begin screening at 55-69 with shared decision making
    - Advocates PSA-testing strategy at 2 year intervals
    - Stop screening at 70, or when life expectancy is <10-15 years

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MRI in Prostate Cancer Screening

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- Current recommendations:
  - Use in men with a prior negative biopsy
  - Consider in men without prior biopsy where there is clinical suspicion for prostate cancer
  - Biopsy should include targeted lesions and systematic / template sampling

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Summary of Screening Tools

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- Screening using PSA alone results in reductions in prostate cancer mortality
  - Best practiced selectively: use shared decision making in men at risk for prostate cancer (age, family history, genetic syndrome, etc)
- mpMRI in men with an elevated PSA decreases unnecessary biopsy, reduces overdiagnosis, and improves detection of clinically significant disease
- Advanced biomarkers exist to improve selection of men for biopsy in the setting of an elevated PSA to reduce the risk of overdiagnosis and improve detection of clinically significant disease
- Urine Based: Endo Dx, miR, MPS, PCA3, Select MDX
- Blood based: 4K, PHI, Proclarix, STHLM-3

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Medical Therapy for BPH

Diagnosis and Evaluation of BPH

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- The evaluation of all patients presenting with LUTS suggestive of bladder outlet obstruction (BOO):
  - Medical history and physical exam
  - Physical examination including digital rectal exam (DRE) and focused neurologic examination
  - Urinalysis should be performed to screen for hematuria and UTI when patients are symptomatic
  - PSA testing is most appropriate for patients likely to have a natural life span greater than 10 years
    - In whom the known presence of prostate cancer would change management or for whom the PSA measurement may change the management of the patient's voiding symptoms.
  - Additionally, PSA has been investigated as means of estimating prostatic size
    - Especially when trying to determine whether a prostate is less than a threshold volume for intervention
    - Studies have proposed age specific criteria for detecting glands >40ml with PSA cutoffs of 1.6ng/ml, 2.0 ng/dl and 2.3ng/dl in men in their 50s, 60s and 70s respectively

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Treatments for BPH

- Behavioral
- Herbal
- Medical

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Behavioral Treatment of BPH

- Behavioral modification strategies:
  - Double voiding
  - Timed voiding (based on voiding diary)
  - Avoidance of caffeine, alcohol and other diuretics
  - Night-time fluid restriction

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Herbal Treatment of BPH

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- Over 30 phytotherapeutic compounds have been described in the management of BPH
  - Given their classification as foods by the US Food and Drug Administration, there is little regulation of production and distribution of these herbal supplements
  - Studies have demonstrated extreme variations in active compounds in products sold OTC
  - One of the most common, saw palmetto, is derived from Serenoa repens
    - In 2011, a randomized controlled trial examined 369 men with LUTS due to BPH treated with placebo vs. saw palmetto demonstrated no difference with active treatment.
    - In 2012, a Cochrane update of 32 trials including 5666 patients also reported no difference between treatment arms in terms of response and adverse effects.
  - Other examples : beta-sitosterols from the Hypoxis rooperi plant and pygeum from the Prunus africana plant.
  - There is no convincing evidence that pumpkin seed (Cucurbita pepo) or stinging nettle (Urtica dioica) are effective for BPH.

Medical Treatment of BPH

- Alpha (α1)-blockers
- 5-α-Reductase Inhibitors
- Combination Therapy
- Antimuscarinics
- Beta-3 Adrenoceptor Agonist
- Phosphodiesterase type 5 Inhibitors

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Mechanism of Action: Alpha (α1)-blockers

- Alpha-Adrenergic Antagonists
  - Alpha (α1)-blockers relax smooth muscle at the bladder neck and prostate
  - Thereby helping to relieve bladder outlet obstruction
  - They represent the most common initial therapy for treating LUTS associated with BPH
  - Commonly used agents in USA
    - Doxazosin
    - Terazosin
    - Tamsulosin
    - Alfuzosin
    - Silodosin

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Outcomes of Alpha (α1)-blockers

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- Outcomes:
- 1st generation agents: phenoxybenzamine (irreversible) and prazosin (frequent daily dosing) no longer used.
- Second generation agents: **terazosin** and **doxazosin**, allow for once-daily dosing but need to be titrated to effect
- α1a-selective blockers: **tamsulosin**, **alfuzosin**, and **silodosin**, developed to avoid the systemic side effects associated with α-blockade
- Improvements in Qmax with use of α-blockers range from **0.59-4.8ml/s**
- Symptom score reductions range from **1-4.2** points.
- Direct comparisons between different types of alpha blockers are limited
- In 2011, a large RCT involving 1228 patients compared tamsulosin, silodosin and placebo
  - Found silodosin to be non-inferior to tamsulosin in improving storage and voiding LUTS while allowing for greater alpha 1a selectivity.

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Adverse Effects of Alpha (α1)-blockers

- Most common side effects associated with alpha blockade include a decline in blood pressure that can result in dizziness (5 to 15% with α1a-selective agents), retrograde ejaculation (6%), and rhinitis (12%).
- The cardiovascular effects particularly seen when less selective drugs and higher doses of α-blockade are used (tamsulosin 0.8mg daily)
- Silodosin is felt be less likely to cause orthostasis given its high α1a-selectivity
- In regards to ejaculatory dysfunction, alfuzosin is thought to pose a reduced risk when compared to other means of alpha blockade

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Intra-operative Floppy Iris Syndrome (IFIS)

- More recently, the use of alpha-blockers, in particular tamsulosin, has been associated with intra-operative floppy iris syndrome (IFIS) with an incidence of 0.9-3.7%
- This problem leads to higher rates of iris trauma and posterior capsule rupture during cataract surgery
- Indeed, IFIS is associated with any prior use, not necessarily current use, of tamsulosin
- Opthalmological consultation may be considered for patients with untreated cataracts who have symptomatic BPH/LUTS with cataracts and are being considered for tamsulosin use
- Although the use of tamsulosin appears to carry the greatest risk of IFIS, the risk does carry across to other alpha-blockers, albeit at a lower rate compared to tamsulosin

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5-α-Reductase Inhibitors

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- Mechanism of Action:
  - 5-ARIs suppress androgen synthesis by blocking the conversion of testosterone to dihydrotestosterone
  - This is associated with reduction in prostate volume and decrease in bladder outlet obstruction
  - Contrary to alpha-blockers, these drugs have a slow onset of action and a clinical benefit is not noticed before at least 6 months of therapy in most patients

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Outcomes of 5-α-Reductase Inhibitors

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- **PLESS Study**: Findings at 4 year f/u:
  - Finasteride arm: **57%** risk reduction in AUR & **55%** risk reduction in the need for surgery
  - Qmax increased by 0.2ml/s in the placebo group vs. 1.9ml/s in the finasteride arm ($p<0.001$)
  - Decrease in symptom score of 1.3 in the placebo group vs. 3.3 in the finasteride group ($p<0.001$)
  - 5α-reductase inhibitors reduced prostate volume **15-32%.**
- **REDUCE Trial**: Post-hoc analysis of the Reduction by Dutasteride of Prostate Cancer Events:
  - Dutasteride in asymptomatic or mildly symptomatic men decreased the risk of BPH-related symptoms, episodes of urinary retention and need for BPH-related surgery.

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Adverse Effects of 5-α-Reductase Inhibitors

- The most common side effects at 1 year f/u:
- Decreased libido (6.4%)
- Erectile dysfunction (8.1%)
- Ejaculatory disorder (0.8%)
- Gynecomastia (0.5%)
- Breast tenderness (0.4%)
- Rash (0.5%)
- Case reports linking finasteride use to IFIS development have been published, although it is unclear what alpha-blocker exposure these patients had experienced
- Despite a change in label for these agents, there currently exists no robust evidence regarding any causal link between 5-ARIs and persistent or long-term sexual side effects

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Combination Therapy

- Alpha-blockers and 5-ARIs may be used in combination to augment therapeutic effect
- Finasteride and terazosin have been examined in combination in the VA Cooperative Study and the Prospective European Doxazosin and Combination Therapy **(PREDICT)** Trial
- Finasteride and alfuzosin have also been studied in combination
- Finasteride and doxazosin have been studied in the largest combination therapy trial, the Medical Therapy of Prostatic Symptoms **(MTOPS)** study
- Combination therapy demonstrated the greatest risk reduction **(66%)** in clinical progression of BPH (as defined by an increase in AUA symptom score of ≥4 over baseline,) acute urinary retention, renal insufficiency, recurrent urinary tract infection, and urinary incontinence
- Combination therapy also reduced the risk of AUA symptom score increase of ≥4 by **64%**, compared to doxazosin alone **(45%)** or finasteride alone **(30%)**
- These results were confirmed in the **CombAT** study, where the combination of 0.5mg dutasteride and 0.4mg tamsulosin was studied

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Combination Therapy

- Current guidelines published by the AUA and EAU recommend combination therapy with alpha-blockers and 5ARIs for patients with moderate-severe symptoms, prostates above 40ml, higher PSA and advanced age.

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Phosphodiesterase type 5 Inhibitors (PDE5i)

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- Mechanism of Action:
- PDE5i function by blocking the breakdown of cGMP to GMP by phosphodiesterase, thus leading to vasodilation
- There are 11 PDE families and the prostate contains several, most abundantly 4, 5 and 11
- All PDE5I have significant cross-reactivity on PDE enzymes other than PDE5
- They have classically been utilized for the treatment of erectile dysfunction (ED), but an age-independent link between LUTS and ED has recently been demonstrated
- Improvements in LUTS have been observed in patients using **sildenafil**, **tadalafil**, and **vardenafil**

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Outcomes of PDE5i

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- In 2012, Oelke et al conducted a randomized, double-blind, multicenter placebo controlled study with randomization to either placebo, tamsulosin 0.4mg or tadalafil 5mg
  - Results revealed similar improvements versus placebo in IPSS and BPH Impact Index in both tamsulosin and tadalafil groups and compared to previous literature Qmax increased significantly compared to placebo (2.4ml/s p=0.009).
- Roehrborn et al conducted a randomized placebo controlled trial including 1500 patients
  - Found a small but statistically significant median Qmax improvement that increased with voided volume
- Pooled analysis of 4 studies investigating the use of tadalafil 5mg did however show IPSS improvement in two-thirds of patients with at least 50% of patients with significant response at 1 week and at least 70% demonstrating improvement at 4 weeks. These results suggest speed of onset comparable with alpha blockade.
- Symptom score improvements have been observed in the 4.3-9.2 range
- While no consensus currently exists regarding what role PDE5i should play in the BPH-related LUTS treatment pathway, daily tadalafil 5 mg has been approved in the US for daily use in men with BPH/LUTS.

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Adverse Effects of PDE5i

- Most common side effects associated with the use of PDE-5 inhibitors:
  - Headache (15%)
  - Dyspepsia (4-10%)
  - Flushing (3-11%)

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Clinical Pathway For BPH

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- Patients should first be thoroughly evaluated with a history, physical exam, IPSS, and objective measures such as Qmax and PVR
- Urodynamics (represents the most definitive way to diagnose BOO) is an invasive test
  - But may be helpful in patients with complex symptoms (co-existing OAB and BOO), co-morbid neurologic conditions, or those with equivocal obstructive LUTS and concomitant bothersome OAB symptoms considering outlet surgery

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Clinical Pathway For BPH

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- For patients with (i) mild symptoms (IPSS≤8) or (ii) moderate to severe symptoms without significant bother, watchful waiting is reasonable assuming no evidence of **recurrent infection, bladder stones, urinary retention, or renal compromise**
  - These patients can be seen annually for f/u visits and symptom assessment with PVR's

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Clinical Pathway For BPH

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- For patients with moderate to severe symptoms with significant bother, physicians should engage in a discussion with patients regarding treatment options
  - Patients may choose from medical therapy (typically first line) or surgical therapy in the event of medication failure
  - For those with small prostates (<30g), initial therapy with α-blockers is reasonable
  - Should symptoms not improve sufficiently, the addition of an anti-cholinergic is beneficial in patients with OAB
  - For patients with larger prostates (≥30g), combination therapy with an α-blocker and 5α-reductase inhibitor should represent the first line of treatment
  - An anti-cholinergic may be added for further symptom control if necessary
  - The use of PDE5i monotherapy may be beneficial in reducing urinary symptoms, particularly in patients with concomitant ED.

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Surgical Therapy for BPH

Overview

- Simple Prostatectomy (Open, Laparoscopic, Robotic)
- Multiple transurethral options are available for treating BPH
  - Monopolar TURP (mTURP):
  - Bipolar TURP (bTURP)
  - Laser therapies
    - Laser ablation, HOLEP
  - Aquablation
  - Minimally invasive technologies

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Prostatic Urethral Lift (Urolift®)

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- The prostatic urethral lift (Urolift®):
  - Implantation of tissue retracting elements inserted under cystoscopic guidance using the Urolift® delivery system
  - Appropriate patient selection based on prostate anatomy is critical for planning:
    - Middle lobes are a relative contraindication due to the inability to place the implants into the bladder or bladder neck.
    - Typically, 4-6 implants are placed

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Prostatic Urethral Lift (Urolift®)

L.I.F.T Study:

- First multicenter, prospective randomized controlled study
  - Randomized 206 patients in a 2:1 fashion to either Urolift® or sham control
  - Statistically significant improvements in AUA symptoms score & Qmax at 12 month f/u
  - No benefits were observed in regards to post-void residual and no differences were noted in regards to ejaculatory or erectile dysfunction
  - Adverse effects were few including dysuria and hematuria and resolved spontaneously
- Roehrborn et al. found an improvement of IPSS at 5 year f/u when compared to sham
  - Side adverse events were few and mild with no effect on ejaculatory of erectile function
- Overall, most studies conducted are small without adequate randomization or control. Further studies are needed to define the role Urolift® will play in the treatment of BPH

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Transurethral Water Vapor Therapy (Rezum®)

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- Transurethral water vapor therapy or the Rezum® system:
  - A narrow sheath, similar in size and shape to a cystoscope, is inserted via the urethra
  - A thin needle is deployed through the urethra into the prostate
  - Water vapor is delivered rapidly into the hyperplastic tissues
  - Delivers targeted and controlled doses of thermal energy directly into the prostate by using sterile water vapor relying on convective energy
  - When the water vapor comes into contact with the prostatic tissue, it condenses into its liquid state and releases stored thermal energy

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Temporarily Implanted Nitinol Device (iTind®)

- Temporary prostatic implant, called the iTind (temporarily implantable nitinol device) approved by the FDA
- Device is placed under direct vision within the prostatic urethra cystoscopically under local anesthesia
- Over the subsequent 5 days the nitinol struts exert a radial outward force causing ischemic necrosis and remodeling of the bladder neck and prostatic urethra
- The device is removed using a tether through an open-ended catheter in an office setting

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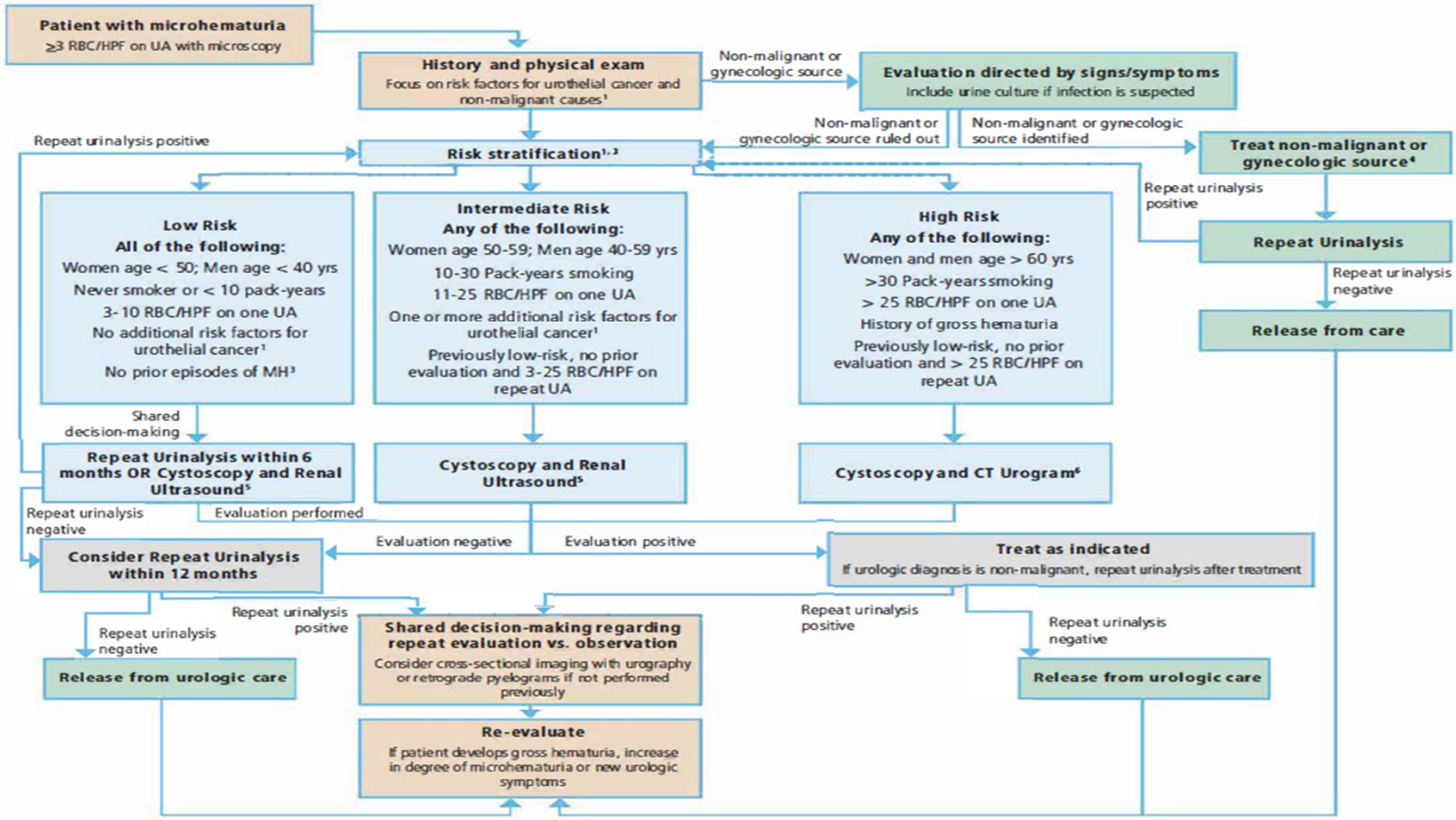
Microhematuria



1. Main risk factors for urothelial cancer are those in the AUA risk stratification system (age, male sex, smoking, degree of microhematuria and history of gross hematuria). Additional risk factors for urothelial carcinoma include but are not limited to irritative lower urinary tract voiding symptoms, history of cyclophosphamide or ifosfamide chemotherapy, family history of urothelial carcinoma or Lynch Syndrome, occupational exposures to benzene chemicals or aromatic amines, history of chronic indwelling foreign body in the urinary tract
2. If medical renal disease is suspected, consider nephrologic evaluation, but pursue concurrent risk-based urological evaluation
3. Patients may be low-risk at first presentation with microhematuria, but may only be considered intermediate- or high-risk if found to have persistent microhematuria
4. There are non-malignant and gynecologic sources of hematuria that do not require treatment and/or may confound the diagnosis of MH. Clinicians can consider catheterized urine specimen in women with vaginal atrophy or pelvic organ prolapse. Clinicians must use careful judgment and patient engagement to decide whether to pursue MH evaluation in the setting of chronic conditions that do not require treatment, such as the aforementioned gynecologic conditions, non-obstructing stones or BPH.
5. Clinician may perform cross-sectional imaging with urography or retrograde pyelograms if hematuria persists after negative renal ultrasound
6. MR Urogram or Non-contrast imaging plus retrograde pyelograms if contraindications to CT Urogram

Low Risk

All of the following:

- Women age < 50; Men age < 40 yrs
- Never smoker or < 10 packs – years
- 3 – 10 RBC/HPF on one UA
- No additional risk factors for urothelial cancer
- No prior episodes of MH
- Repeat Urinalysis within 6 months OR Cystoscopy and Renal Ultrasound

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Intermediate Risk

Any of the following:

- Women age 50-59, Men age 40-59 yrs
- 10-30 packs-years smoking
- 11-25 RBC/HPF on one UA
- One or more additional risk factors for urothelial cancer
- Previously low-risk, no prior evaluation and 3-25 RBC/HPF on repeat UA
- Cystoscopy and Renal Ultrasound

AUA Guidelines

High Risk

Any of the following:

- Women and men > 60 yrs
- > 30 pack-years smoking
- > 25 RBC/HPF on one UA
- History of gross hematuria
- Previously low-risk, no prior evaluation and > 25 RBC/HPF on repeat UA
- Cystoscopy and CT Urogram

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Additional Urothelial Cancer Risk Factors

- Irritative lower urinary tract symptoms
- Prior pelvic radiation therapy
- Family history of UCC or Lynch Syndrome
- Prior cyclophosphamide or ifosfamide chemotherapy
- Occupational exposure to benzene or aromatic amides
- Chronic indwelling foreign body in the urinary tract

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