• Benign prostatic hyperplasia
• Microhematuria
• Small renal masses

...Updates on common urologic problems

Disclosures / Conflicts of interest

• None
Objectives

- Basic evaluation and treatment of benign prostatic hyperplasia and lower urinary tract symptoms. Familiarization with current medical and procedural treatments. (25 min)
- Review etiologies of hematuria and risk stratification methods for further evaluation. (5 min)
- Review current management of small renal masses and understand which warrant further evaluation/treatment vs. surveillance. (5 min)

Benign prostatic hyperplasia
Definitions / Pathophysiology

**Benign prostatic hyperplasia (BPH)**
- **Histologic:** Proliferation of smooth muscle and epithelial cells in the transition zone of the prostate

**Benign prostatic enlargement (BPE)**
- **Anatomic:** enlargement due to BPH

**Benign prostatic obstruction (BPO)**
- **Pathophysiologic:** Compression of urethra → compromise of urinary flow → obstruction of the bladder

**Lower urinary tract symptoms (LUTS)** - generalized term used when etiology is unclear or multifactorial

Although often used interchangeably,

BPH ≠ BPE ≠ BPO ≠ LUTS


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**Causes of lower urinary tract symptoms**

Benign prostatic obstruction often leads to or coexists with detrusor overactivity ("overactive bladder") given physiologic effects outlet obstruction has on the bladder function.

Diagnosis / Evaluation

Evaluation of patients presenting with LUTS suggestive of benign prostatic hyperplasia

- Medical history
- Review medication and lifestyle habits
- Discuss emotional and psychological factors
- Physical exam including digital rectal exam (DRE) and focused neurologic examination
- Urinalysis to screen for hematuria and UTI
- PSA testing
  - In patients with anticipated longevity > 10 years*
  - If known presence of prostate cancer would change management


### International Prostate Symptom Score (i-PSS)

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#### 1. Incomplete Emptying
- Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?

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#### 2. Frequency
- Over the past month, how often have you had to urinate again less than half an hour after you finished urinating?

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#### 3. Intermitency
- Over the past month, how often have you had dribbling and started again several times when you urinated?

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#### 4. Urgency
- Over the past month, how often have you found it difficult to postpone urination?

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#### 5. Weak Stream
- Over the past month, how often have you had a weak urinary stream?

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#### 6. Straining
- Over the past month, how often have you had to push or strain to begin urination?

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#### 7. Nocturia
- Over the past month, how many times did you need to get up each night to urinate more than once a month? You may count the times you went to bed until the time you got up in the morning?

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Total i-PSS Score

### Quality of Life due to Urinary Symptoms

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<th>0-7 mildly symptomatic</th>
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<th>20-35 severely symptomatic</th>
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Score = 0 (best) to 35 (worst) with a QOL score 0-6
Diagnosis / Evaluation

Selective evaluation of patients presenting with LUTS suggestive of BPO
- Frequency-voiding chart / Voiding diary
- Post-void residual measurement
- Cystoscopy
- Trans-rectal ultrasound of the prostate
- Urodynamics with Pressure/flow studies for complex presentations
- Renal ultrasound (only in cases of very elevated PVR)

Treatments
- Behavioral
- Herbal
- Medical
- Surgical
BPO Treatments: Medical

- Alpha (α1)-blockers
- 5-α-reductase inhibitors (5-ARI)
- Anticholinergics
- Beta-3 agonists
- Phosphodiesterase inhibitors, type 5 (PDE-5i)
- Combination therapy

BPO Treatment: Alpha-1 blockers

- Mechanism: relax smooth muscle at the bladder neck and prostate
- Most common initial therapy for treating LUTS/BPH.
- Classes
  - Second generation agents (terazosin, doxazosin) need to be titrated to effect.
  - Alpha 1a-selective blockers (tamsulosin, alfuzosin, silodosin) were developed to avoid the systemic side effects associated with α-blockade.
- Outcomes
  - Improvements in flow rate from 0.59-4.8ml/s. (Normal flow rate >20 ml/s)
  - Symptom score reductions range from 1-4.2 points
  - All have similar efficacy in appropriate doses.
  - α1-blockers do not prevent occurrence of urinary retention or need for surgery.
Treatment: Alpha-blockers

- Adverse Effects:
  - Most common: decline in blood pressure that can result in dizziness (5-15% with α1a-selective agents), retrograde ejaculation (6%), and rhinitis (12%). CV effects are dose and alpha-selectivity dependent.
  - α-blockers, particularly tamsulosin, have been associated with intra-operative floppy iris syndrome (IFIS) (incidence 0.9-3.7%). This problem leads to higher rates of iris trauma and posterior capsule rupture during cataract surgery. IFIS is associated with any prior use of α-blockers.
  - α-blockers (particularly non-selective) and 5-ARI linked to small but statistically significant increase risk of CHF in populations studies (HR 1.22, 95% CI 1.18-1.26 for alpha-blocker alone). Findings previously observed in ALLHAT and REDUCE trials.
  - α-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but can cause abnormal ejaculation.
  - A single observational study in 2018 found that tamsulosin use may increases long-term risk of dementia. Subsequent observational studies to date have contradicted this.

References:
5. The ALLHAT Officers. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker or diuretic. JAMA 2002 288: 2981.

Treatment: 5-alpha-reductase inhibitors

- Drugs:
  - finasteride (Proscar®)
  - dutasteride (Avodart®)
- Mechanism:
  - 5-ARIs block the conversion of testosterone to dihydrotestosterone (DHT) → reduction in prostate volume and decrease in symptoms associated with BPO.
- Outcomes:
  - 57% risk reduction in urinary retention and 55% risk reduction in the need for BPH-related surgery over 4 years.
  - Mean increase in flow rate 1.5-2.2ml/s
  - Reduction in symptom scores ranging from 0.8-4.5
  - Reduced prostate volume 15-32%.

References:
Updated 1/21/21.
Treatment: 5-alpha-reductase inhibitors

- **Adverse Effects:**
  - Decreased libido (6.4%)
  - Erectile dysfunction (8.1%)
  - Ejaculatory disorder (0.8%)
  - Gynecomastia (0.5%) / breast tenderness (0.4%)

- **Additional points:**
  - Indicated for:
    - Moderate to severe LUTS
    - Patients with prostate volume > 30 ml; **most beneficial when >40 ml**
  - **50% drop in PSA** with 9-12 months’ use of 5-ARI. **Caution when interpreting “normal levels”**.
  - Counsel patients on **slow onset of action**: 3-6 months.


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Treatment: PDE-5 inhibitor

- **Mechanism:**
  - Phosphodiesterase inhibitor, type 5, with cross-reactivity of other types found in prostate causes a vasodilation effect, however the mechanism leading to improvement in urinary symptoms is unknown.

- **Outcomes:**
  - Improvements in LUTS observed with use of **sildenafil, tadalafil, and vardenafil**
  - Mean increase in flow rate **0.2.4ml/s**
  - Reduction in symptom scores ranging from **1.4-4.6 points**

- **Adverse Effects:**
  - Headache (15%), dyspepsia (4-10%), and flushing (3-11%) - dose dependent relationship
  - Contraindicated in NYHA class 3+ CHF

- **Additional points:**
  - Only tadalafil has FDA approval for BPO/LUTS at 5 mg daily dosing.
  - Generic status makes this an option for more patients

Treatment: Anticholinergics

- Drugs: oxybutynin, tolterodine, fesoterodine, trospium, darifenacin, solifenacin
- Mechanism: Anticholinergics block the acetylcholine signal at the neuromuscular junctions of the detrusor muscle → inhibition of detrusor contractions
- Rationale: Minimize LUTS from detrusor overactivity occurring with or independently of BPH
- Outcome
  - Addition of anticholinergics to therapy for BPH improved symptom scores by 6-8.5 with mixed effects on flow and post-void residual
  - Low acute urinary retention rate of 0.3% at 12 weeks of follow-up.
- Adverse Effects:
  - Dry mouth (20-71%), constipation (10-21%), blurry vision (5%), dizziness (up to 16%)
  - Cognitive effects (highest: oxybutynin, lowest: darifenacin and trospium)
- Additional considerations:
  - Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of anticholinergics in men of any age with LUTS are not yet available.
  - Relative contraindication when post-void residual > 150 ml


Treatment: Beta-3 agonists

- Drugs:
  - Mirabegron (Myrbetriq®)
  - Vibegron (Gemtesa®)
- Mechanism:
  - Beta-3 is the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.
- Outcome
  - Systematic review demonstrates mirabegron significantly reduced nocturia episodes, incontinence episodes and mean number of micturitions compared to placebo and tolterodine
  - Similar treatment-emergent adverse event rates as placebo.
- Adverse Effects (rare):
  - Hypertension, UTI, headache, nasopharyngitis


Treatment: Combination therapy

- Combinations of α1-blockers and 5-ARI drugs have been extensively studied
  - Combination therapy demonstrated the greatest risk reduction (66%) in clinical progression of LUTS/BPH, acute urinary retention, renal insufficiency, recurrent urinary tract infection, and urinary incontinence.
  - Combination therapy with α1-blocker and anticholinergic vs beta-3 agonist also supported in RCTs
- Low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPO offers no advantages in symptom improvement over either agent alone.

Anecdotal comments

- If you don’t ask about it, many men will not tell you it’s a problem.
- Common ≠ normal
- Isolated nocturia → Think about OSA!
- Healthy young (<40 y/o) male with moderate/severe LUTS and no s/s of infection → consider pelvic floor dysfunction (Rx: pelvic floor physical therapy)
Treatments: Surgical

Indications:
- BPO/LUTS refractory to medical therapy OR a desired surgical alternative
- Urinary retention due to BPO
- Recurrent UTI or urosepsis
- Recurrent gross hematuria or bladder calculi due to BPO
- Renal insufficiency secondary to BPO


Treatments: Surgical: Options...

TURP

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TURP

UROLIFT®

BPH Relief. In Sight.™

Simple prostatectomy

AQUABEAM®

ROBOTIC SYSTEM
Treatments: Surgical

Transurethral procedures

- Ablative / extirpative therapies
  - TURP
  - Laser therapies – thulium, holmium, KTP lasers: ablative and laser enucleation techniques (AKA HoLEP or ThuLEP)
  - Aquablation

- Minimally invasive surgical therapies (MIST)
  - Transurethral needle ablation (TUNA) of the prostate - no longer recommended
  - Transurethral microwave thermotherapy (TUMT) – lack of efficacy – obsolete
  - Prostatic urethral lift (UroLift ™)
  - Convective Water Vapor Therapy (Rezum ™)
  - Prostatic stents (iTind)
  - Intra-prostatic injection – multiple agents currently under investigation

Simple prostatectomy (open, laparoscopic, robotic)

Prostatic arterial embolization – not recommended

https://www.auanet.org/guidelines/guidelines/benign-prostatic-hyperplasia-(bph)-guideline

Treatments: Transurethral resection of the prostate

An electro-cautery loop is used to resect redundant prostatic tissue creating a wider urethral channel.
Treatments: TURP

Advantages
- Gold standard treatment for BPH with established durability and safety
- Best improvements in validated QOL metrics: Change in flow (10-18 ml/s), symptom score (14 points)
- Most durable results as shown by studies with a follow-up of 8-22 years
- Lowest re-operation rate: 3-8%

Disadvantages:
- Sexual dysfunction (ejaculatory - 60%, ED - rare)
- Urethral stricture / bladder neck contracture risk ~0-4% risk
- Incontinence - 10%, but usually urge-related and self-limited
- Postop catheterization (1-7 days)
- Post-procedural symptoms 2-6 weeks (dysuria, urgency, frequency, hematuria, urge incontinence)
- Blood loss (avg 0.6-1.6g/dL) and urinary clot retention (4-5%) (reduced since advent of bipolar TURP in 2001)


Treatments: Laser Prostatectomy

Laser is used to...

... ablate or vaporize the prostate adenoma

OR

... enucleate the prostate adenoma
Treatments: Laser prostatectomy or enucleation

Advantages
- Most RCTs show comparable efficacy to TURP. The enucleation approach may be superior to TURP for very large prostates (>80 ml)
- May be superior for patients on anticoagulation

Disadvantages:
- Average operative time slower compared to TURP
- Similar side-effect profile and recovery period to TURP with regard to post-procedural LUTS
- The enucleation technique has a very steep learning curve - few urologists perform this approach.


Treatments: Image-guided robotic waterjet ablation (Aquablation)

Treatments: Aquablation

Advantages
• Similar outcomes to TURP with lower risk of anejaculation
• Theoretically a faster, more consistent procedure.

Disadvantages:
• Similar to TURP with regard to postop catheterization, healing period, blood loss
• Healing period 2-6 weeks (dysuria, urgency, frequency, hematuria, urge incontinence)
• Requires general anesthesia
• Limitations with prostate size, but not shape
• Limited availability - expensive capital investment

Treatments: Urolift

Advantages
- Mean improvement symptom score - 52%, QOL - 53%, Flow rate - 51% - at 12-months
- Office-based procedural option
- Post-procedural symptom relief within 2 weeks
- No loss of sexual function
- Most patients require no post-procedural catheterization

Disadvantages:
- Inferior results to TURP (Avg IPSS reduction of 11 vs 14)
- Limitations with regard to prostate size/shape
- Not indicated for patients in urinary retention
- Permanent implant – rare risk of misplaced implants requiring re-operation or TURP
- 6.5% progress to TURP in 1 year, 13.6% in 5 years
- Large comparative trials with long-term data lacking


Treatments: Convective water vapor therapy (Rezum®)
Treatments: Convective water vapor therapy (Rezum®)

Advantages
- Mean improvement in IPSS - 11 points, flow rate 6.2 ml/s throughout 12 months
- Office-based procedure
- No loss of sexual function
- Can treat median lobes
- 4.4% re-intervention in 4 years

Disadvantages:
- Inferior results to TURP (Avg IPSS reduction of 11 vs 14)
- Post-procedural catheterization necessary
- Similar recovery period to TURP with regard to post-procedural LUTS
- Large comparative trials with long-term data lacking


Treatments: Prostate stents (iTind®)

1. Implantation
2. Expanded after 5 days
3. Device is removed
Treatments: iTind (temporarily implantable nitinol device)

Advantages
- Mean improvement IPSS - 12 points, Flow rate - 8.4 ml/s at 3 months
- Office-based procedure
- Post-procedural symptom relief within 1 week
- No loss of sexual function
- No post-procedural catheterization

Disadvantages:
- Newer device with short term data (3 years)
- Inferior results to TURP (Avg IPSS reduction of 12 vs 14)
- Limitations with regard to prostate size/shape
- Not indicated for patients in urinary retention
- Large comparative trials with long-term data lacking


Treatments: Simple prostatectomy

- Appropriate alternative for patients in whom transurethral procedures are not feasible due to prostate size
- Reserved for prostates larger than 80ml and/or in patients with large bladder diverticula or bladder stones requiring concomitant procedures
- Simple prostatectomy involves enucleation of the gland with the capsule
- The procedure can be performed open, laparoscopically, or robotically

Microhemosaturia (asymptomatic)
Microhematuria: Relevance

- Kidney & bladder cancer ~ 138,000 cases annually
- Practice-pattern assessments have demonstrated significant deficiencies in the evaluation of patients presenting with hematuria.
- Cystoscopy and imaging occur in < 20% of patients in most series; varies by sex and race.
- Delays in diagnosis of bladder cancer have been suggested to contribute to a 34% increased risk of cancer-specific mortality and a 15% increased risk of all-cause mortality.

Microhematuria (MH):

- Definition
  - >3 red blood cells per high-power field (RBC/HPF) on microscopic evaluation of a single, properly collected urine specimen
- Urine dips have false positives!
  - Dehydration, exercise, hemoglobinuria, menstrual blood, myoglobinuria
- Glomerular sources of MH should have nephrology evaluation (eg. red cell casts, dysmorphic RBCs)
- If MH is identified for other benign condition (eg. UTI), repeat UA should be performed upon resolution of disease process (~ 6 weeks)
Microhematuria: Background

- Likelihood of identifying a malignancy among patients with MH is relatively low but highly dependent on risk factors\textsuperscript{1,2}
  - Overall risk \textasciitilde 3%
  - Low risk patients 0.2%
  - High risk patients 11.1%
  - Gross hematuria 23%
- Benefits and potential harms of diagnostic evaluation must be considered both at the patient and health system level.


Urothelial Cancer Risk Factors

- Risk factors for stratification
  - Age
  - Male sex
  - Smoking history
  - Degree of microhematuria
  - Persistence of microhematuria
  - Gross hematuria - always high risk
- Other risk factors
  - Irritative LUTS
  - Prior pelvic radiotherapy
  - Prior cyclophosphamide/ifosfamide chemotherapy
  - FH of urothelial cancer or Lynch Syndrome
  - Occupational exposures to benzene chemicals or aromatic amines (eg rubber, petrochemicals, dyes)
  - Chronic indwelling foreign body in the urinary tract

Microhematuria: Old guidelines

- Previously advised cystoscopy and CT Urogram for all patients over 35 y/o with microhematuria.

Microhematuria: Risk Stratification

- Low Risk: All of the following:
  - Women age < 50; Men age < 40 yrs
  - Never smoker or < 10 pack-years
  - 3-10 RBC/HFF 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

- Intermediate Risk: Any of the following:
  - Women age 50-59; Men age 40-59 yrs
  - 10-30 Pack-years smoking
  - 11-25 RBC/HFF on one UA
  - One or more additional risk factors for urothelial cancer
  - Previously low-risk, no prior evaluation and 3-25 RBC/HFF on repeat UA

  Cystoscopy and Renal Ultrasound

- High Risk: Any of the following:
  - Women and men age > 60 yrs
  - >30 Pack-years smoking
  - > 25 RBC/HFF on one UA
  - History of gross hematuria
  - Previously low-risk, no prior evaluation and > 25 RBC/HFF on repeat UA

  Cystoscopy and CT Urogram

Note: urine cytology and urine biomarkers not recommended
Microhematuria:

• With this evaluation strategy, a (benign or malignant) cause for hematuria is identified in
  • 57% of patients with asymptomatic microhematuria
  • 92% of patients with gross hematuria
• Following an unrevealing work-up for hematuria:
  • Repeat UA in 1 year
  • Patients with persistent asymptomatic hematuria after a negative initial evaluation —> shared decision making about role for repeat workup

Small renal masses (SRMs)

- **Relevance**
  - SRMs have become important clinical issues in recent years given the increase in “incidentalomas” following growth trends in abdominal imaging.
  - 60,000 new kidney cancers were diagnosed in 2015 in the US, 40% were less than 7 cm at detection (stage I cut point).
  - Early detection of SRMs has not translated to a substantial improvement in cancer-specific survival.

- **Definition: Small renal mass**
  - Solid, enhancing renal cortical mass or Bozniak 3 or 4 complex cysts <4 cm (cT1a)
  - Characterized by cross-sectional imaging (renal US not adequate)

- **SRM statistics:**
  1. Low rates for metastasis (<2%)
  2. Slow growth: on avg (2-3 mm / year)
  3. >15-45% are benign

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Table 2. Risk of Metastatic Renal Cell Carcinoma (RCC) and Benign Lesion Based on Tumor Size

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Benign Pathology</th>
<th>Metastatic (M1) RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 cm</td>
<td>35%–45%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>20%–25%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>2–3 cm</td>
<td>15%–20%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>3–4 cm</td>
<td>15%–20%</td>
<td>2%</td>
</tr>
<tr>
<td>4–5 cm</td>
<td>10%</td>
<td>2%–5%</td>
</tr>
<tr>
<td>5–6 cm</td>
<td>10%</td>
<td>5%–10%</td>
</tr>
<tr>
<td>6–7 cm</td>
<td>5%</td>
<td>5%–10%</td>
</tr>
<tr>
<td>≥ 7 cm</td>
<td>5%</td>
<td>15%–20%</td>
</tr>
</tbody>
</table>

Adapted from Thompson et al., J Urol. 2009;181.
Small renal masses

- Surgical excision may not improve overall survival for all patients with small renal masses.¹,²
- Contemporary studies indicate that patients over the age of 75 are more likely to die of cardiovascular and other non-cancerous comorbidities than of their small renal mass.²,³,⁴
- Active surveillance is non-inferior to primary intervention based on excellent metastasis-free and cancer-specific survival.⁵


Small renal masses

- Current society guidelines support the use of active surveillance in patients with: ¹
  - SRM <2 cm
  - SRM <4 cm in those with competing health risks

SRM Algorithm:

References

• Benign prostatic hyperplasia
• Microhematuria
• Small renal masses

...Updates on common urologic problems

Q & A