Benign Prostatic Hyperplasia: LUTS--BPH and Beyond

Robert Langan, MD, FAAFP

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Dr. Langan earned his medical degree from Albany Medical College, New York, and completed his family medicine residency at Naval Hospital Pensacola, Florida. In 2015, he was named the Pennsylvania Academy of Family Physicians Exemplary Teacher of the Year. He is on the editorial board for FP Essentials™ and is a senior author with The Core Content Review of Family Medicine. Dr. Langan has been published in journals including American Family Physician, Osteopathic Family Physician, and The Journal of Family Practice. His interests cover all aspects of family medicine.

AAFP Learning Objectives

1. Perform a differential diagnosis to distinguish between prostatitis, BPH, and other urologic conditions in male patients.
2. Use current evidence-based recommendations to determine appropriate pharmacologic, surgical, CAM, or watchful waiting treatment strategy.
3. Develop collaborative care plans with patients, emphasizing adherence to prescribed pharmacotherapies.
4. Coordinate referral and follow-up care with other specialists (e.g., urologist, surgeon) when red flags identified during diagnosis and evaluation indicate necessity.

Learning Objectives

OVERACTIVE BLADDER

ACUTE PROSTATITIS

URETHRITIS

BPH

URETHRITIS
AES Question:
Which of the following is MOST accurate about the American Urological Association (AUA) Symptom Index?
1. It is administered by a physician.
2. A 10-point change in symptoms is considered significant.
3. It can be used to guide initial therapy.
4. It has not been validated.
5. It only assesses obstructive symptoms.

AES Question:
Which of the following is MOST accurate about α-adrenergic blockers?
1. They are effective antihypertensive agents.
2. They may be safely combined with PDE-5 inhibitors.
3. More selective agents have fewer CNS side effects.
4. They must be titrated over 6-8 weeks.
5. Long-term use is associated with intraoperative floppy iris syndrome.

AES Question:
Which of the following is MOST accurate about 5α-reductase inhibitors?
1. They are associated with reductions in libido.
2. They produce less symptom relief than α-blockers.
3. They reduce the risk of acute urinary retention and surgery.
4. More selective agents reduce symptoms more than nonselective agents.
5. They are recommended as chemoprophylaxis for patients at high risk for prostate cancer.
Which of the following is MOST ACCURATE about 5α-reductase inhibitors?
1. They are associated with reductions in libido.
2. They produce less symptom relief than α-blockers.
3. THEY REDUCE THE RISK OF ACUTE URINARY RETENTION AND SURGERY.
4. More selective agents reduce symptoms more than nonselective agents.
5. They are recommended as chemoprophylaxis for patients at high risk for prostate cancer.

Lower Urinary Tract Symptoms

What Are Lower Urinary Tract Symptoms (LUTS)?

IRRITATIVE
1. Nocturia
2. Urinary Frequency
3. Urinary Urgency
4. Dysuria

OBSTRUCTIVE
1. Hesitancy
2. Weak Stream
3. Incomplete Bladder Emptying
4. Straining to Void

Urethritis

- Infection-induced inflammation of the urethra
- Typically reserved for STI
- Often asymptomatic
- Most common in men aged 20-24 years
- Symptoms:
  - Urethral discharge
  - Dysuria, worse with first void of day
  - No urinary frequency or urgency

Urethritis

- Gonococcal: Due to Neisseria gonorrhoea (700,000 per year)
- Non-gonococcal: Due to Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium, Trichomonas vaginalis; rarely HSV 1&2, adenovirus, GNR, syphilis (3,000,000 per year)
- Traumatic (s/p catheterization, instrumentation)
- Morbidity uncommon (1-2%), includes urethral stricture, prostatitis, epididymitis, abscess
Urethritis

• Testing:
  – POC: Gram stain, methylene blue/gentian violet stain microscopy, 1st void urine with microscopy
  – NAAT from urine for GC, chlamydia
• Imaging, further testing usually not needed
• Treatment (CDC, 2015):
  – NGU: azithromycin 1 g x 1
  OR doxycycline 100 mg BID x 7 days
  – GU: ceftriaxone 250 mg IM x 1 AND azithromycin 1 g x 1

Pathophysiology

• Pathophysiology is incompletely understood
  – Anatomic obstruction
  – Disruption of neural mediators of smooth muscle (α-adrenergic (1A, 1B, 1D), muscarinic (M2, M3), phosphodiesterase enzymes (type 5))
• Gland size on physical exam or ultrasound does NOT correlate with symptoms
• BPH may be asymptomatic, produce troublesome symptoms (50%), or cause impaired voiding, hydronephrosis and acute renal insufficiency (<1%)

Risk Factors

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<thead>
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<th>Proven</th>
<th>Unproven</th>
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<tr>
<td>Increasing Age</td>
<td>Race (African American)</td>
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<tr>
<td>Genetics</td>
<td>Physical Inactivity</td>
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<td>Obesity</td>
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<tr>
<td></td>
<td>Tobacco Use</td>
</tr>
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<td></td>
<td>Excessive Alcohol Use</td>
</tr>
<tr>
<td></td>
<td>Post Vasectomy</td>
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<td></td>
<td>Metabolic Syndrome/DM</td>
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</tbody>
</table>

BENIGN PROSTATIC HYPERPLASIA

Risk of BPH by Age
History

- PMHX:
  - Conditions that can lead to neurogenic bladder (Parkinson’s Disease, stroke)
  - Conditions that can lead to urethral stricture (STI, trauma, urinary tract instrumentation)
  - Cystitis, prostatitis, bladder tumor
  - Diabetes mellitus

History Continued

- MEDICATIONS
  - Antihistamines (↓ parasympathetic tone)
  - Decongestants (↑ α-adrenergic stimulation)
  - Diuretics (↑ urine production)
  - Opiates (impaired autonomic function)
  - Tricyclic antidepressants (anticholinergic effects)

American Urological Association (AUA) Symptom Index

- 7 question, validated tool to objectively assess the severity of LUTS in men
- Can be self-administered and scored by nurse or physician
- Score ranges from 0 to 35
- A 3-point change in symptoms is considered clinically significant

AUA Symptom Index

- In the past month, how often have you experienced the following symptoms*:
  1. Sensation of not completely emptying your bladder
  2. Need to urinate < 2 hours after urinating
  3. Stopped and started again while urinating
  4. Found it difficult to postpone urination
  5. Had a weak urinary stream
  6. Had to push or strain to begin urination
  7. How many times do you get up at night to urinate?

*0: Not at all          1: Less than 20% of the time          2: Less than 50% of the time
3: 50% 4: More than 50% of the time         5: All the time

AUA Symptom Index Score

<table>
<thead>
<tr>
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*Surgical therapy should be considered if complications are present and/or patient failed medical therapy.

International Prostate Symptom Score (I-PSS)

- First 7 questions are identical to the AUA Symptoms Index; scoring is also identical
- Eighth question:
  - If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?
- Score ranges from 0 (delighted) to 6 (terrible)
Physical Examination

• Mental status
• Palpation of flanks/abdomen
• Inspection of external genitalia
• Digital rectal examination
  – Sphincter tone
  – Anal/rectal masses
  – Size, symmetry, nodules of prostate

Laboratory Evaluation

• Urinalysis
  – Evaluate for UTI, hematuria
• Serum creatinine
  – Exclude obstructive uropathy

Should I obtain a PSA on a man with LUTS?

• European Association of Urology (2017)
  – PSA if diagnosis of prostate cancer will change management
• Canadian Urological Association (2010)
  – PSA if life expectancy >10 years
• American Urological Association (2010):
  – PSA recommended if life expectancy >10 years

PSA and Prostate Volume

PPV: 78% for predicting a prostate volume of >30 mL

Other Evaluation

• Not routinely recommended:
  – Upper urinary tract imaging
  – Postvoid residual urine volume
• Cystourethroscopy is recommended only in patients with additional risk factors
  – Hematuria, urethral injury/stricture, bladder cancer, previous lower urinary tract surgery

AUA Symptom Index Score

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Evidence for Watchful Waiting

- Medical Therapy of Prostatic Symptoms (MTOPS) trial
- Median follow up of 4.5 years
- Annual progression rate 4.5% (defined as increase in AUA score of >4 points, acute urinary retention, or recurrent UTI)
- No renal failure noted

Watchful Waiting Continued

- Watchful waiting ≠ no intervention
- Moderate the use of alcohol
- Moderate the use of caffeine
- Limit salt
- Maintain time-voiding schedule
- Decrease total fluid intake
- Reassess symptoms annually

Pharmacotherapy

- α-Adrenergic blockers
  - Nonselective
  - α1, short-acting
  - α1, long acting
  - α1A selective
- 5α-Reductase inhibitors
- Others

α-Adrenergic blockers

- Obstructive symptoms of BPH may be caused by increased smooth muscle tension in the prostate stroma, urethra, and bladder neck
- α-Adrenergic blockers relax the smooth muscle and may also influence sympathetic / parasympathetic outflows to the bladder

α-Adrenergic blockers

- Partial relief in 48 hours
- Maximum effect in 4 weeks
- Improve symptoms scores by 30-40%
- Lower BP but less effective than thiazides, ACE-I
  - Increased mortality (ALLHAT)
- Do not combine with PDE-5 inhibitors (↓ BP)
**α-Adrenergic blockers**

- Intraoperative Floppy Iris Syndrome
  - Described in 2005 as progressive intraoperative miosis, billowing of a flaccid iris, and iris prolapse towards the incision site during cataract surgery in men who recently started α-blockers
  - α-blockers should not be started prior to planned cataract surgery; insufficient evidence about withholding or discontinuing current therapy
  - Highest risk with tamsulosin

**5-α REDUCTASE INHIBITORS**

- **5-α REDUCTASE**
  - TESTOSTERONE
  - DIHYDROTESTOSTERONE

**5α-Reductase Inhibitors**

- Most beneficial when prostate >40 mL
- Degree of symptomatic improvement similar to that achieved with α-blockers (4-5 points)
- May reduce prostate size and prevent progression of BPH, reducing the risk of acute urinary retention (NNT: 26) and surgical intervention (NNT: 18) after 4 years
- Patients may not notice a change in symptoms for 3-6 months

**5α-Reductase Inhibitors and Cancer Risk**

- Prostate Cancer Prevention Trial (PCPT)
  - Enrolled men >55, PSA <3, to receive finasteride or placebo for 5 years
  - Finasteride arm had:
    - Lower incidence of prostate cancer (NNT: 17)
    - Increased incidence of moderate- to high-grade prostate cancer (NNH: 77)
  - After 18 years, no significant difference in survival between finasteride and placebo
- NOT recommended for chemoprophylaxis
Combination Therapy

- MTOPS Trial (2003)
  - Doxazosin/finasteride combination superior to either
    agent alone in reducing LUTS
- CombAT Trial (2007)
  - Tamsulosin/dutasteride combination superior to either
    agent alone in reducing LUTS
- Conduct Trial (2013)
  - Tamsulosin/dutasteride (fixed dose) combination
    superior to either agent alone in reducing LUTS

AUA BPH Guideline (2014)

- Option: The combination of an alpha-blocker
  and a 5α-reductase inhibitor (combination
  therapy) is an appropriate and effective
  treatment for patients with LUTS associated
  with demonstrable prostatic enlargement
  based on volume measurement, PSA level as
  a proxy for volume, and/or enlargement on
  DRE. (LEVEL OF EVIDENCE C)

Other Pharmacotherapies

- Saw palmetto
  - Most studied phytotherapy; no evidence of efficacy
- Other phytotherapy (lack of evidence):
  - African plum bark, purple cone flower roots, stinging
    nettle, South African star grass, rye pollen extract,
    pumpkin seeds
- Tadalafil (PDE-5 inhibitor)
  - 5 mg daily; FDA approved; small trial over 6 months
    showed 2-3 point improvement

Surgical Therapy

Indications for surgical therapy:
1. Failure of medical therapy
2. Refractory urinary retention
3. Recurrent UTI
4. Persistent hematuria
5. Bladder stones
6. Renal insufficiency

Transurethral Resection of the Prostate (TURP)

- Most common surgical procedure for BPH
- Reduces symptoms in 88% of patients
- Bleeding in 1% of cases
- Long-term complications: retrograde
  ejaculation, impotence, incontinence
- 10% of patients will require retreatment
  within 5 years
Acute Bacterial Prostatitis

- True prevalence and incidence are unknown
- Organism must be identified on culture
  - Coliform bacteria (E. coli, Klebsiella sp., Proteus sp.)
  - N. gonorrhoea and C. trachomatis in at-risk men
- Untreated may lead to sepsis
- Presents with irritative or obstructive LUTS
- Pain may be pelvic, suprapubic
- Systemic symptoms common (fever, chills, malaise, nausea, vomiting)

Acute Bacterial Prostatitis

- DRE should be done but prostatic massage avoided
- Bladder can be palpated if >300 mL urine present
- Focused evaluation:
  - Midstream UA and culture (all), CBC/BMP/blood culture (ill)
  - Imaging not typically required
- Treatment:
  - 4-6 weeks of treatment recommended
  - Sulfa drugs, fluoroquinolones have the best penetration into prostate tissue

Does Prostate Cancer Cause LUTS?

- 1366 men undergoing prostate biopsy
- 706 (52%) diagnosed with prostate cancer
  - Prostate Cancer: IPSS score of 10.6±7.6
  - No Prostate Cancer: IPSS score of 12.7±8.1
- Higher IPSS score associated with lower incidence of prostate cancer

Does Prostate Cancer Cause LUTS?

- 1330 men undergoing prostate biopsy
- 665 (50%) diagnosed with prostate cancer
  - Prostate Cancer: IPSS score of 6.5
  - No Prostate Cancer: IPSS score of 7
- No difference in LUTS between 2 groups

Does the Presence of LUTS Increase the Risk of Prostate Cancer?

- Observational studies have shown that men presenting with LUTS, particularly at a younger age, are more likely to be diagnosed with prostate cancer
- This is likely due to more monitoring done over their lifetime
- Most cancers found are low risk
Comparison of PSA Screening Recommendations

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*Draft recommendation as of 1 June 2017

POSSIBLE BENEFITS
• Die of prostate cancer with no screening: 5 in 1000
• Die of prostate cancer with screening: 4-5 in 1000
• Do not die of prostate cancer because of screening: 0-1 in 1000

POSSIBLE HARMS
• At least 1 false positive screening PSA test: 100-120 in 1000
• Prostate cancer diagnosis: 110 in 1000
• MI due to tx: 2 in 1000
• DVT/PE due to tx: 1 in 1000
• ED due to tx: 29 in 1000
• Incontinence: 18 in 1000
• Death due to tx: <1 in 1000

OVERACTIVE BLADDER

OVERACTIVE BLADDER

• A symptom complex composed of:
  – Urgency
  – Frequency
  – Nocturia
  – Urgency incontinence
• Excludes other medical conditions
  – UTI
  – BPH
  – Neurological conditions

Overactive Bladder H&P

• Important History:
  – Neurological disorders (CVA, MS, spinal cord injury)
  – Mobility deficits
  – Diabetes mellitus
  – Recurrent UTI, gross hematuria
  – Pelvic surgery, pelvic cancer, pelvic radiation
• Important PE:
  – DRE
  – Fluid status
  – Neurological exam

Overactive Bladder Workup

• Recommended workup
  – Urine culture (exclude UTI)
  – PVR (only for obstructive symptoms, history of incontinence or prostate surgery, neurological conditions)
  – Bladder diary (useful for patients prior to starting behavioral changes)
  – Urodynamics, cystoscopy, renal u/s, bladder u/s
  – NOT routinely recommended
Overactive Bladder Treatment

• Behavioral Therapy
• Pharmacotherapy
• Other

Behavioral Therapy (GRADE B Evidence)
– Bladder training, pelvic floor muscle strengthening, weight loss, fluid management
– No one therapy preferred
– May improve symptoms similar to medication
– Most studies done in women with incontinence

Pharmacotherapy
• Oral anti-muscarinics (oxybutynin, tolterodine)
  – SE: dry mouth, dry eyes, blurry vision, urinary retention, cognitive impairment, constipation
• Oral β3-adrenoceptor agonists (mirabegron)
  – Similar efficacy to anti-muscarinics, ↓ SE

Other (GRADE C)
• Medication failure, intolerable SE
• Intradetrusor botulinum toxin
• Peripheral tibial nerve stimulation
• Sacral neuromodulation
• Do NOT use indwelling catheters

Practice Recommendations
• α-blockers are an effective treatment for moderate to severe LUTS due to BPH (SORT A)
• Complementary and alternative therapies are not recommended for BPH (SORT B)
• Referral for surgical therapy for BPH is recommended for medical failure, refractory urinary retention, recurrent UTI, or impaired renal function (SORT A)

Summary

OVERACTIVE BLADDER
ACUTE PROSTATITIS
URETHRITIS
BPH
Questions

REFERENCES


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