Best Practices in Urology: BPH, Hematuria, UTIs

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DISCLOSURES

- Tropikos LLC (maker of Ellura®) – scientific investigator
- PI of NIH Grant (R01DK101719) evaluating novel cystometrics for the sub-characterization of Overactive Bladder
BENIGN PROSTATE HYPERPLASIA (BPH)
BPH Definitions

• Benign Prostatic Hyperplasia (BPH) – a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.¹

• Lower urinary tract symptoms (LUTS) – any storage/voiding symptoms²
  – Storage symptoms – urgency, frequency, urge UI, nocturia
  – Voiding symptoms – hesitancy, postvoid dribble, slow stream

¹AUA Guidelines: BPH. 2010
BPH: Epidemiology

- Multiple definitions based on:
  - Prostate histology
  - Prostate volume
  - Lower urinary tract symptoms
Diagnosis of BPH

• History– GU hx, meds, pelvic surgery, neuro dz
• PE– including a DRE
• Quantification of Urinary Sx – AUASI
• Laboratory tests– UA, PSA (Not Creatinine)
• Frequency/Volume Chart
AUA symptom index

- Seven item questionnaire; graded 0–5
  - 1–Incomplete emptying
  - 2–Voiding < 2 Hours
  - 3–Stopping and Starting
  - 4–Difficulty postponing urination
  - 5–Weak stream
  - 6–Straining to urinate
  - 7–Nocturia

- Mild (0–7); moderate (8–19); severe (20–35)

- QOL question: “If you were to spend the rest of your life with your urinary condition the way it is now, no better no worse, how would you feel?” (Delighted = 0, Terrible = 6)
Frequency–Volume Chart: Polyuria

- Also called: Void Diary
- Polyuria: ≥3L Urine Output/Day
- Nocturnal Polyuria: ≥33% of total urine output occurs at night
\[ \alpha_1 \text{-Adrenergic Blockers in BPH} \]

- **Terazosin**—Long-acting \( \alpha_1 \)-blocker, available in 1-, 2-, 5-, and 10-mg, requires titration
- **Doxazosin**—Long-acting \( \alpha_1 \)-blocker, available in 1-, 2-, 4-, and 8-mg, requires titration
- **Alfuzosin**—Long-acting \( \alpha_1 \)-blocker, available as 10 mg qd, no titration
- **Tamsulosin**—Long-acting \( \alpha_{1A} \)-blocker, available as tablet in 0.4-mg, no titration
- **Silodosin**—Long-acting \( \alpha_{1A} \)-blocker, available as 8mg qd, no titration
α1–Blockers: Efficacy

- Several randomized trials have demonstrated that α1–blockers significantly improve peak flow rate and AUASI score over placebo.
- Flow rate and symptoms improve as early as 2 weeks, with full therapeutic benefit obtained by 2–3 months.

Alpha blockers: Side effects and interactions

- WATCH FOR CHF, don’t use if CHF risk
- DIZZINESS, FATIGUE, ASTHENIA: worse with Terazosin and Doxazosin
- RETROGRADE EJACULATION: worse with Tamsulosin/Silodosin
- USE CAUTION WITH PDE-5 inhibitors
5-ALPHA-REDUCTASE

- Key androgen involved in control of prostate growth
Proscar Long-Term Efficacy and Safety Study (PLESS)

• >3000 men randomized to receive either finasteride 5 mg daily or matching placebo over 4 years
Finasteride in BPH: 
PLESS—Prostate Volume


<table>
<thead>
<tr>
<th>Years</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Finasteride</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>+14</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td>32% reduction in volume</td>
<td>P &lt; 0.001</td>
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</table>

Prostate volume (mean ± SE % change from baseline)

Finasteride in BPH: PLESS—AUASI Score Overall Analysis


Baseline Placebo (n = 1438)

Baseline Finasteride (n = 1437)

Years

Quasi-AUASI score (mean ± SE change from baseline)

0 1 2 3 4

P < 0.001

2 point drop in sx score (similar to Alpha blockers)

Finasteride in BPH: PLESS—Acute Urinary Retention


% of patients

Placebo (n = 1503)

Finasteride (n = 1513)

P < 0.001

>50% reduced risk of retention. Best w/5ARs

**COMBO TX: MTOPS: Risk of AUR**

- **Placebo**
- **Doxazosin**
- **Finasteride**
- **Combination**

<table>
<thead>
<tr>
<th>Risk of AUR</th>
<th>Placebo</th>
<th>Doxazosin</th>
<th>Finasteride</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude Rate per 100 Pt-YRS</td>
<td>Best Solo w 5ARS</td>
<td>Combo even better</td>
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</table>
MTOPS: AUA Symptom Score

AUA SS Improvement at 4 years

- Placebo
- Doxazosin
- Finasteride
- Combination

Best Solo w Alpha Blockers
Combo even better

Treatment Groups
BPH and ED: 1st Level-1 evidence for PDE-5 inhibitor therapy
BPH and ED: Level-1 evidence for PDE-5 inhibitor therapy

- Improvement in IPSS for both Tadalafil and Tamsulosin
- Improvement by one week with durable response
- No Increased AEs vs. Placebo for both drugs but improvement in ED with Tadalafil for sexually active men
Alternative Therapy: Phytotherapies for BPH

- Saw palmetto (Serenoa repens)
- South African star grass (Hypoxis rooperi)
- African plum (Pygeum africanum)
- Stinging nettle (Urtica dioica)
- Rye pollen (Secale cereale)
- Pumpkin seeds (Cucurbita pepo)
UTIs
Epidemiology

- 150 million affected annually worldwide\(^1\)
- Lifetime Prevalence: >50% women, 12% men\(^2\)
- US: 10.5M UTI office visits (0.9% ambulatory visits) and 2–3M ER visits\(^1\)
- Societal Cost: 3.5Billion/Yr in US alone\(^1\)

(1) Flores-Mireles et al. Nature Reviews Microbiology. 13, p269. 2015
Uncomplicated vs. Complicated UTI

- **Uncomplicated**: Individuals who are otherwise healthy and have no structural or neurological UT abnormalities
- **Complicated**: Associated with factors that compromise the urinary tract or host defense: obstruction, urinary retention caused by neurological disease, immunosuppression, renal failure or transplant, pregnancy, foreign bodies such as calculi or catheters

**RISK FACTORS:**
- Female
- Old or Young Age
- Prior UTI Hx
- Sex
- Vaginal Infxn
- Obesity
- Fam Hx

**RISK FACTORS:**
- Indwelling Catheters
- Immunosup
- UT obstruction
- Abx exposure

(1)Flores-Mireles et al. Nature Reviews Microbiology. 13, p269. 2015
Catheter–Associated UTI (CAUTI)

- CAUTI account for 70–80% of complicated UTI
- 1 million US cases/Yr
- Most common cause of secondary blood stream infections
- Risk for CAUTI: prolonged catheterization, female gender, older age, DM
- Enterococci don’t bind to catheters in vitro → NEEDS FIBRINOGEN PRODUCED BY BLADDER UROTHELIUM IN RESPONSE TO CATH INFLAMMATION

http://www.hitecmed.com/foley/058a77d8-968f-0df7-966e-041cf7db2610.shtml

(1) Flores-Mireles et al. Nature Reviews Microbiology. 13, p269. 2015
IDSNA – 2012 Guidelines for Acute Uncomplicated Cystitis (AUC) in Women

**Sx:** acute onset dysuria, frequency, or urgency

- If complicating conditions → Tx as complicated UTI
  - If back pain → Consider pyelo
  - If Vaginal discharge → Consider STD

90% probability of UTI

**Empiric TX for Acute Uncomplicated Cystitis in the US:**
- Nitrofurantoin 100mg BID x 5days
- TMP-SMX 16/800mg BID x 3D (unless Resistance prev >20%)
- Fosfomycin 3 gm single dose (lower efficacy/avoid in pyelo)

UA/C&S NOT NEEDED

http://www.idsociety.org/Organ_System/
UTIs and Sexual Practices

- Increased risk with use of spermicides or vaginal diaphragms\(^1\)
- Alternative Sexual Behaviors\(^2\)

UTIs after Menopause

• Role of vaginal estrogens
  – Small studies show a benefit especially if atrophic vaginitis is seen on exam\(^1\)

Hygiene, behavior, and UTI: Myth Busters

• No association between recurrent UTIs and¹:
  - Pre– or Post–Coital Voiding
  - Frequency of urination
  - Delayed voiding habits
  - Wiping patterns
  - Douching
  - Use of Hot Tubs
  - Bubble Baths
  - BMI
  - Tight Clothing
  - Type of Clothing
  - Volume of fluid consumed

¹Int Urogynecol J (2015) 26:795–804

http://www.topjoltcycle.com/about-us/
http://www.sunleafmedical.com/hot-tubs-beneficial-in-more-ways-than-one/

Recurrent UTI

- **Definitions:** Recurrent Uncomplicated Cystitis
  - 3 UTIs within 12 months
  - 2 UTIs within 6 months

- **Treatment Options**
  - **Continuous Suppressive Tx**\(^1\)
    - Cochrane Review\(^1\) of 19 studies (1120 women): found reduction in pre- and post-menopausal AUC compared to placebo
  - **Self-Start Tx**\(^2\)
    - Several Trials demonstrate efficacy with patient-initiated therapy
  - **Post-Coital Tx**\(^1\)
    - Cochrane Review: “post coital prophylaxis seems to be as effective as daily intake”

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\(^1\) Cochrane Database Syst Rev. 2004;(3):CD001209.
\(^2\) Schaeffer AJ et al., J Urol 161(1):207–211. 1999
Non-Antibiotic Tx for Recurrent UTIs

- Cranberry/Polyanthocyanidins (PACs)
- Methenamine hippurate: 1g po BID
- Urease Inhibitors: Acetohydroxamic acid (AHA)
- D-Mannose
- Probiotics
- Allergy referral for selective ABX desensitization
- ID referral for MDR organisms
- New Stuff
  - Vaccines, e coli chaperone protein inhibitors, Bacterial Interference (OM-89)
GU Work-up for complicated UTIs

- H&P
- Physical Exam
- Cystoscopy
- Upper Tract Imaging
- Urodynamics

TO IDENTIFY TREATABLE SOURCE OF UTI
- CALCULI
- FUNGUS BALLS
- DIVERTICULI
- STRICTURES
- CANCER
- HYDRONEPHROSIS
- NEUROGENIC BLADDER

Hematuria
Asymptomatic Gross vs. Microscopic Hematuria

• THIS IS A NO-BRAINER!
• Referral for GU evaluation is mandatory!
• Much higher rates of malignancy (can be as high as 50%)

AUA Guidelines for Asymptomatic Microscopic Hematuria (AMH): 2012

http://www.auanet.org/education/guidelines/asymptomatic-microhematuria.cfm
AMH: Definition and Risk Factors

- **Definition:** >3RBC/HPF on UA
- **Overall Prevalence of AMH (2–31%)** varies depending on Risk Factors

<table>
<thead>
<tr>
<th>Table 1: Common Risk Factors for Urinary Tract Malignancy in Patients with Microhematuria</th>
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<tbody>
<tr>
<td>Male gender</td>
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<tr>
<td>Age (&gt; 35 years)</td>
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<tr>
<td>Past or current smoking</td>
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<tr>
<td>Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)</td>
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<tr>
<td>Analgesic abuse</td>
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<tr>
<td>History of gross hematuria</td>
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<tr>
<td>History of urologic disorder or disease</td>
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<tr>
<td>History of irritative voiding symptoms</td>
</tr>
<tr>
<td>History of pelvic irradiation</td>
</tr>
<tr>
<td>History of chronic urinary tract infection</td>
</tr>
<tr>
<td>History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents</td>
</tr>
<tr>
<td>History of chronic indwelling foreign body</td>
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</tbody>
</table>
AMH: How many +UAs are needed prior to GU referral?

- AMH caused by serious underlying conditions (malignancy) can be highly intermittent.
- Single sample urinary tract malignancy detection = 3.3%
- Single sample calculus detection = 6.0%
- Single sample urethral stricture detection = 1.4%

**THEREFORE:** REFER FOR GU WORK-UP AFTER ONLY 1 +UA if NO IDENTIFIABLE CAUSE ON H&P
AMH: Is a positive dipstick enough?

NO!

AUA GUIDELINE STATEMENT

Asymptomatic microhемaturia (AMH) is defined as three or greater RBC/HPF on a properly collected urinary specimen in the absence of an obvious benign cause. A positive dipstick does not define AMH, and evaluation should be based solely on findings from microscopic examination of urinary sediment and not on a dipstick reading. A positive dipstick reading merits microscopic examination to confirm or refute the diagnosis of AMH. Expert Opinion
AMH: What’s adequate collection?

- NOT: 1\textsuperscript{st} am void
- NOT: 1\textsuperscript{st} void after vigorous exercise
- NOT: 1\textsuperscript{st} void after sex
- Mid-stream collection (discard 1\textsuperscript{st} 10ml)
  - Males: retract foreskin, cleanse meatus
  - Females: spreading labia, cleanse meatus

http://baligadiagnostics.com/urinary-infection/
AMH: Do we need to worry if the patient is taking anticoagulants?

YES!

AUA GUIDELINE STATEMENT

Microhematuria that occurs in patients who are taking anti-coagulants requires urologic evaluation and nephrologic evaluation regardless of the type or level of anti-coagulation therapy. Recommendation
AMH: When to refer to nephrology?

• Once AMH is confirmed: 1\textsuperscript{st} step of Work-up is Renal Function Testing
  – Calculated eGFR
  – Creatinine
  – BUN

\textbf{WHY?}

• Nephrogenic causes
• IV dye/gadolinium
• If renal malignancy, tx reduces renal function
AMH: When to refer to nephrology?

- Refer for altered renal function, urinary casts, dysmorphic RBCs
- Suggest medical renal etiology for AMH
  - Most common: nephropathies and nephritis
  - Higher rates in patients with \textit{persistent} AMH
  - More common in younger patients (<40)

REMEMBER: EVEN IF NEPHROLOGY REFERRAL REQUIRED, PT STILL NEEDS \textit{GU} EVALUATION
AMH: What’s the best imaging

- CTU—Recommended by American College of Radiology appropriateness committee for AMH
- Multi-detector CTU highest sensitivity/specificity (>90%) for detecting lesions of renal parenchymal and upper tracts

https://www.studyblue.com/notes/n/gu-radiology-/deck/3202004
AMH: Who needs cystoscopy?

- Perform in all patients with risk factors (irritative voiding sx, tobacco use, chem exposures), but can be optional in patients <35 without risk factors

Bladder Tumor


AMH: Follow-up after work-up completed?

AUA GUIDELINE STATEMENTS

If a patient with a history of persistent asymptomatic microhematuria has two consecutive negative annual urinalyses (one per year for two years from the time of initial evaluation or beyond), then no further urinalyses for the purpose of evaluation of AMH are necessary. *Expert Opinion*

For persistent asymptomatic microhematuria after negative urologic workup, yearly urinalyses should be conducted. *Recommendation*

For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered. *Expert Opinion*
THANK YOU