Common GU Issues: Diagnosis and Treatment

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Hematuria

Recurrent UTI
HEMATURIA IN WOMEN
HEMATURIA

• Gross Hematuria
  – Significant GH: ANY = 1 episode

• Microscopic Hematuria
  – Normal healthy adult kidneys may excrete up to 85,000 RBC/hour:
    • 1 – 2 RBC/HPF
  – Significant MH:
    • ≥ 3 RBC/HPF on a properly collected sample
      – Dipstick serves only as a screening test for UA micro
    • Absence of an obvious benign cause.
Source of Bleeding

• Glomerular Hematuria
  – Renal source
  – Needs *nephrologist*

• Non-glomerular (Epithelial) Hematuria
  – Epithelial (renal parenchyma) source
  – Urothelial (collecting system) source
  – Needs *urologist*
Differential Diagnosis for Female Hematuria: Pee on THIS (with 4 T’s)

P  Period (menses) – cyclic pseudohematuria
O  Obstructive uropathy
N  Nephritis
T  Trauma (even vigorous exercise)
T  Tumor (renal, urothelial, urethral, etc.)
T  TB
T  Thrombosis (Renal Vein Thrombosis)
H  Hematologic (bleeding/coagulation disorders)
I  Infection / Inflammation
S  Stones
Common Causes of Hematuria in Women by Age

- **0 – 20:**
  - Poststrep GN
  - Acute UTI
  - Exercise-induced orthostatic hematuria
  - Cong renal issues: UPJ obstruction MCDK,
  - Malignancy: Wilm’s tumor rhabdomyosarcoma, leiomyosarcoma, Renal Cell Ca Transitional Cell Ca

- **20 – 40:**
  - Acute UTI
  - Urolithiasis (stone)
  - Benign recurrent hematuria
  - Bladder tumor

- **40 – 60:**
  - Acute UTI
  - Urolithiasis (stone)
  - Bladder tumor
  - Renal tumor

- **>60:**
  - Bladder tumor
  - Acute UTI
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  - Bladder tumor
  - Renal tumor

- **>60:**
  - Bladder tumor
  - Acute UTI
HEMATURIA EVALUATION

- Microscopic vs Gross?
- Microscopic?
  - Routine outpatient work up
- Gross?
  - Is the patient hemodynamically stable? Vitals? HCT?
  - Clotting? Urinary Retention?
  - Does the patient need a catheter and/or bladder irrigation to evacuate out large clots and keep from clotting off?
  - Or can the patient drink enough fluids to keep urine from clotting (light cherry/pink/clear)?

- Reasons for admission:
  • Resuscitation, correct coagulopathy
  • 3-way irrigation / clot prevention / clot evacuation
HEMATURIA EVALUATION

- UA dipstick
- UA microscopic
- Urine culture
- Urine cytology
- Blood Labs:
  - AMH = BUN/Cr, GFR,
  - GH = BUN/Cr, GFR, + consider CBC-diff, PT/PTT, bleed time
- Lower tract visualization: Office Cystoscopy
- Upper tract visualization:
  - Renal U/S
  - IVP
  - CT - KUB: CT scan w/o IV contrast
  - CT - IVP: CT scan with/wout IV contrast (triple phase)
  - MRI
  - Retrograde Pyelogram
  - Ureteroscopy
HEMATUREIA EVALUATION

• **UA dip**
  - Sens 91-100%; spec 65-99% for 2-5 RBC/HPF
    - FP: myoglobin, free hemoglobin, oxidizing contaminants like Betadine

• **UA micro:**
  - Significant MH:
    - > 3 RBC/HPF on appropriately collected sample *(not defined by UA dip)*
  - RBC casts:
    - Glomerular source: Tamm Horsfall mucoprotein within the renal tubule causing trapping of RBC clusters
    - Refer to nephrologist – may need renal biopsy
  - RBC morphology:
    - Dysmorphic RBC’s = glomerular, tubulointerstitial
    - Isomorphc RBC’s = urothelial
  - Significant Proteinuria:
    - > 2+ proteinuria – needs 24 hr urine
    - > 150 mg protein/24 hr – refer to nephrologist
      (NI healthy adult kidneys excrete 80-150 mg protein/24 hr)
  - Significant Pyuria:
    - > 3 WBC/HPF on clean catch specimen
HEMATURIA EVALUATION

- **UA dip – UA micro:**
  - Pseudohematuria
    - Urine grossly appears red, but UA negative
      - Contamination (menses, other vaginal source)
      - Beets, berries (anthocyanins)
      - Food coloring (rhodamine B)
      - Laxatives (phenolphthalein)
      - Urinary tract analgesics (phenazopyridine)
      - Rifampin
HEMATURIA EVALUATION

• Urine culture

  – UTI on clean catch sample:

  – > 100,000 colonies/ml single organism

  or

  – < 100 colonies/ml single organism, but with significant lower urinary tract symptoms.
HEMATURIA EVALUATION

• **Urine cytology**
  - **NOT** part of initial w/u for asymptomatic microscopic hematuria;
  - Approp use: Persistant AMH after neg w/u or RFs for CA/CIS
  - **Sensitivity** of cytology increases with more aggressive, poorly differentiated tumors
    - Grade I  <50%
    - Grade II  65 – 85%
    - Grade III / CIS  >90%
  - **Subsequent risk** of developing TCCa with + cytology:
    - Asymptomatic patient:  94%  (Bladder 75%;  Upper tract 5%)
    - Symptomatic patient:  70%
  - **If +, needs:**
    - Selective bladder and ureteral washings for cytology / markers
    - Direct urothelial visualization (cystoscopy, ureteroscopy, renoscopy)
    - Biopsy as indicated by direct visual findings
HEMATURIA EVALUATION

• **Lower tract visualization:**
  Office Flexible Cystoscopy:
    - **ALL** patients with **RFs** for GU malignancies
    - IVS, h/o smoking, chemical exposures
    - **ALL** patients > 35 yr old
    - Physician’s discretion for < 35 yr old

• **Upper tract visualization:**
  Renal U/S
  IVP
  CT-KUB: CT scan w/o IV contrast
  CT-IVP: CT scan w-w/o IV contrast (triple phase)
    - no oral/rectal contrast
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Hematuria Algorithm Panel Review

+AMH
(≥ 3 RBC per HPF on UA with microscopy)

Repeat UA after treatment of other cause(s)

Release from care

History & Physical Assess for other potential AMH causes
(e.g., infection, menstruation, recent urologic procedures)

Concurrent nephrologic work up if proteinuria, red cell morphology or other signs indicate nephrologic causes.

Renal Function Testing
Cystoscopy
Imaging (CTU)

If unable to undergo CTU, less optimal imaging options include:
- MR Urogram
- Retrograde pyelograms in combination with non-contrast CT, MRI, or US

Follow up with at least one UA/micro yearly for at least two years

Follow persistent MH with annual UA. Consider nephrologic evaluation. Repeat anatomic evaluation within three to five years or sooner, if clinically indicated.

Release from care

Treatment

Follow up as indicated by diagnosis. Re-evaluate for MH after resolution of identified condition.
HEMATURIA EVALUATION

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• Urine cytology / markers (NMP22, BTA-stat, UroVysion FISH)
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SUMMARY:
Asymptomatic Microscopic Hematuria

Initial Evaluation

1. UA dipstick: simply initial screening tool
2. UA micro: MH > 3 RBCs/hpf on UA micro
3. Renal Function: BUN/Cr, GFR
4. Cystoscopy: if + RF and/or > 35yrs old
5. CT-IVP

1. Cytology – NO role for initial AMH eval
RECURRENT URINARY TRACT INFECTIONS IN WOMEN
RECURRENT UTI

• Most common human bacterial infection

• Fecal flora (*E. Coli*) most common pathogen, assoc with vaginal and periurethral colonization

• 8 million office visits / year
• 200,000 hospitalizations / year

• Estimated cost in US alone $3.5 billion / year
RECURRENT UTI

- 35% of women experience at least one UTI
- 20% of these experience a recurrence
- 11% of all women have a 1 UTI / year
- 5-20% of women have multiple recurrences
  - Recurrent: > 3 in 12 months or 2 in 6 months

  - Genetic predisposition: increased bacterial attachment to epithelial cell receptors

- Intercourse is primary risk factor
  - 85% of women with recurrent UTIs have onset of symptoms within 24-48 hours of intercourse
  - Urinate after sex!
DEFINITIONS: UTIs

- **Uncomplicated** – o/w healthy patients
- **Complicated** - patients with abnormalities (structural or functional)

- **Catheter Associated (CA) “UTIs”**
  - **CA-Bacteriuria:**
    - Defined by a colony count on a urine culture
    - Includes both CA-ASB and CA-UTI
  - **CA-ASB:** CA-asymptomatic bacteriuria
    - Asymptomatic, but significant bacteriuria
  - **CA-UTI:** CA-urinary tract infection
    - Symptomatic, and significant bacteriuria
DEFINITIONS: RECURRENT UTIs

• **Unresolved / Incompletely treated**
  – Inappropriate ATB (choice, dose, course)
  – Drug-resistant organism

• **Persistence**
  – Recurrence of infection from site within the GU tract: stones, diverticuli, fistulae
  – Suspicion high if:
    • UTI recurs within 2 weeks after appropriate ATB treatment
    • Same pathogen is repeatedly isolated

• **Reinfection**
  – Arises from site outside of GU tract
  – Far more common than Persistence
CA-UTIs

- Significant problem: to the patient
  - Morbidity, cost, lost productivity, inconvenience, QOL

- Significant problem: to the health care system
  - Largest component of HAI (Hospital Associated Infections)
  - Medicare/Medicaid not reimbursing for costs to treat CA-UTI
CA-UTI pathogenesis

- Larger bacterial load in urinary tract due to foreign body in communication with “outside world”
  - Bacterial ascendance inside and outside catheter

- Urothelial trauma
  - Catheter
  - Poor drainage
Indications for chronic catheter

• Urinary retention
  – Inability to perform CIC
    • impaired hand fxn
    • cognitive fxn

• NOT incontinence management
Common sense prevention

• Secure catheters to decrease trauma
  – not just a nursing issue

• Maintain drainage

• Adequate fluid intake for 2L UOP/24 h

• Good bowel program
Recommended algorithm for the management of women with recurrent cystitis by primary care providers

Fig. 2. Recommended management of women with recurrent cystitis.
Urologic Evaluation

• History
  – Number, frequency and temporal associations of UTI’s
  – Menopausal status
  – Recent antibiotic use/exposure
  – Sexual history
    • Partners
    • Method of contraception
    • Spermicide use
Urologic Evaluation

• Physical Examination
  – Pelvic examination
    • Quality of the vaginal epithelium
    • Presence of pelvic organ prolapse
    • Urethral palpation for evidence of Skene gland cyst or urethral diverticulum

• Urine culture (UTI on clean catch sample):
  – > 100,000 colonies/ml single organism
  or
  – > 100 colonies/ml single organism, but with significant lower urinary tract symptoms.
Further Urologic Evaluation

• Most of the time this is unnecessary
  – In young, healthy women with lower urinary tract recurrent UTI, imaging and cysto are low yield
    (Urology, 2001; 57:1068-1072)

• However:
  – if you suspect a complicating factor or
  – truly PERSISTANT UTIs
    • Assess PVR / Urodynamics
    • Urinary tract imaging (ultrasound or CT)
    • Cystoscopy
What you hope to find

Staghorn stone

Cystocele

Urethral diverticulum
What you hope to find

Colovesical Fistula

Eroded Mesh Sling

Foreign body in the bladder

Elevated voiding pressures consistent with bladder outlet obstruction
Thorough History and Physical Examination

Normal Examination and No Correctable or Complicating Factors

- Self Start Therapy
- Antimicrobial Prophylaxis
  - Postcoital
  - Continuous
- Non-Antimicrobial Prophylaxis

Hickling et al, Reviews in Urology, vol 15, no2, 2013
Antimicrobial resistance mechanisms:
- Alterations of drug target
- Enhanced drug efflux
- Limitation of drug influx
- Via chromosomal point mutations
- Plasmid mediated
• Extended spectrum β-lactamases (ESBL)
  – Plasmid-borne hydrolytic enzymes that inactivate **penicillins** and **cephalosporins**
  – Present in a variety of gram negative rods

• Carbapenemases
  – β-lactamases that are resistant to carbapenems
    • Most clinically important is **Klebsiella pneumonia carbapenemase** (KPC)

  – KPC detected in **E Coli**, **Proteus**, **Klebsiella**, and **Pseudomonas**
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Normal Examination and No Correctable or Complicating Factors

Self Start Therapy

Antimicrobial Prophylaxis

Postcoital

Continuous

Non-Antimicrobial Prophylaxis

Hickling et al, Reviews in Urology, vol 15, no2, 2013
Non-Antimicrobial Prophylaxis

• Estrogen
• Probiotics
• Dietary Supplements
  – Cranberry
  – D-Mannose
  – Vit C
  – Adequate hydration
• Antiseptics
  • Methenamine Salts (Hiprex)
• Immunoactive prophylaxis
  – Oral immunostimulant (OM-89)
  – Vaginal Vaccine
Vaginal Estrogen

- Proposed mechanism of action:
  - Increases vaginal colonization of lactobacilli, which decreases vaginal pH and thereby decreases mucosal adherence of uropathogens

- Estriol Cream and Estring are the only two formulations that have been studied

- Both studies showed that vaginal estrogens significantly reduced the proportion of women with a UTI, but there was significant heterogeneity and a random effects meta-analysis revealed an insignificant pooled effect
Cranberries

- Mechanism of action: remains unknown
- Proanthocyanidins (PAC) in cranberries inhibit the adherence of P fimbriae of E. coli to the uroepithelial cell receptors

- In the 2013 meta-analysis, cranberry juice and tablets reduced the occurrence of UTI’s compared to placebo in women with r UTI’s (30-40%)

- Conversely, a 2012 Cochrane review concluded that cranberries did not significantly reduce the occurrence of symptomatic UTI, but inclusion criteria for the studies was less strict

- Need 30-35mg PAC for adequate prevention = ELLURA

- Bottom Line: Can’t Hurt, Might Help and the risk to the patient is very low.
JAMA update on Cranberry

• *No difference* in bacteriuria noted with/without cranberry supplements over 1 year.¹

• Accompanying editorial endorsed the use of ATB for prophylaxis.¹

• REBUTTAL²:
  – Patients WITHOUT recurrent UTI history
    • 70% without a UTI in the last year; Only 3% with “recurrent UTIs”
  – Asymptomatic Bacteriuria and WBCs considered a + outcome (UTI)

¹JAMA Oct 2016; Effects of cranberry capsules on bacteriuria plus pyuria among older women in nursing homes: A RCT.
²UROLOGY Nov 2016; Efficacy of cranberry in preventing UTIs: Have we learned anything new?
D-Mannose

- D-Mannose binds to type 1 pili of enteric bacteria, thereby blocking their adhesion to uroepithelial cells
- Reduces bacteriuria in animal models
- 308 women with rUTI randomized to D-mannose, nitrofurantoin, or placebo
  - Overall 32% had r UTI
    - 14.6% D-Mannose, 20.4% nitrofurantoin, 61% placebo
    - D-Mannose RR 0.239, Nitrofurantoin RR 0.335
    - D-Mannose patients had sig fewer side effects

Kranjcec et al, World J Urol, 2013
Methenamine (Hiprex)

- Methenamine salts are hydrolyzed in the urine to form *ammonia* and *formaldehyde*.
- Formaldehyde is bacteriostatic and lacks bacterial resistance.
- Limited data suggest a beneficial dose of 1 gm po BID (Cochrane review 2012).
- Most effective with urine pH < 6.0
  - Given with Vit C 500 mg po BID.
- Contraindication: CrCl <50ml/min
  - Decreased excretion, serum toxicity.
- Generally well-tolerated: rash, GI upset
  - Hemorrhagic cystitis in overdose setting.
OM 89 (Uro-Vaxom®)

- Not available in US
- Daily oral capsule containing 18 heat-killed E Coli strains
  - Stimulates innate immunity by increasing neutrophils and macrophage phagocytosis and via up-regulation of dendritic cells
- 4 studies with 891 participants
  - RR for getting 1 UTI = 0.61, CI 0.48-0.78
  - Half the mean number of UTI’s as placebo
- Recent trial compared OM 89 to daily Nitrofurantoin
  NO BENEFIT; but ... NO BENEFIT for N either.
- Main adverse events: Headache and GI complaints
Vaginal Vaccine

- **Urovac** -- Not currently available in US
- Await Phase 3 Clinical Trials
- **10 heat killed uropathogenic bacteria**
  - 6 E Coli, 1 Proteus, 1 Klebsiella, 1 Morganella, 1 Enterococcus
  - Induces IgG and IgA in the urogenital tract,
  - reducing colonization of the vagina and bladder

- **Available data favors:**
  Primary immunization + monthly boosters
- Phase 2 trial randomized 54 women with rUTI to placebo, primary immunization or primary immunization + booster
  - Time to first recurrence was significantly longer in the booster group
  - No reinfections at 6 months:
    - 55.6% booster
    - 22.2% primary immunization
    - 22.2% placebo
# Antibiotic Prophylaxis

*(1/3rd to 1/4th of treatment dose)*

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-Sulfa</td>
<td>40mg/200mg</td>
<td>Daily or 3x/week</td>
</tr>
<tr>
<td>TMP</td>
<td>100mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50-100mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>125-250mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>125mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>200mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>100mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>3g</td>
<td>every 10 days</td>
</tr>
</tbody>
</table>

Adapted from Hickling et al, Reviews in Urology, vol 15, no2, 2013
Recommended First Line Treatment of Symptomatic UTI

1. Trimethoprim-Sulfamethoxazole DS
   1 tab PO BID x 3 days
2. Nitrofurantoin 100mg BID x 3 days
3. Fosfomycin 3 gm PO Once

4. Fluoroquinolones should NOT be first line therapy
TREATMENT – Simple UTIs

• UTI during pregnancy
  – Need to treat promptly
  – 1/3rd progress to acute pyelonephritis
    • Upper tract dilatation with resultant urine stasis seen during pregnancy

• Pericoital vs daily ATB prophylaxis
  – Cephalosporins
  – PCNs
  – Nitrofurantoin
TREATMENT – CA-UTIs

• ? Symptoms
• ? Constitutionally ill

• Avoid abx if at all possible
  – If no abx:
    • Increase fluids
    • Make sure constipation addressed
  – If abx
    • Obtain abx sensitivities if possible
    • Remember to assess upper tracts if septic
TREATMENT – CA-UTIs

• Culture specific antibiotic use

• Adhere to antibiotic stewardship principles
  – narrow spectrum
  – inexpensive
  – easy to take

• ? Change catheters
MYTHS about CA-UTI

• MYTHS: Certain types of catheters may be better than others at UTI prevention
  – Antibiotic coated
    • Short term benefit only (days)
  – Hydrophilic catheters
    • Minimize trauma
  – Suprapubic vs. urethral

• Fastidious perineal/catheter cleaning
Options when faced with “intractable” UTIs despite above maneuvers

• Fecal microbiotic transplant
  – To eradicate ESBL E.coli colonization

• Ileal conduit diversion/cystectomy
  – Lose native UVJ valves

• ??
Special consideration for women with chronic urethral catheter

➔ Urethral erosion

Related to catheter; NOT related to UTI
Summary: Recurrent UTI

- UTI on clean catch sample:
  - > 100,000 col/ml single organism  or
  - > 100 col/ml single organism + signif LUTS
- Fecal flora (E. Coli) most common pathogen, assoc with vaginal and periurethral colonization
- Intercourse is primary risk factor – Void after sex!

- Unresolved ? – Persistence ? – Reinfection ?
- Recurrence of UTIs – with the same pathogen -- within 2 weeks of appropriate ATB treatment suggests persistence of infection, rather than reinfection, and warrants further evaluation with cystoscopy and upper tract imaging.
Summary: Recurrent UTI

- Exhaust **non-ATB prophylaxis** options first.

- DON’T treat asymptomatic CA-ASB (asymptomatic bacteriuria)

- ONLY treat symptomatic CA-UTIs

- Culture-specific ATB use only

- Narrow spectrum as possible

- Exhaust **non-ATB prophylaxis** options first.
AUA Guidelines at a Glance/ App

QUESTIONS