Progress Meeting 2019
Presentation Title: “Evidence-Based Treatment or Urinary Tract Infections: Simple to Complex”
Presenter: David R. Ellington, MD, FACOG

Presentation Objectives:

- Describe pertinent history in the evaluation of UTIs
- Describe the pathophysiology of UTIs
- Describe diagnostic methods and criteria of various types of UTIs
- Describe techniques, accuracy, sensitivity, and specificity of: dipstick urinalysis, microscopic urinalysis, and urine culture
- Describe indications for upper tract imaging/cystoscopy
- Describe evidence for various treatment options

Presentation Outline:

- Definitions
  - Bacteriuria:
    - presence of bacteria in urine
  - Pyuria:
    - presence of WBC in urine
  - UTI:
    - inflammatory response of the urothelium to bacterial invasion
- What if both are NOT present?
- Bacteriuria without pyuria
  - Colonization
  - Contamination
- Pyuria without bacteriuria
  - Bladder Stones
  - Cancer
  - Bladder Pain Syndrome or Interstitial Cystitis
  - TB

Cystitis – Clinical syndrome

- Dysuria
- Urinary Frequency
- Urinary Urgency
- Suprapubic Pain
**Uncomplicated vs Complicated**

- Uncomplicated UTI
  - Healthy female patient
  - Structurally and functionally normal urinary tract
  - Recurrent uncomplicated UTI’s NOT associated with progressive renal damage

- Complicated UTI
  - Structural or functional abnormality of urinary tract
    - CKD
    - Stones
    - Bladder diverticula
    - UPJ obstruction
  - Higher risk
    - Increased risk of acquiring bacteriuria
    - Increased risk of ascending infection
    - Decreased efficacy of treatment
  - Recurrent complicated UTI’s \(\rightarrow\) progressive renal damage

- Uncomplicated vs Complicated

**Complicated UTI**

- Immunosuppression
- Males
- Pregnant women
- Elderly
- Diabetics with long-term sequelae
- Recent antibiotic use
- Indwelling urinary catheter, stent, PNT
- Urinary tract instrumentation
- Hospital acquired infection
- Long duration of symptoms (>7 days before presentation)

**More Definitions…**

- Unresolved/Persistent infection
  - no response to antimicrobial

- Recurrent Infection
  - \(\geq 2\) UTIs in 6 months, or 3 or more UTI’s in a year
  - Urine culture based diagnoses
  - occurs after documented resolution of preceding infection

- Relapse
  - recurrent UTI caused by same bacteria within 7 days of treatment
  - focus of infection within urinary tract (think bladder calculi)
Epidemiology

- The most common bacterial infection
- 1.2% of office visits by women (11 million visits)
- Annual incidence of 11-12%\(^1\)\(^-\)\(^2\)

Bacteriuria

- Overall prevalence 3.5%
- Increasing prevalence with age
  - 1% in school age girls (5-14 yo)
  - 20% of women >70 yo
  - 80% of women > 80 yo

- Incidence of Urinary Tract Infection (UTI) is high
  - Sexually active women 0.5 to 0.7 UTIs per person-year \(^3\)
  - Post-menopausal women 0.7 UTIs per person-year \(^4\)

Risk Factors

- Behavioral Factors\(^5\)-\(^11\)
  - Sexual intercourse
  - Spermicide use
  - Diaphragm use
  - History of recurrent UTIs
  - New sexual partner
  - History of UTI ≤ 15 years of age
  - Anybody Go to the Movies Last Weekend?

- Anatomic abnormalities
  - Urinary tract obstruction
  - Urinary retention
  - Bladder stones
  - Foreign bodies
  - Vesicovaginal fistula
  - Urethral diverticula
  - Vaginal Prolapse - Cystocele
  - Risk Factors

Genetics

- Increased risk having a mother with a history of UTIs
- Nonsecretors of ABH Blood Group Antigens\(^12\)-\(^13\)
  - Uroepithelial cells demonstrate enhanced adherence of uropathic \(E.\) \(coli\)
- Interleukin (IL)-8 receptor\(^14\)-\(^15\)
- CXCR1\(^16\)
Special Populations
UTI in the Post-Menopausal Women

- Urologic Factors
  - Urinary Incontinence
  - Presence of a cystocele
  - Elevated post-void residual (PVR)
  - History of a UTI before menopause

- General Considerations
  - Decrease in lactobacilli colonization of vagina – Change in vaginal pH
  - Increase in colonization of uropathogens
  - Less likely to have localizing LUTS
  - 80% of women > 80 yo have Bacteriuria
  - Fever, confusion, n/v, falls (Geriatric Population Specific)
  - Less likely to respond to short courses of ABX
  - Increased risk of C. difficile

- Mechanism of Recurrent UTIs in Postmenopausal Women

Special Populations
UTI in Pregnancy

- ASB 4-7% of pregnancies
  - Cystitis, pyelonephritis, preterm labor, low birth weight
  - Up to 30% will develop cystitis
  - 20-40% pyelonephritis
  - Treatment reduces risk of preterm delivery

- General Considerations
  - Incomplete bladder emptying
  - Progesterone - ureteric relaxation and stasis
  - Increased bacterial growth

Risk Factors – Not Supported by Evidence

- Pre- or Post-coital voiding patterns
- Hygiene Patterns
- Beverage Consumption
- Voiding habits (delayed)
- Douching
- Tampons
- Type of undergarments
- Hot Tubs
- BMI
Natural Defenses of Urinary Tract

- Normal flora of vagina and urethra
  - Lactobacilli, Coagulase-negative staphylococci, Corynebacteria, Streptococci
  - Altered by changes in vaginal pH, estrogen, antibiotics, spermicides
- Urine composition
  - High osmolality
  - High urea concentration
  - Tamm-Horsfall protein
- Urine flow/washout effect
- Immune response
  - Neutrophils
  - Lactoferrin
- Bacterial Virulence Factors
  - UPEC (uropathogenic E. coli)
    - Expression of virulence factors (O, K, H antigen)\cite{18,19}
      - Flagella, Type 1 fimbria (P-fimbria and S-fimbria) polysaccharide coatings, etc
    - Allow adherence to perineum and urethra
    - Migration to the bladder/kidneys
      - Inoculation via sexual activity
      - Colonization in postmenopausal women

The Usual Suspects

- 75-90% of UTIs are Escherichia coli
- The rest are by other Enterobacteriaceae
  - Staphylococcus saprophyticus\cite{21}
- Other pathogens
  - Klebsiella
  - Enterobacter
  - Serratia
  - Proteus
  - Pseudomonas
  - Providencia
  - Morganella species
**Presenting Symptoms**
- Acute onset dysuria
- Urinary Frequency
- Urinary Urgency
- Nocturia
- Suprapubic discomfort
- Urinary Incontinence
- Microscopic hematuria
- Gross hematuria uncommon
- Differential Diagnosis
- Vaginitis
- Urethritis
- Herpetic Outbreak
- Neisseria Gonorrhoeae/Chlamydia Trachomatis
- Urethral Diverticulum
- Urethral Stricture
- Pelvic Inflammatory Disease
- Nephrolithiasis
- PBS/IC

**Diagnosis**
- New onset frequency, dysuria, urgency without vaginal discharge or pain
  - PPV 90% for UTI
- Urine Collection
  - Voided vs. Catheterized
  - Suprapubic aspiration...most accurate...pediatrics
- Urinalysis
  - Pyuria (10 Leukocytes per ml)
  - Bacteriuria
  - Hematuria
  - Leukocyte esterase
  - Nitrite
    - reduction of urinary nitrates
    - some bacteria do not reduce nitrates
- Utility of a Dip UA
- Urine dipstick is considered positive if
  - + LE or + Nitrites
  - Sensitivity 75%, specificity 82%[22]
    - In patients w > 100,000 cfu/ml
- Adds very little in symptomatic patients
- Most utility is in patients with complicating factors or unclear diagnosis
  - (OAB and IC)
Diagnosing a UTI

- CDC Diagnostic Criteria
  - Urine culture w > 100,000 cfu/ml of ≤ 2 bacteria **AND**
    - One sign or symptom of cystitis w/o another cause
      - Urgency, frequency, dysuria, SPT and/or fever
  - At least 2 signs or symptoms **AND**
    - UA positive for LE, nitrites OR pyuria
    - + gram stain on spun urine

- Tradition Breaker!
  Important Update
  - Urine Culture
    - No specific cutoff
    - Historically 100,000 cfu/ml
      - 20% chance of contamination rather than infection
      - Up to 50% of women with UTI have lower colony count
    - $10^3$ cfu/ml of known uropathogen in a symptomatic patient
      - Dilute urine, slow growth, antibiotic use, early phase infection
      - Coag-negative staph grows slowly-treat even low colony counts
    - 10-20% of symptomatic women will have negative culture

- Microscopic UA and UTI
- Microscopic UA is not helpful in diagnosing a UTI
  - Approximately 50% of UTIs do not demonstrate hematuria on micro UA
  - Bacteriuria may be absent with low colony count

Considerations for Further Investigation

- Recurrent UTI’s (documented)
- Persistent infection
- Childhood h/o UTI’s
- Hematuria
- Prior pelvic surgery (mesh, suture material)

When To Consider Imaging...

- Severely ill patients
- Persistent fever >72 hours of Abx
- Upper tract abnormalities
- History of stones
- Bacterial persistence
- Suspected urinary obstruction
- Symptoms for > 5 days before presentation
- Urea-splitting organism
Infectious Diseases Society of America (IDSA) Cystitis Recommendations

- Nitrofurantoin 100 mg BID x 5 days
- TMP/SMX 160/800 mg BID x 3 days
  - If resistance < 20% or known sensitivity
  - TMP 100 mg BID x 3 days acceptable alternative
- Fosfomycin trometamol 3 grams x 1 dose ($$$)
- Pivmecillinam—not available in US
- Fluoroquinolones
  - 3 day course
  - 2nd line option
- Beta lactams
  - 3-7 day course
  - 2nd line option
  - Amoxicillin & ampicillin should not be used empirically
  - AUA Recommendations

Uncomplicated UTI (cystitis, some pyelonephritis):

- 3 day course of oral TMP/SMX is 95% effective; 7 days is no more effective.
- If TMP/SMX resistance is > 10 - 20% (U.S. West coast, Europe), use fluoroquinolones.
- Higher percentages of resistance to TMP/SMX also implies possible resistance to ampicillin, cephalosporins, tetracycline.

Other uncomplicated UTI:

- A full 7 - 10 day antibiotic course should be used in patients with: diabetes, symptom duration before treatment of > 7 days, pregnancy, age > 65 years, or past history of pyelonephritis or UTI with resistant organisms
- Resistance Concerns
- Consequence of indiscriminate prescribing practices
- Increase in the prevalence of resistance to amoxicillin and trimethoprim-sulfamethoxazole (as high as 30%)
- Employ local community or hospital data
  - UAB – as high as 33% in 2011
- Resistance rates higher than 15-20% necessitate a change in antibiotic class
- Alternative Therapies
- Probiotics
  - limited data
- Methenamine Salts (hippurate and mandelate)
  - limited data
Alternative Therapies

- Cranberry juice
  - Inhibition of uropathogen adherence to uroepithelium
  - Conflicting Data
- Topical estrogen
  - RCTs support this strategy to normalize the vaginal flora in post-menopausal women
  - Reduces risk of recurrent UTIs
- Continuous Prophylaxis?
- Low dose continuous antibiotic prophylaxis (CAP)
  - Nitrofurantoin, SMX/TMP, TMP, cephalexin, Fluroquinolone
  - Quarter of normal daily dose at bedtime
  - Daily or every other day
  - Avoid nitrofurantoin in elderly
  - 6 months
  - 50% recurrence within 3 months of discontinuation
- Post-Coital Prophylaxis?
  - 92% effective
  - Single dose of antimicrobial agent as soon as feasible after intercourse (After Cuddling...)
  - Nitrofurantoin 50-100mg
  - TMP-SMX 40mg and 200mg
  - or TMP-SMX 80mg and 400mg
  - TMP 100mg
  - Cephalexin 250mg
  - ACOG 2008 Guidelines
**Level A evidence:**
- Screening for and treatment of asymptomatic bacteriuria is not recommended in nonpregnant, premenopausal women.
- Resistance rates higher than 15 to 20% necessitate a change in antibiotic class.
- A 3-day antimicrobial regimen is the preferred treatment duration for uncomplicated acute bacterial cystitis in women, including women aged 65 years and older.
- ACOG 2008 Guidelines

**Level B evidence:**
- The initial treatment of a symptomatic lower urinary tract infection (UTI) with pyuria or bacteriuria or both does not require a urine culture.
- ACOG 2008 Guidelines

**Level C evidence:**
- Beta-lactams, such as first-generation cephalosporins and amoxicillin, are less effective in the treatment of acute uncomplicated cystitis.
- To diagnose bacteriuria, decreasing the colony count to 1,000 to 10,000 bacteria per milliliter in symptomatic patients will improve the sensitivity without significantly compromising specificity.

**Useful Links**
- [www.acog.org](http://www.acog.org)
- [www.cdc.gov](http://www.cdc.gov)
References/Suggested Reading

24. Hooten, TM. Uncomplicated UTIs. NEJM 2012, 366;11.