Evidence-Based Treatments of Urinary Tract Infections

David R. Ellington, MD, FACOG
Assistant Professor
Division of Urogynecology and Pelvic Reconstructive Surgery

Disclosures
No Relevant Disclosures

Case Study
26 year old G0P0 woman calls your office to report:
- 3 days of progressive urinary urgency and dysuria
- She denies fevers, chills, low back pain, or vaginal discharge
- Two months ago you treated her with a 3-day course of Macrolid for presumptive urinary tract infection (UTI), and her symptoms resolved
- She is otherwise healthy, but this episode would make her 4th in the past 12 months.
Objectives

- Participant will be able to:
  - 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

Definitions

- Bacteriuria:
  - Presence of bacteria in urine
  - Infection, colonization, contamination

- Pyuria:
  - Presence of WBC in urine
  - Inflammatory response of urothelium

- UTI:
  - Inflammatory response of the urothelium to bacterial invasion
  - Associated with bacteriuria and pyuria
What if both are NOT present?

- Bacteriuria without pyuria
  - Colonization
  - Contamination

- Pyuria without bacteriuria
  - Bladder Stones
  - Cancer
  - Bladder Pain Syndrome or Interstitial Cystitis
  - TB

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Cystitis

- Clinical syndrome
  - Dysuria
  - Urinary Frequency
  - Urinary Urgency
  - Suprapubic Pain

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Uncomplicated vs Complicated

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

- 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 → progressive renal damage

- Uncomplicated 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)
  - 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)

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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 0.07 UTIs per person-year\(^4\)

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical effect</strong></td>
<td>optimal health, activity, ability to sleep, normal urinary output</td>
<td>infection is recurrent/relapsing; no response to antimicrobial therapy</td>
</tr>
<tr>
<td><strong>Clinical symptoms</strong></td>
<td>back pain, fever, pain on urination, frequency, urgency</td>
<td>fever, chills, dysuria, malaise, clouded mental state</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>mild leukocytes in urine, pyuria</td>
<td>pyuria, pyelonephritis, renal scarring</td>
</tr>
<tr>
<td><strong>Complicated/recurrent UTI</strong></td>
<td>recurrent UTI caused by same bacteria within 7 days of initial infection</td>
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<tr>
<td><strong>Focus of infection</strong></td>
<td>within urinary tract (think bladder calculi)</td>
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\(^{1}\) Fihn, et al. 2003
\(^{2}\) Griebling, et al. 2007
\(^{3}\) Hooten, et al. 1996
\(^{4}\) Jackson, et al. 2004
**Risk Factors**

**Behavioral Factors**
- Sexual intercourse
- Spermicide use
- Diaphragm use
- History of recurrent UTIs
- New sexual partner
- History of UTI ≤ 15 years of age

**Anatomic abnormalities**
- Urinary tract obstruction
- Urinary retention
- Bladder stones
- Foreign bodies
- Enterovesical/urovaginal fistula
- Urethral diverticula
- Vaginal Prolapse - Cystocele
Risk Factors – Other Considerations

- Institutionalization (nursing homes)
- Hospitalization (almost 40% of nosocomial infections)
- Spinal cord injuries
- Diabetes
- Multiple Sclerosis
- HIV/AIDS

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\(^{14-15}\)
  - CXCR\(^{16}\)

12. Lomerberg, et al. 1986
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

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)
- Doucheing
- 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

- Immune response
  - Neutrophils

- Lactoferrin

Bacterial Virulence Factors

- UPEC (uropathogenic E. coli)
  - Expression of virulence factors (O, K, H antigen)
  - 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

Fig. 1. Bacteria affect UPEC pathogenesis in many ways. Colonization of the vaginal and urethral mucosa by UPEC contributes to the development of UTI in the urinary bladder. Processes such as adhesion/fimbria play a role in UPEC pathogenesis. Above, these bacteria are shown to invade the urinary tract after initial adherence to the mucosa.
Mechanism of Recurrent UTIs in Postmenopausal Women

- Falling Estrogen levels
- Changes in vaginal epithelium
- Lactobacilli fail to thrive
- Vaginal pH rises to 7
- Bacteria colonize the vagina
- Ascending bladder infections

The Usual Suspects

- 75-90% of UTIs are Escherichia coli
- The rest are by other Enterobacteriaceae
  - Staphylococcus saprophyticus
  - 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%
  - 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
- Ureaproducing 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 sensivity
  - 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
- Beta lactams
  - 3-7 day course
- 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%)[26,27]
- 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

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**Alternative Therapies**

- Adhesion blockers (D-mannose)
  - Mannosides block adhesion of bacteria
  - No data
- Probiotics
  - limited data
- Methenamine Salts (hippurate and mandelate)
  - limited data

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[27] Gupta, et al. 1999
Alternative Therapies

- Cranberry juice\(^{28-32}\)
  - Inhibition of uropathogen adherence to uroepithelium
- Conflicting Data
- Topical estrogen\(^{33}\)
  - RCTs support this strategy to normalize the vaginal flora in post-menopausal women
  - Reduces risk of recurrent UTIs

Table 4: Strategies for Nonantimicrobial Prevention of Recurrent Asymptomatic Bacterial Cystitis\(^{34}\)

<table>
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| Behavioral counseling        | Recurrent dyspareunia or reduction in frequency of intercourse
gender-insensitive: small interventions in the form of behavioral strategies for conventional or prevention of recurrence

- Respiratory fluids or antibiotics
  - Intravenous or oral administration, various modes of delivery, including oral, rectal, and urinary routes.

- Biological modifiers
  - Estrogen, progesterone, and other hormones

- Topical agents
  - Vaginal creams, suppositories, and ointments

- Adjunctive therapies
  - Topical antibiotics or antifungals

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 than those antimicrobials listed in the Table below.
- 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.

ACUTE UNCOMPROMICATED CYSTITIS AND PYELONEPHRITIS

- Acute uncomplicated cystitis early progresses to severe disease, even if untreated, thus the primary goal of treatment is to ameliorate symptoms.
- New treatment guidelines for cystitis from the Infectious Diseases Society of America recommend that, unless effective, second- or third-generation cephalosporins and amoxicillin-clavulanate are considered to be second-line agents for cystitis, even though these have demonstrated good activity for E. coli, enterococci, and staphylococci.
- With respect to both efficacy and adverse effects, amoxicillin-clavulanate is the only option that is equivalent to first-generation cephalosporins in the treatment of acute uncomplicated cystitis.
- Recurrent cystitis should be managed with prophylactic antimicrobial therapy only after novatrimicrobial provocation testing is not effective.
- Fluoroquinolones have other important indications and thus should be considered second-line agents for cystitis, but they are the drugs of choice for empirical treatment of pyelonephritis.
Case Study

- 26 year old G0P0 woman calls your office to report:
  - 3 days of progressive urinary urgency and dysuria
  - She denies fevers, chills, low back pain, or vaginal discharge
  - Two months ago you treated her with a 3-day course of Macrobid for presumptive urinary tract infection (UTI), and her symptoms resolved
  - She is otherwise healthy, but this episode would make her 4th in the past 12 months:

References/Suggested Reading

24. Hooten, TM. Uncomplicated UTIs. NEJM 2012, 366;11.
References/Suggested Reading


Useful Links

- http://www.idsociety.org/idsa_practice_guidelines/
- www.acog.org
- www.cdc.gov

Questions?
**TMP & SMX/TMP**

- **Mechanism:** Inhibit bacterial folate metabolism
  - Strep, staph, GNR
  - Not pseudomonas
- **Advantages**
  - First line empiric therapy
  - Minimal effect on fecal flora
- **Disadvantages**
  - Resistance increasing
  - Interacts with warfarin
  - SMX/TMP (Bactrim, Septra)
    - Often no more effective than TMP alone
    - Requires dose reduction in renal insufficiency

**Fluroquinolones**

- Ciprofloxacin, Levaquin
- Mechanism: Inhibits bacterial DNA gyrase
- Mostly gram negative activity
- **Advantages**
  - Often first line empiric therapy
  - Only PO antibiotic for Pseudomonas aeruginosa
- **Disadvantages**
  - Not first line for gram positive infections
  - Contraindicated during pregnancy (developing cartilage)
  - Relative contraindication in children
  - Tendon rupture, seizures, false + urine opiate test

**Nitrofurantoin**

- Macrodantin, Furadantin, Macrobid
- Multiple mechanisms of action
- E. coli, staph saprophyticus, often Enterococcus
- **Advantages**
  - Resistance is uncommon
  - Safe during most of pregnancy
  - Avoid near term (neonatal hemolysis)
  - Unlikely to cause candidal vaginitis
- **Disadvantages**
  - Low serum and tissue levels (not adequate for pyelonephritis)
  - Does not cover proteus or pseudomonas
  - 7 days—uncomplicated infections
Nitrofurantoin

- Nausea common—take with food
- Requires dose reduction in renal insufficiency
- Not for pyelonephritis
- Neurotoxicity
- Pulmonary fibrosis/interstitial pneumonitis
- Avoid in G6PD deficiency (hemolysis)

Amoxicillin/Ampicillin

- Not first line empiric therapy—resistance
- Mechanism: Inhibit bacterial cell wall synthesis
- Risks: Candidal vaginitis, acute interstitial nephritis
- Augmentin (amoxicillin/clavulanic acid)
  - Broad spectrum due to beta-lactamase
  - C. difficile colitis
- Ampicillin
- Enterococcus
- Extended spectrum PCN
  - Piperacillin/tazobactam
  - Broad spectrum empiric coverage

Special Populations

UTI in Pregnancy

- Safe during pregnancy:
  - PCN
  - Cephalosporins
  - Clindamycin
- Avoid in 1st trimester:
  - TMP (folate antagonist)
- Avoid near term
  - Nitrofurantoin (hemolytic anemia)
  - Sulfonamides (hyperbilirubinemia)
- 3-day course minimum with post-treatment culture