Urinary Tract Infections: Evidence Based Treatment (From the Simple to Complex)

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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

Disclosures

- No Relevant Disclosures (I wish)
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.

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
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 UTIs → 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
  - (>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\(^4\)

1. Fihn, et al. 2003
2. Griebling, et al. 2007

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

7. Fihn, et al. 1998
11. ACOG PB91 2008
Risk Factors

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

- Genetics
  - Increased risk having a mother with a history of UTIs
  - Nonsecretors of ABH Blood Group Antigens
  - Uroepithelial cells demonstrate enhanced adherence of uropathic E. coli
  - Interleukin (IL)-8 receptor
  - CXCR1

References:
12. Lomberg, et al. 1986
16. Lundstedt, et al. 2007
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

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

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

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**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
  - Mannitoluria protein
- Urine flow/washout effect
- Immune response
  - Neutrophils
  - Lactoferrin

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**Bacterial Virulence Factors**

- UPEC (uropathogenic E. coli)
  - Expression of virulence factors (O, K, H antigen)\(^{18-19}\)
    - 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
  - Hooten, et al. 2001
  - Hooten, et al. 1996
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%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

Table 1: Empirical Treatment of Acute Uncomplicated Cystitis

<table>
<thead>
<tr>
<th>Antibacterial Regimen</th>
<th>Efficacy</th>
<th>Comments</th>
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<tr>
<td>Nitrofurantoin (U.S.)</td>
<td>98%</td>
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<td>TMP/SMX (U.S.)</td>
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<td>Fosfomycin trometamol</td>
<td>90%</td>
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<tr>
<td>Pivmecillinam</td>
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<td>Fluoroquinolones</td>
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<td>Beta lactams</td>
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AUA Recommendations

- **Uncomplicated UTI (cystitis, some pyelonephritis):**
  - A 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 imply possible resistance to ampicillin, cephalosporins, and tetracycline.

- **Other uncomplicated UTIs:**
  - 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

- Adhesion blockers (D-mannose)
  - Mannosides block adhesion of bacteria
  - No data

- Probiotics
  - limited data

- Methenamine Salts (hippurate and mandelate)
  - limited data

Cranberry juice\textsuperscript{28,32}

- Inhibition of uropathogen adherence to uroepithelium
- Conflicting Data

Topical estrogen\textsuperscript{33}

- 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, Fluoroquinolone
  - 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 bacteruria, decreasing the colony count to 1,000 to 10,000 bacteria per milliliter in symptomatic patients will improve the sensitivity without significantly compromising specificity.

Case Study
- 26 year old G0P0 woman calls your office to report:
  - 3 days of progressive urinary urgency and dysuria
  - She denies 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.

KEY CLINICAL POINTS
ACUTE UNCOMPLICATED CYSTITIS AND PYELONEPHRITIS
- Acute uncomplicated cystitis rarely 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 Disease Society of America recommend that antibiotic choice be based on sensitivity to antimicrobial agents, not just antibiotic resistance.
- With respect to both urinary tract infections and the urination of tricyclics, trimethoprim-sulfamethoxazole, cephalosporins, and amoxicillin were considered first-line agents for cystitis, even though these drugs are known to be resistant to trimethoprim-sulfamethoxazole and have suboptimal efficacy in treating cystitis.
- Recurrent cystitis should be managed with prophylactic antimicrobial therapy only when nonantimicrobial preventive strategies are 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.
References/Suggested Reading


References/Suggested Reading


Table 1: Features of Uncomplicated versus Complicated Cystitis and Pyelonephritis.

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<td>Diagnosis</td>
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<td>Matching resistance common and less predictable (antimicrobial resistance not uncommon)</td>
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<td>Afebrile with appropriate agent for recommended antimicrobial therapy</td>
<td>Long-term febrile response, persistent symptoms, or relapse or recurrence regardless of antimicrobial susceptibility; may require instrumentation for care</td>
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* Complicated urinary tract infections (UTIs) are heterogeneous, in that the risk of infection and of treatment failure vary. Current classification schemes are overly simplistic, especially for patients with complicated infections. The value of more complex classification schemes has not yet been shown. MDRAs denotes multidrug-resistant Staphylococcus aureus.

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### Table 4. Strategies for Nonantimicrobial Prevention of Recurrent Acute Uncomplicated Cystitis

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<tr>
<td>Hydration</td>
<td>Increased water intake helps maintain sterile urine and dilute cystitis-producing bacteria.</td>
</tr>
<tr>
<td>Bladder emptying</td>
<td>Voiding every 2–4 hours helps maintain sterile urine.</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>Promotes alkaline urine, which is more effective in eliminating acid urine-producing bacteria.</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Promotes alkaline urine, which is more effective in eliminating acid urine-producing bacteria.</td>
</tr>
<tr>
<td>Cranberry products</td>
<td>Contains compounds that prevent bacteria from attaching to the bladder wall.</td>
</tr>
</tbody>
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*Guards against the four and some of these strategies is appropriate for women who have one or more recurrent UTIs, or who have symptoms of recurrent cystitis as determined by a healthcare provider.*

### Table 5. Strategies for Antimicrobial Management of Recurrent Acute Uncomplicated Cystitis

<table>
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<tr>
<td>Self-diagnosis and self-treatment</td>
<td>If symptoms persist or worsen, self-treatment is not recommended.</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis</td>
<td>Use of prophylactic antibiotics is not recommended for primary prevention of UTIs.</td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>Single dose or intermittent therapy is recommended for women with recurrent UTIs.</td>
</tr>
<tr>
<td>TMP-SMX or TMP alone</td>
<td>Often used for prophylaxis due to its broad spectrum of activity against bacteria that cause UTIs.</td>
</tr>
</tbody>
</table>

### 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
  - Avoid during pregnancy and G6PD deficiency
  - 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)**
  - Broader spectrum due to beta-lactamase
  - C. difficile colitis
- **Ampicillin**
  - Enterococcus
- **Extended spectrum PCN**
  - Piperacillin/tazobactam
  - Broad spectrum empiric coverage

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**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**