Treatment of Acute and Recurring Urinary Tract Infections in Women

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Disclosures

Clinical trainer for The Prometheus Group

Urinary Tract Infection (UTI)

Urinary tract infection (UTI) as an infection of the lower and/or upper genitourinary tract which is diagnosed based on the presence of a pathogen in the urinary tract and associated symptoms
Frequent vs Recurrent UTI (rUTI)

Recurrent
- 2 in 6 months
- 3 in 12 months
- With evidence of cure in between

Epidemiology

40-50% of women will be diagnosed with a UTI in their lifetime

20-30% will have recurrence

Epidemiology

- In 2007 > 8 million ambulatory visits (84% women) in the U.S. due to UTI; 21% were ER visits
- After a single UTI, 30% to 44% of women will have a recurrent UTI; 50% will have a 3rd if they have had 2 UTIs in 6 months
- In a study of college women with a UTI, 19% recurrence within 6 months

References:
Pathophysiology

- *E. coli* causes most (70%–95%) community-acquired UTIs.
- Studies in older women
  - *E. coli* accounts for more than half of UTIs
    - common organisms are *Klebsiella pneumoniae*, *Proteus mirabilis*, and *E. faecalis*
  - *E. coli* is also the most common cause of rUTI (66%)
- Non-*E. coli* pathogens and resistant organisms are more likely to be associated with rUTI


Risk Factors

Uncomplicated UTI

- Sexual activity
- Spermicide use
  - Including spermicide coated condoms, especially if used with a diaphragm.
  - Spermicides alter the vaginal flora and favor colonization of uropathogens

Risk Factors

Recurring UTIs

- History of UTI before age 15
- Maternal UTI history
  - A case-control study of more than 400 women reported an increased risk of rUTIs in women having a first-degree female relative with a history of at least 5 UTIs
- Women with pelvic floor disorders
  - especially postmenopausal women with urinary incontinence.
- Association between postvoid residual of at least 50 mL
- The association with prolapse is unclear

Gupta K, Trautner BW. Diagnosis and management of recurrent urinary tract infections in non-pregnant women. *BMJ* 2013;346:f3140


Risk Factors for UTI

After Surgery for Stress Urinary Incontinence

- Risk (11%) after retropubic vaginal tape with or without concomitant prolapse repair.
- >6 weeks postop, reported UTI in 2.3% to 2.4% of participants in 2 RCTs.
- 2-12 months postop, women with midurethral sling had UTI rate of 2.3%.
- No cases of UTI were reported during a recent 10-year f/u of 71 women with transobturator midurethral slings.

Reducing Risk for UTI?

- Many commonly recommended behaviors
  - wiping away from the urethra
  - voiding before and after intercourse
  - increased frequency of voiding
  - wearing certain types of underwear
  - avoiding douching
  - avoiding hot tubs and bubble baths
  - tampons
- Clinicians should consider the contribution of fecal soilage, as in women with fecal incontinence.

Symptoms

- Dysuria
- Urgency/frequency
- Hematuria
- Suprapubic pain
- In young women
  - 90% probability of a UTI with reported dysuria and frequency in the absence of vaginal discharge or irritation
  - probability of UTI is reduced with hx of vaginal discharge or irritation
- Consider pyelonephritis
  - flank pain, fever and chills, and nausea and vomiting
UTI Symptoms in the Aging Female

- Less clear
- Acute dysuria remains a reliable symptom
- New-onset frequency or urgency
- New-onset urinary incontinence


UTI Symptoms in the Aging Female

- Nontraditional symptoms, such as cloudy or odorous urine may prompt patients to seek care
- Cognitive limitations can cause difficulty reporting symptoms;
  - Family/caregivers may alert health care providers to changes in mentation or energy levels
  - Diagnostic challenge
- Worsening of chronic incontinence or other urinary symptoms not reliable


Uncomplicated vs complicated UTI & Pyelonephritis

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<thead>
<tr>
<th>Variable</th>
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<th>Complicated</th>
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<tr>
<td>Typical patient</td>
<td>Healthy female without urogenital history</td>
<td>Extrinsic, metabolic or anatomical conditions that may increase the risk of treatment failure or serious outcomes (obstructions, stone, pregnancy, nephrogenic diabetes, renal insufficiency, immunosuppression)</td>
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<tr>
<td>Clinical spectrum</td>
<td>Mild to severe pyelonephritis</td>
<td>Mild to life-threatening complications</td>
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<td>Diagnosis</td>
<td>Infection suspected on basis of typical symptoms</td>
<td>Typical or atypical symptoms that are subtle (e.g., having to administer required dosing or altered mental status). Ur and culture indicated</td>
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<td>Empirical antimicrobial</td>
<td>UTI: First line short course antimicrobial. Pyelonephritis: first line oral or IV antimicrobial 5-14 days depending on severity &amp; need for hospitalization</td>
<td>UTI: 2-7 days fluoroquinolone preferred. Pyelonephritis: broad spectrum (piperacillin-tazobactam or carbapenem + vancomycin + minocycline) 14-21 days recommended</td>
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<td>Response to treatment</td>
<td>Predictive with appropriate agent for recommended treatment duration/persistent or early recurrence suggestive presence of complicating factor</td>
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### Physical Exam

- Unnecessary for a woman with infrequent UTI
- Always as part of the rUTI evaluation & repeat as needed if status changes
  - detect underlying etiology
  - findings suggestive of upper tract involvement

### Physical Exam rUTI

- Assess general status
- Palpation for costovertebral angle and suprapubic tenderness.
- Pelvic examination, including bimanual exam
  - Post void residual and cath UA
  - vulvar skin and/or architecture changes
  - urethral diverticulum
  - tenderness in pelvic floor muscles, urethra or bladder
  - vaginal discharge
  - pelvic masses
  - pelvic organ prolapse
  - presence of foreign body (retained pessary or eroded mesh or sutures)

### Diagnosis

Is this a UTI?

- Dipstick
  - Nonspecific (leukocytes and nitrates)
- Urinalysis with reflex culture
  - Not good for women with frequent/recurring UTIs
- Urine culture
  - 72 hours for final results with sensitivities
JAMA 2002

Objective: review accuracy and precision of history taking and physical examination for diagnosis of UTI in women

MEDLINE search 1966-2001

“in all of the included studies, UTI was defined by the presence of bacteriuria”. 

However all women are bacteriuric
Urobiome microbiota in the female bladder

There is clear, reproduced evidence that human urine is not sterile

AND

There is a complex, generally beneficial microbiome in the human urinary tract

H. Pylori

- The discovery of H. Pylori infection revolutionized GI treatment
- Not everyone who was "infected" developed clinically significant disease
- Literature suggests that promoting "good" stomach bacteria can be helpful in treating H. pylori "infection"

Detecting Bacterial DNA 16S rRNA Gene Sequencing

DNA extraction

Amplify V4 region of the 16S rRNA gene

Urine is low biomass:
Some samples do not amplify And thus do not get sequenced
What do we know?

Are the bacteria alive?

Are negative urine culture truly negative?

Standard urine cultures do not grow 98% of known microbes

Urinary Tract Infection (UTI)

Urinary tract infection (UTI) as an infection of the lower and/or upper genitourinary tract which is diagnosed based on the presence of a pathogen in the urinary tract and associated symptoms

This definition assumes symptoms are caused by the detected uropathogens. However, neither the uropathogen detection method nor any specific symptoms are inherent in this UTI definition.

No gold standard

Urinary Tract Infection

Urinary tract infection is among the most common reasons for antibiotic treatment in humans
"UTI" remains deeply entrenched in clinical medicine, fortified by familiarity, convenience, the generally good outcomes and now fading biological plausibility.

In current practice, "I think this patient has a UTI" often means, "I want to give this patient antibiotics".
World Health Organization & United Nations

- Declaration to address rising number of drug resistant infections
- Challenging all health care providers to re-evaluate antibiotic prescribing practices

FDA 2016
New Treatment Recommendations

- Serious side effects associated with fluoroquinolones generally outweigh the benefits for patients with acute sinusitis, acute bronchitis and uncomplicated UTIs who have other treatment options.
- Fluoroquinolones are associated with disabling and potentially permanent serious side effects that can involve the tendons, muscles, joints, nerves and central nervous system.
Clinicians considering intervention should not ask whether the individual has a real "UTI" but should ask instead whether there is evidence that bacteriuria is more likely to benefit than harm this individual.

Microbiome studies suggest that treatment is even less beneficial and more harmful than is already believed.
Infrequent Uncomplicated UTI
Are Antibiotics Required?

- Increasing bacterial resistance
- Significant impact of short courses on gut microbiota
  (same could be true for vaginal and perineal microbiota)
- In 2 RCTs, bacteriologic cure rates 4-7 weeks post tx were only marginally better among the antibiotic group. Symptoms resolved quicker with antibiotics


Frequent/Recurrent UTI

- Mismatched microbiomes (coital UTI)
- Intracellular Bacterial Communities (Biofilms)
Biofilm Formation in the Bladder

Diagnosis
Is this a UTI?

- Dipstick
  - Nonspecific (leukocytes and nitrites)
- Urinalysis with reflex culture
  - Not good for women with frequent/recurring UTIs
- Urine culture
  - Consider expanded protocol
  - Limitations of current standard urine culture

UTI: Goal of Treatment

- Symptom relief
- "Bacteriologic cure" using standard culture
- Sufficient antibiotic therapy to limit resistance
- Most common ESBL-producing E. coli identified has fewer virulence factors than other uropathogens.
  - Virulence appears related to initial antibiotic rx.
Uropathogens of rUTI

The uropathogens associated with rUTI are the same microbes associated with episodic (non-rUTI) UTI episodes. However, non-e-coli pathogens and resistant organisms are more likely to be associated with UTI episodes in women with rUTI.

Diagnosis

- Women with frequent UTI may experience diagnostic delay if clinicians do not review the UTI history.
- Clinicians should order pretreatment urine cultures to document rUTI (culture-proven UTI ≥2 in 6 months or ≥3 in 12 months).
- Although infrequent UTI can be assessed with less rigor and treated empirically, women with frequent UTI who are being formally assessed for rUTI should have detailed symptom assessment and pretreatment urine culture and sensitivity.


International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis & Pyelonephritis in Women 2010 Update

Women with uncomplicated cystitis or pyelonephritis should be treated with an antimicrobial, based on antibiogram and availability.

- Nitrofurantoin 100mg bid x 5 days
- Trimethoprim-sulfamethoxazole 160/800mg (1 DS tablet) bid x 3 days (avoid if resistance prevalence is known to exceed 20% or if used for UTI previous 3 months)
- Fosfomycin trometamol 3 gm single dose (lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)
- Pivmecillinam 400mg bid x 5 days (lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

Consider alternate diagnosis (such as pyelonephritis or complicated UTI) & treat accordingly (see text). Flouroquinolones Resistance prevalence high in some areas. B-lactams (avoid ampicillin or amoxicillin alone; lower efficacy than other available agents; requires close follow up).
### Nitrofurantoin

- Effective only in the lower urinary tract
- Effective against *E. coli* and many gram- species with low levels of resistance.
- Ineffective against
  - some *Proteus* species
  - some strains of *Enterobacter* and *Klebsiella*.
- Duration of treatment 7 to 10 days.
- Recent evidence shows 5-day regimens are effective in uncomplicated UTI

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### Nitrofurantoin

2015 American Geriatrics Society Beers Criteria Update Expert Panel
decrease the CrCl threshold for using Nitrofurantoin from 60 ml/min to 30 ml/min
Based on 2 retrospective studies

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### Trimethoprim-sulfamethoxazole

- Broad-spectrum antibiotic that covers gram+ and most gram- bacteria
  - methicillin-resistant *Staphylococcus aureus*
  - gram-negative bacteria, excluding *Pseudomonas*
- >20% local *E. coli* resistance, consider alternative treatment
- Treatment duration 3-14 days
  - 3-day course has similar efficacy to 5- to 10-day regimens
Fosfomycin tromethamine

- Single dose
  - highly concentrated in the urine
  - urine levels persist 30-40 hrs

- Effective against gram+ and gram- bacteria
  - S. aureus, Enterococcus, Pseudomonas aeruginosa, and K. pneumoniae

- Relatively low levels of resistance
  - drug of choice in infections with multidrug-resistant organisms

- Important therapeutic agent for treatment of extended-spectrum beta-lactamase (ESBL) E. coli

Second-line Antimicrobial Agents
β-lactams, and fluoroquinolones

- First-line medications unavailable or cannot be prescribed
  - allergies or intolerances
  - bacterial resistance

- β-Lactams (such as cefixime and cefpodoxime) have
  - in vitro activity against most gram- uropathogens except Pseudomonas

- Generally, cephalosporins have a lower cure rate than TMP-SMX and fluoroquinolones.

- Less studied β-lactams (cephalexin) can be used if first-line inappropriate.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Rate of AE</th>
<th>Type of AE</th>
<th>Considerations</th>
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</thead>
<tbody>
<tr>
<td>Fosfomycin</td>
<td>5.3-8%</td>
<td>Diarrhea, vaginitis, nausea, headache</td>
<td>Half-life of single dose 30-40 hrs, serious adverse events are rare.</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>5.0-9.6%</td>
<td>Nausea, headache</td>
<td>Decreased efficacy, increased risk of toxicity, baseline Cr, taking potassium supplements.</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>3.0-4%</td>
<td>Nausea, vomiting, rash, headache</td>
<td>Increased risk of toxicity, baseline Cr, hyperkalemia, increased risk of long-term use.</td>
</tr>
<tr>
<td>Penicillin</td>
<td>3.8%</td>
<td>Nausea, vomiting, rash, headache</td>
<td>Increased risk of toxicity, baseline Cr, taking potassium supplements.</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4-27%</td>
<td>Nausea, vomiting, rash, headache</td>
<td>Increased risk of tendonitis, tendinopathy, myasthenia gravis, peripheral neuropathy, QT interval prolongation.</td>
</tr>
<tr>
<td>B-Lactams</td>
<td>10-27%</td>
<td>Nausea, vomiting, rash, headache</td>
<td>Inferior efficacy and more adverse events, associated with a higher risk of collateral damage (selection for ESBL producing strains, MRSA &amp; C.-Diff colitis).</td>
</tr>
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</table>
### β-lactams Not Recommended

Unless there is clear evidence of sensitivity to certain β-lactams, including amoxicillin and ampicillin, these antibiotics should rarely be used because of poor efficacy thought to be due in part to the lack of concentration in the urine.

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### Second-line Antimicrobial Agents

- 3-day fluoroquinolones regimen (ciprofloxacin and levofloxacin)
  - highly efficacious

- Not first-line agents
  - increasing resistance
  - higher expense
  - serious adverse events (2016 Food and Drug Administration warning)

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### Complicating Factors

- Women with complicating factors require additional vigilance in diagnosis:
  - abnormal GU anatomy
  - immunosuppression
  - chronic catheterization
Intravesical antibiotics

- Gentamycin 80mg mixed with 30-60ml saline with overnight dwell
- Most studied antibiotic for treatment UTI
- No RCTs
- All studies reported a meaningful reduction in UTIs
- No elevated serum gentamycin levels were recorded

Prophylactic

- Post coital antibiotic is effective in women with coitally-related rUTI.
- Daily low-dose antibiotic suppression (3-6 months) is effective in non-coitally related rUTI.
  - Trimethoprim 100mg qHS
  - Nitrofurantoin 50-100mg qHS
- Effective non-antibiotic measures:
  - Cessation of spermacides
  - Vaginal estrogen
  - Methenamine
  - D-Mannose

Vaginal Estrogen

- Oral estrogen ineffective for rUTI prevention
- Vaginal estrogen should be used in hypoestrogenic women whenever possible as it clearly decreases UTI recurrence
  - Vaginal tablet twice weekly at bedtime
  - Vaginal cream twice weekly at bedtime, thin film to urethra qHS
  - Vaginal ring change every 3 months (increased compliance)
Methenamine salts

- 2012 Cochrane Review
- Evidence that methenamine hippurate may be effective for preventing UTIs, specifically when used for prophylaxis.
- Methenamine salts are converted to formaldehyde and ammonia in the urine
- Formaldehyde is bacteriostatic and does not induce resistance

Probiotics

- No strong evidence

Cranberry

- Current evidence does not support routine use of cranberry products in the care of women with rUTIs
- RCT of 185 elderly women
- Cranberry capsules (72mg equivalent to 20 oz cranberry juice) vs placebo
- No significant difference in bacteriuria + pyuria
- The study was not powered to detect differences in symptomatic UTI
D-Mannose

- Recent RCT of 308 women with acute UTIs and rUTI history
- Women were first treated for their acute UTI and then

<table>
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<th>Randomized</th>
<th>rUTI rate</th>
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<tr>
<td>2g of D-Mannose daily for 6 months</td>
<td>(15%)</td>
</tr>
<tr>
<td>50mg Nitrofurantoin daily</td>
<td>(20%)</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>(60%)</td>
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The D-Mannose group had significantly fewer side effects and equal adherence.

Immunoactive prophylaxis

- Insufficient evidence to recommend clinical use at this time
- OM-89 is an oral immunostimulant extracted from 18 different heat killed UPEC serotypes.
- Systematic review of four studies (n=891) showed an approximately 50% reduction in the mean number of UTI with a similar rate of adverse events.

Vaginal Vaccination

- Urovac is a vaginal vaccination that contains six serotypes of UPEC, one strain of Proteus vulgaris, Klebsiella pneumoniae, Morganella morgani, and Enterococcus faecalis.
- Pooled results from three small studies suggest a slight reduction in rUTI (RR 0.81, 95% CI 0.68-0.96) but only in the groups that received booster therapy after the primary immunization.