Update in diagnosis and management of UTIs
Brian S. Schwartz, MD
UCSF, Division of Infectious Diseases

I have no disclosures

Lecture outline
- Challenges in cystitis
- Complicated UTI/pyelonephritis
- Asymptomatic bacteriuria
- Recurrent UTIs
- Pre-op urine screening

Case
- 27 y/o woman presents to your clinic with 4 days of dysuria and frequency. Denies vaginal discharge or pelvic pain. Urinalysis reveals:
  - 3+ Leukocyte esterase
  - 1+ Heme
  - 2+ Nitrite
- What do you do next?
Do you obtain a urine culture?
A. Yes
B. No

Do you give empiric antibiotics?
A. No
B. Nitrofurantoin x 5 days
C. TMP-SMX x 5 days
D. Ciprofloxacin x 3 days
E. Cefazolin x 7 days

When should you get a urine culture for uncomplicated cystitis?
- Uncomplicated UTI: culture not needed
  - Will likely be susceptible E coli
- Culture if:
  - Complicated UTIs (pyelo)
  - Recurrent UTIs
  - High local rates of resistance

Hooton TM. NEJM. 2012

UCSF E. coli urine isolates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/clavulanate (when used for lower urinary tract infections)</td>
<td>68%</td>
</tr>
<tr>
<td>Cephalexin (when used for lower urinary tract infections)</td>
<td>90%</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>69%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>73%</td>
</tr>
<tr>
<td>Nitrofurantoin*</td>
<td>97%</td>
</tr>
</tbody>
</table>

Hooton TM. NEJM. 2012
**IDSA guidelines for uncomplicated UTI**

*Goal: Low resistance, low “collateral damage”*

- **Nitrofurantoin**: 100 mg PO BID x 5 days
- **TMP-SMX**: DS PO BID x 3 days  
  – avoid if resistance >20%, recent usage
- **Fosfomycin**: 3 gm PO x 1

*Gupta K. CID 2011*

**Nitrofurantoin in elderly?**

- Study of older women (mean age 79)  
  – Mean GFR was 38 mL/min
- Evaluated for (FQ/TMP-SMX) vs. nitrofurantoin

<table>
<thead>
<tr>
<th>Treatment failure</th>
<th>Low GFR</th>
<th>High GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>516/3,739 (13.8%)</td>
<td>7,759/70,758 (11%)</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>184/1463 (12.6%)</td>
<td>3,683/37,665 (9.8%)</td>
</tr>
<tr>
<td>FQ (cipro/nor)</td>
<td>264/4021 (6.5%)</td>
<td>4,447/74,211 (6.0%)</td>
</tr>
</tbody>
</table>

*Singh N. CMAJ. 2015*

**Safety of nitrofurantoin in elderly?**

- Age > 65 years with Dx cystitis
- N=13,421 (2007-12)
- Evaluated for nitrofurantoin use ≠ lung injury
- Nitrofurantoin exposure ≠ lung injury
- Chronic use ≠ lung injury (aRR 1.53 [1.04-2.24])

*Santos JM. JAGS. 2016*

**Take home on nitrofurantoin and elderly?**

- Less efficacious than FQs
- Unlikely dangerous for Rx
- Danger increase for chronic suppression
Is Fosfomycin the answer?

- Study: RCT (513 patients enrolled)
- Patients: Women > 18 w/ symptoms + UA
- Nitrofurantoin 100 BID x 5 vs. Fosfomycin x 1d

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin</th>
<th>Fosfomycin</th>
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</thead>
<tbody>
<tr>
<td>Clinical (28d)</td>
<td>171/244 (70%)</td>
<td>139/241 (58%)</td>
</tr>
<tr>
<td>Micro</td>
<td>129/175 (74%)</td>
<td>103/163 (63%)</td>
</tr>
</tbody>
</table>

What would you do next?
A. Change to amoxicillin
B. Continue TMP-SMX

Utility of the midstream void culture?
- > 200 pre-menopausal women w/ dysuria
- Midstream void and catheter specimen
- Cultures positive
  - 99% midstream
  - 74% catheter specimens

Utility of the midstream void culture?
- *E. coli, Klebsiella, S. saprophyticus*
  - Strong correlation (10^3) with catheter specimen
- Multiple bacteria in urine (86% midstream)
  - *When E. coli* in midstream, often in catheter specimen
- Enterococcus and Group B strep (10% midstream)
  - Nearly never found in catheter specimens
  - 61% had *E. coli* grew from catheter cultures
- Midstream cultures going to change treatment?
A. Change to amoxicillin
B. Continue present Rx

How is guideline compliance?

Grigoryan. Open Forum Infect Dis. 2015

Ciprofloxacin

Duration according to guideline

Days of treatment for uncomplicated cystitis

Percentage of days

Grigoryan. Open Forum Infect Dis. 2015

TMP-SMX

Duration according to guideline

Days of treatment for uncomplicated cystitis

Percentage of days

Grigoryan. Open Forum Infect Dis. 2015
Treatment of UTI in men

• Diagnosis:
  – Obtain culture
  – Assess for STDs (urethritis)

• Treatment:
  – Quinolone, TMP-SMX favored
  – Duration 7-14 days
  – If recurrent consider prostatitis

Shorter course of antibiotics many be OK in men with UTI?

• 39,149 Veterans with UTI
• Antibiotic duration
  ≤ 7 days: 35% (median 7 days)
  > 7 days: 65% (median 10 days)
• Veterans who received > 7 days:
  – No reduction in recurrences, more C. difficile

ESBL trends at UCSF

Extended Spectrum Beta Lactamase Producing Gram Negative Rods In- and out- Adult and Pediatric Patients

Laboratory diagnosis of ESBL on multiplex and identifi cation.
Co-affected microorganism pathogen isolates.
Empiric Rx of an healthy woman with fever, flank pain, and positive UA?

A. Ceftriaxone 1 gm IV q24
B. Moxifloxacin 400 mg IV/PO q24
C. Nitrofurantoin 100 mg PO q12
D. Cefpodoxime 200 mg PO q12

Empiric treatment of pyelonephritis

- **Recommended**
  - Cipro 500 mg PO/IV q12 (*Levo ok, not Moxi*)
  - Ceftriaxone 1 gm IV q24
- **Not recommended**
  - TMP-SMX
  - Nitrofurantoin
  - Cefpodoxime

**Health-care associated:**
- Ertapenem (Meropenem if critical ill or h/o pseudomonas)

**Catheter-associated UTI**

- **Hard to Dx:**
  - Bacteriuria common
  - Often unable to give symptoms
- **Pathogens**
  - More resistant GNRs
  - Candiduria common, most cases don’t treat
- **Treatment**
  - Change Foley
  - Antibiotics 7-14d

Oral antibiotics active against ESBL Gram negative pathogens

- Fosfomycin for ESBL UTI: 3gm PO QOD x 4-5 doses

**High-Risk for Resistant Bacteria (ESBL)**
- Prior resistant bacteria
- Recent hospitalization
- Recent FQ/B-lactam
- Recent travel to Asia/Middle East/Africa
Case

- 65 y/o female w/ DM presents to clinic for routine evaluation. She has been feeling well. A urinalysis is sent to look for proteinuria and the lab processes for culture because bacteria are seen
- UA: WBC-0, RBC-0, Protein-300
- The next day you are called because the urine culture has >100,000 *Klebsiella pneumoniae*

What do you recommend?
A. No antibiotics indicated
B. Ciprofloxacin and await susceptibilities
C. Repeat culture in 1 week and if bacteria still present then treat

Case

- 65 y/o female w/ DM presents to clinic for routine evaluation. She has been feeling well. A UA is sent to look for proteinuria and when the **leukocyte esterase is +++**, the lab sends culture
- UA: **WBC>=50**, RBC-0, Protein-300
- The next day you are called because the urine culture has >100,000 *Klebsiella pneumoniae*

What do you recommend?
A. No antibiotics indicated
B. Ciprofloxacin and await susceptibilities
C. Repeat culture in 1 week and if bacteria still present then treat
Answers: Antibiotics?

1a. Asymptomatic bacteriuria, no pyuria  
   - no antibiotics indicated

1b. Asymptomatic bacteriuria, with pyuria  
   - no antibiotics indicated

Definition: Asymptomatic bacteriuria

• Bacteriuria without symptoms  
  – Midstream: ≥10^5 CFU/ml  
  – Cath: ≥10^2 CFU/ml

• Pyuria is present > 50% of patients

<table>
<thead>
<tr>
<th>Asymptomatic bacteriuria</th>
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</thead>
<tbody>
<tr>
<td>Pre-menopausal women</td>
</tr>
<tr>
<td>Pregnant women</td>
</tr>
<tr>
<td>Post-menopausal women, 50-70 yrs</td>
</tr>
<tr>
<td>Diabetics</td>
</tr>
<tr>
<td>Elderly in LTC facilities (women, men)</td>
</tr>
<tr>
<td>Pts with spinal cord injuries</td>
</tr>
<tr>
<td>Pts undergoing HD</td>
</tr>
<tr>
<td>Pts with indwelling catheters</td>
</tr>
</tbody>
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Nicolle, CID. 2005

Which patient(s) should be treated for asymptomatic bacteriuria?

A. Patients with T2 paralysis
B. Patients > 75 years of age
C. Patient 1 year post renal transplant
D. Patient undergoing TURP
Who should you treat with asymptomatic bacteriuria?

- Clear benefit
  - Pregnant women
  - Patients undergoing traumatic urologic interventions with mucosal bleeding (TURP)
- Possible benefit
  - Neutropenic

Who does not benefit from Rx of asymptomatic bacteriuria?

- Premenopausal (non-pregnant) women
- Postmenopausal women
- Institutionalized men and women
- Patients with spinal cord injuries
- Patients with urinary catheters
- Diabetics
- Patients > 3 months post renal transplant

Treatment of asymptomatic bacteriuria in diabetic women

- Placebo controlled, RCT (N=105)
- Diabetic women w/ asymptomatic bacteriuria
- Intervention: Antimicrobial vs. placebo x 14d
- 1° endpoint: Time to 1st symptomatic UTI
- 42% Rx vs. 40% placebo, p=0.42

Asymptomatic bacteriuria in renal transplant recipients

- RCT: Antibiotics vs. placebo (N=112)
- Patients: > 2 mo post transplant + ASB
- 1° outcome: Pyelonephritis
  - 7.5% vs. 8.4% (OR 0.88, 95% CI 0.22-3.47)
- 2° outcomes: C diff, UTI, MDR infx, rejection
  - No significance difference
The patient with bacteriuria unable to tell you if they have symptoms?

- No concern for infection = no treatment
- Concern for infection exists
  1. Always look for other sources (blood, lungs, etc.)
  2. If no pyuria, do not treat
  3. If candiduria, most cases don’t treat
  4. Rx for UTI as a diagnosis of exclusion

Is asymptomatic bacteriuria protective?

- 712 women with asymptomatic bacteriuria

<table>
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<tr>
<th>Follow-up</th>
<th>No Antibiotics</th>
<th>Antibiotics</th>
<th>Stats</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>11 (4%)</td>
<td>32 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>6 months</td>
<td>23 (8%)</td>
<td>98 (30%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>12 months</td>
<td>41 (15%)</td>
<td>169 (73%)</td>
<td>p&lt;0.0001</td>
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[Source: Cai T. Clin Infect Dis. 2012]

65 y/o woman has had 3 UTIs in the last 6 months. What would be your next step to prevent recurrent UTIs?

A. Daily suppressive nitrofurantoin  
B. Intra-vaginal estrogen  
C. Cranberry tablets  
D. Urology consult

Recurrent UTIs in women

- 20-30% will have a recurrent UTI in 6 mo
- Risk factors:
  - Frequent sex, spermicide, new partner
  - Genetic: Age of 1st UTI ≤ 15 yrs; Mother h/o UTIs
  - Urinary incontinence

[Source: Scholes D. JID. 2000; Raz R. CID 2000]

Pathogenesis of UTI in women

- Prevent vaginal colonization with uropathogens
- Prevent growth of uropathogens in bladder
- Correct anatomic/neurologic problems
Prevention of recurrent UTIs
• Prevent vaginal colonization with uropathogens
  – Avoid spermicide
  – Oral probiotics
  – Intravaginal probiotics
  – Intravaginal estrogen (post-menopausal)
• Prevent growth of uropathogens in bladder
• Correct anatomic/neurologic problems

Intravaginal estrogen for UTI prevention?

How does this work?
• Alters vaginal mucosa → promotes lactobacillus
  – Reduced pH inhibits growth of enteric flora
• Reverses atrophy of urethral epithelium
  – Improves bladder emptying

Raz R. JID 2001

Intra-vaginal estrogen
Show me the data!
• 93 post-menopausal women with recurrent UTIs

RCT (estriol intravaginal vs. placebo)
~0.5 mg estriol QD x 2 wk → 2x/wk x 8 mo

1° outcome: Recurrent UTIs
~0.5 (estriol) vs. 5.9 (placebo) UTI/pt-yr; p < 0.001

Raz R. NEJM 1993

<table>
<thead>
<tr>
<th>% Colonized with organism</th>
<th>Pre-Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estriol</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>67</td>
</tr>
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Raz R. NEJM 1993
Intra-vaginal estrogen

Show me the data!

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<th>Pre-Rx</th>
<th>Post-Rx</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estriol</td>
<td>Placebo</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>0 → 61</td>
<td>0 → 0</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>67 → 31</td>
<td>67 → 63</td>
</tr>
</tbody>
</table>

Raz R. NEJM. 1993

Prevention of recurrent UTIs

- Prevent vaginal colonization with uropathogens
- Prevent growth of uropathogens in bladder
  - Increase voiding
  - Methenamine hippurate
  - Cranberry juice
  - Postcoital or daily antibiotics
- Correct anatomic/neurologic problems

Can increasing fluids reduce UTI risk?

- Premenopausal women with recurrent UTI
- Randomized: +1.5L/d vs. no change (n=140)
- Fluid group: more fluid, voids, reduce urine Osm
- 1° outcome: recurrent UTIs episodes in 12 m
  - 1.7 vs. 3.2; 95% CI (1.2-1.8), p<0.001

Hooton TM. JAMA Intern Med 2018

Methenamine hippurate

- FDA approved for prevention of recurrent UTI
- Methenamine: formaldehyde
- Reduced UTIs in women with no renal tract abnormalities
  - RR 0.24, (95% CI 0.07 to 0.89)

Cochrane Review. 2012
Finally put to cranberry to rest...

- RCT, placebo controlled
- Subjects: 185 women >64 years
- Intervention: 2 cranberry tabs daily (= 20 oz juice)
- Outcomes:

<table>
<thead>
<tr>
<th></th>
<th>Cranberry</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriuria + Pyuria</td>
<td>29%</td>
<td>29%</td>
<td>0.98</td>
</tr>
<tr>
<td>Sympt UTIs</td>
<td>10</td>
<td>12</td>
<td>NS</td>
</tr>
</tbody>
</table>

Juthani-Mehta M. JAMA. 2016

Postcoital antibiotics

- RCT in college women
- Intervention: 1/2 TMP-SMX SS vs. placebo post-coitol

<table>
<thead>
<tr>
<th></th>
<th>TMP-SMX N=16</th>
<th>Placebo N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI x 6 months</td>
<td>2 (13%)</td>
<td>9 (82%)</td>
</tr>
</tbody>
</table>

Stapelton A. JAMA. 1990

Continuous antibiotic prophylaxis

- Highly efficacious
- Studied regimens:
  - TMP-SMX: 1/2 SS tab nightly or SS 3X/week
  - TMP: 100 mg nightly
  - Nitrofurantoin: 50-100mg nightly
- Associated with antibiotic resistance
- 30% have recurrence 6 mo after stopping

Nicolle LE. Infection. 1992

Prevention of recurrent UTIs

- Prevent vaginal colonization w/ uropathogens
- Prevent growth of uropathogens in bladder
- Correct anatomic/neurologic problems
When to evaluate for anatomic abnormalities in women with recurrent UTIs?

- Rads and cystoscopy unrevealing in most cases
- Red flags suggesting that a urologist is needed
  - Hematuria w/o dysuria
  - Incontinence
  - Elevated creatinine
  - Recurrent Proteus infections (struvite stones)

Management of Recurrent UTIs*

<table>
<thead>
<tr>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid spermicide Increase fluids (+1.5L/d)</td>
<td>Intra-vaginal estrogen Increase fluids (+1.5L/d)</td>
</tr>
<tr>
<td>Methenamine hippurate</td>
<td>Methenamine hippurate</td>
</tr>
<tr>
<td>Post-coital antibiotics</td>
<td>Post-coital antibiotics</td>
</tr>
<tr>
<td>Antibiotic suppression in select cases</td>
<td></td>
</tr>
</tbody>
</table>

*Obtain imaging and/or urology evaluation if hematuria w/o dysuria, elevated Cr, incontinence, stones, recurrent Proteus UTI

Does pre-op asymptomatic bacteriuria predispose to prosthetic joint infections?

- RCT 471 pts for hip replacement
- Pyuria+ → culture+ → randomized
- Treatment vs. placebo for bacteriuria
- Results:
  - No reduction in prosthetic joint infections (PJI)
  - No correlation of urine culture and PJI organisms

Summary

- Nitrofurantoin is 1st choice for uncomplicated cystitis, TMP-SMX ok too
- Be aware of ESBL E. coli and limited Rx options
- Asymptomatic bacteriuria should be treated in select patients only
- Think about non-antibiotic Rx 1st for recurrent UTIs, such as intra-vaginal estrogen, fluids