Urinary tract infections

Brian S. Schwartz, MD
UCSF, Division of Infectious Diseases

Lecture outline

• Asymptomatic bacteriuria
• Uncomplicated UTI
• Complicated UTI/pyelonephritis
• Pathogenesis and management of recurrent UTI
• Urine screening pre-op
• Prostatitis

Question 1a

• 65 y/o female w/ DM presents to clinic for routine evaluation. She has been feeling well. A urinalysis is sent to look for protein and the lab accidently also sends for culture.

• UA: WBC-0, RBC-0, Protein-300
• The next day you are called because the urine culture has >100,000 Klebsiella pneumoniae

1a: What do you recommend?

A. No antibiotics indicated
B. Empiric ciprofloxacin and await susceptibilities
C. Repeat culture in 1 week and if bacteria still present then treat

Question 1b

• 65 y/o female w/ DM presents to clinic for routine evaluation. She has been feeling well. A urinalysis is sent to look for protein and when the leukocyte esterase is positive, the lab reflexively sends for culture.

• UA: WBC->100, RBC-0, Protein-300
• The next day you are called because the urine culture has >100,000 Klebsiella pneumoniae
1b: What do you recommend?

A. No antibiotics indicated
B. Empiric ciprofloxacin and await susceptibilities
C. Repeat culture in 1 week and if bacteria still present then treat

Question 1c

- 65 y/o female w/ DM presents to clinic for evaluation. She complains of dysuria and frequency. A urinalysis and urine culture are sent.
- UA: WBC >100, RBC-0, Protein-300
- The next day you are called because the urine culture has >100,000 Klebsiella pneumoniae

1c: What do you recommend?

A. No antibiotics indicated
B. Empiric 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
1c. Cystitis (symptoms and pyuria)
   - Antibiotics indicated

Definition: Asymptomatic bacteriuria

- Bacteriuria without symptoms
- Pyuria is frequently present > 50% of patients

Asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal women</td>
<td>1-5%</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>2-10%</td>
</tr>
<tr>
<td>Post-menopausal women, 50-70 yrs</td>
<td>3-9%</td>
</tr>
<tr>
<td>Diabetics (women; men)</td>
<td>9-27%; 1-11%</td>
</tr>
<tr>
<td>Elderly in LTC facilities (women; men)</td>
<td>25-50%; 15-40%</td>
</tr>
<tr>
<td>Pts with spinal cord injuries</td>
<td>23-89%</td>
</tr>
<tr>
<td>Pts undergoing HD</td>
<td>28%</td>
</tr>
<tr>
<td>Pts with indwelling catheters</td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td>9-23%</td>
</tr>
<tr>
<td>Long-term</td>
<td>100%</td>
</tr>
</tbody>
</table>

Nicolle. CID. 2005
**Question 2:** Which patient(s) should be treated for asymptomatic bacteriuria?

A. Patients with spinal cord injuries  
B. Patients with indwelling catheters  
C. Prior to transurethral resection of prostate  
D. Pregnant women  
E. C and D

**Who should you treat with asymptomatic bacteriuria?**

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

Nicolle. CID. 2005

**Who does not benefit from Rx for asymptomatic bacteriuria?**

- Premenopausal, nonpregnant women  
- Postmenopausal ambulatory women  
- Institutionalized men and women  
- Patients with spinal cord injuries  
- Patients with urinary catheters  
- Diabetics


**Treatment of asymptomatic bacteriuria in diabetic women**

- Placebo controlled, RCT  
- Diabetic women w/ asymptomatic bacteriuria  
- Intervention: Antimicrobial vs. placebo x 14d  
  - Cipro or TMP-SMX as appropriate  
- 1° endpoint: Time to 1st symptomatic UTI

Harding GKM. NEJM 2003

**Results: treatment of asymptomatic bacteriuria in diabetic women**

- 105 pts enrolled  
- Symptomatic UTI  
  - 42% Rx vs. 40% placebo  
  - RR 1.19 (0.28–1.81), p=0.42  
- Rx group required longer course of Abx when Rx for symptomatic UTI

Harding GKM. NEJM 2003

**If you have been treating asymptomatic bacteriuria unnecessarily, you are not the only one...**
Provider prescribing practice for urine culture + enterococcus?
- 339 hospitalized pts urine + Enterococcus
  - 54% had asymptomatic bacteriuria
    - 1/3 unnecessarily treated with antibiotics
- Pyuria was associated with antibiotic use
- 2% asymptomatic bacteriuria had UTI

Lin E. Arch Int Med. 2012

Inappropriate quinolone use
- Prospective eval of quinolone use in hospital
- Identified 1,773 use days over 6 weeks
- 690 (39%) use days were “inappropriate”
  - #1 cause of inappropriate use was...
    - Asymptomatic bacteriuria/UTIs

Werner NL. BMC Infect Dis. 2011

What about the patient with asymptomatic bacteriuria unable to tell you if they have symptoms?
- Concern for infection? No
  - No treatment
- Concern for infection? Yes
  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. If other source identified, stop UTI treatment

Is asymptomatic bacteriuria protective?
- 712 women with asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Symptomatic UTI (%)</th>
<th>Follow-up</th>
<th>No Antibiotics</th>
<th>Antibiotics</th>
<th>Stats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
<td>11 (4%)</td>
<td>32 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>23 (8%)</td>
<td>98 (30%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>41 (15%)</td>
<td>169 (73%)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>


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Types of symptomatic UTIs

Uncomplicated
healthy women cystitis

Lower tract
cystitis

vs.

Complicated
everyone else

Upper tract
pyelonephritis
Clinical signs and symptoms of UTIs

**Lower tract**
- Dysuria (1.5x)
- Frequency (1.8x)
- Hematuria (2.0x)
- Above with absence of vaginal discharge or irritation (28x)

**Upper tract**
- Fever
- CVA tenderness
- Nausea/vomiting
- Peripheral leukocytosis
- Symptoms of cystitis may not be present

Bent S. JAMA 2002

Laboratory diagnosis of uncomplicated UTI

- Urinalysis
  - Pyuria: 95% sensitive; 71% specific
  - Bacteria visible: 40-70% sensitive
  - Squamous epithelial cells: suggests contamination

- Dipstick
  - Leukocyte esterase
  - Nitrite

Enterobacteriaceae

Bent S. JAMA 2002

Microbiologic diagnosis of UTI

- Uncomplicated UTI
  - culture not needed

- Culture if...
  - Complicated UTIs
  - Recurrent UTIs
  - High local rates of resistance

- What is a positive urine culture?

Fihn SD. NEJM. 2003; Stamm WE. NEJM. 1982

Pathogens causing UTIs

- **E. coli**
- *Staphylococcus saprophyticus*
- Other Gram negative rods
  - *Proteus spp*
  - *Klebsiella spp*
  - *Pseudomonas spp*
- *Enterococci spp*

Czaja CJ. CID 2008

Question: According to the updated Infectious Diseases Society of America Guidelines - what is the 1st line treatment for an uncomplicated UTI?

A. Ciprofloxacin 250mg BID x 3d
B. Nitrofurantoin 100mg BID x 5d
C. TMP-SMX DS BID x 7d
D. Cephalexin 500 mg QID x 7d

IDSA updated guidelines for uncomplicated UTI - March 2011

Goal: Low resistance and 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 2

Gupta K. CID 2011
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Treatment of complicated UTI

• “Complicated UTI” — UTI in everyone other than non-diabetic, non-pregnant women not recently treated for a UTI
• Empiric therapy (7-14 days):
  – Non-pregnant: ciprofloxacin/levofloxacin
  – Pregnant women: Nitrofurantoin or cephalixin

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
  – Increased late UTI recurrences
  – Increase Clostridium difficile infection

Empiric treatment of pyelonephritis

• Recommended
  – Ciprofloxacin 500 mg PO/IV q12 (Levo ok, not Moxi)
  – Ceftriaxone 1 gm IV q24
• Not recommended
  – TMP-SMX
  – Nitrofurantoin
  – Cefpodoxime
• Health-care associated pyelonephritis
  – Use antipseudomonal agent other than fluoroquinolone

Question 4: Recommended empiric Rx of pyelonephritis in a young woman?

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
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**Question 6:** 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:
  - Sex activity: Frequent sex, spermicide, new partner
  - Genetic(?): Age of 1st UTI ≤ 15 yrs; Mother h/o UTIs
  - Urinary incontinence

**Pathogenesis of UTI in women**

- Prevent vaginal colonization w/ uropathogens
- Prevent growth of uropathogens in bladder
- Correct anatomic/neurologic problems

**Prevention of recurrent UTIs**

- Prevent vaginal colonization w/ uropathogens
- Prevent growth of uropathogens in bladder
- Correct anatomic/neurologic problems

**Prevention of recurrent UTIs**

- Prevent vaginal colonization w/ uropathogens
  - Avoid spermicide
  - Intra-vaginal estrogen (post-menopausal)
  - Oral probiotics
  - Intravaginal probiotics
- 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, trigone of bladder = ↓ urge incontinence
  - Improves bladder emptying

Raz R. JID 2001

Intra-vaginal estrogen

Show me the data!

• 93 post-menopausal women w/ recurrent UTIs

- RCT (estriol vs. placebo)
  - 0.5 mg estriol vag cream QD x 2 week →
  - 2x/week x 8 mo
- Primary endpoint: 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>
<th>Estriol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

Raz R. NEJM. 1993

Prevention of recurrent UTIs

- Prevent vaginal colonization w/ uropathogens
- Prevent growth of uropathogens in bladder
  - Methenamine hippurate
  - Cranberry juice
  - Postcoitol or daily antibiotics
- Correct anatomic/neurologic problems

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
Cranberry Juice to prevent UTIs

How does it work?

• Inhibits adhesions produced by *E. coli*
• Only vaccinium berries
  – Cranberry, blueberry, lingonberry, huckleberry
• Lots of studies done
• Many different formulations, many different endpoints

Raz R. CID. 2004

Cranberry Juice and UTIs

most recent meta-analyses

• Wang meta-analysis (included 10 studies)
  – RR: 0.62 (95% CI, 0.49-0.80)
  – Excluded large negative study
• Cochrane review 2012 (included 24 studies)
  – RR 0.86 (95% CI, 0.71-1.04)
  – No benefit seen in subgroups
• Conclusion: small benefit may exist


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?

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

Fowler JE. NEJM. 1981; Mogensen P B J Urol. 1983

Postcoital antibiotics

• RCT in college women
• Intervention:
  – ½ TMP-SMX 55 vs. placebo post-coitol

Stapelton A. JAMA. 1990
Intermittent self-administration of antibiotics

- Healthy women with ≥ 2 UTIs in past 12 mos
- Given sterile cups and Rx for levofloxacin
- 172 episodes of self-initiation performed
  - 84% micro confirmed
- Conclusion: self-treatment can be successful

Gupta K et al Ann Int Med 2001;135:9

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

 TMP-SMX resistance of stool E. coli during TMP-SMX prophylaxis

Management of Recurrent UTIs*

- Pre-menopausal
  - Avoid spermicide
  - Cranberry juice.tabs? Methenamine hippurate
  - Post-coital antibiotics
  - Self-Rx with antibiotics
- Post-menopausal
  - Intra-vaginal estrogen
  - Cranberry juice.tabs? Methenamine hippurate
  - Post-coital antibiotics
  - Antibiotic suppression in select cases

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

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Screening for asymptomatic bacteriuria pre-op?

- When should we do it?
  - Urologic surgeries, particularly TURP
- Is it needed for other surgeries?

Drekonja D. JAMA Int Med. 2013
Pre-op urine culture results and outcomes

- 1,934 ortho, CT, or vasc surg evaluated
- 11% (54) identified with ASB
- 30% (16/54) with ASB received antibiotics
- Surgical site infection:
  - 45% (antibiotics) vs. 14% (none); p=0.03
- UTI
  - 15% (antibiotics) vs. 7% (none)

Drekonja D. JAMA Int Med. 2013

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Prostatitis (NIH classification)

I. Acute bacterial prostatitis (< 1%)
II. Chronic bacterial prostatitis (5-10%)
III. Chronic prostatitis/pelvic pain (80-90%)
   - Inflam and non-inflam forms
IV. Asymptomatic inflam prostatitis (10%)

Lipsky BA. Clin Inf Dis. 2010

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IV. Asymptomatic inflam prostatitis (10%)

Lipsky BA. Clin Inf Dis. 2010

Bacterial prostatitis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dx</th>
<th>Bugs</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (&lt;1%)</td>
<td>Fever/chills, pelvic pain, hesitancy, FUO</td>
<td>Boggy prostate, + Urine Cx, ? US or CT</td>
<td>Enteric GNRs</td>
</tr>
<tr>
<td>Chronic (5-10%)</td>
<td>Recurrent UTIs, mild UTI sx, perineal discomfort</td>
<td>Urine Cx • Pre-/post-prostatic massage; Anatomic evaluation</td>
<td>Enteric GNRs, chlamydia</td>
</tr>
</tbody>
</table>

Schaeffer AJ. NEJM. 2006

Diagnosis of chronic prostatitis

Pre-prostate massage urine cultures

1 minute prostate massage

Post-prostate massage urine cultures

# CFUs of bacteria

Schaeffer AJ. NEJM. 2006
Treating elevated PSAs with antibiotics?

- 153 men in routine clinic practice
  - PSA 4-10 ng/ml and negative digital rectal exam
- Randomized: quinolone for 14d vs. no antibiotics
- Antibiotic group: 60% reduction PSA
- No antibiotic group: 60% reduction PSA
- Conclusion: Do not treat elevated PSAs with abx

Shtricker A. Int Braz J Urol. 2009

Summary

- Asymptomatic bacteriuria should be treated in select patients only
- IDSA now recommend nitrofurantoin as 1st choice for Rx of uncomplicated cystitis
- Be aware of ESBL E. coli and limited Rx options
- Think about non-antibiotic Rx 1st for recurrent UTIs, such as intra-vaginal estrogen
- Consider prostatitis in men with recurrent UTIs

Thank you

brian.schwartz@ucsf.edu