Update in diagnosis and management of UTIs
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- I have no disclosures

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

Case
- 27 y/o female 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

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**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

**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

Hooton TM. NEJM. 2012  
Gupta K. CID 2011
Nitrofurantoin in elderly?
- Study of older women (mean age 79)
  - Mean GFR was 38 mL/min
- Evaluated for Rx failure on different abx
  - Other vs. nitrofurantoin
    - 130/1989 (6.5%) vs. 516/3739 (13.8%), CI 0.36-0.53
- However, higher Rx failure in high GFR group too
- Cipro more effective than nitrofurantoin in all
- Failure rate same for nitrofurantoin vs. TMP-SMX

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])

Take home on nitrofurantoin and elderly?
- May be less efficacious
- Unlikely dangerous for Rx
- Danger increase for chronic suppression

You start TMP-SMX… Day 2 - Urine culture: > 100K CFU/mL of enterococcus (S - Amox; R-TMP-SMX). Clinical: symptoms a little better

A. Change to amoxicillin
B. Continue present Rx
C. Stop all antibiotics
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 (10^2) with catheter specimen
- Mixed culture (86%)
  - E. coli often in catheter specimen
- Enterococcus and Group B strep (10% cultures)
  - Nearly never found in catheter specimens
  - 61% had E. coli grew from catheter cultures
- Midstream cultures going to change treatment?

You start TMP-SMX... Day 2 - Urine culture: > 100K CFU/mL of enterococcus (S - Amox; R-TMP-SMX). Clinical: symptoms a little better

A. Change to amoxicillin
B. Continue present Rx
C. Stop all antibiotics

How is guideline compliance?
TMP/SMX, only 16% of all visits had guideline recommended duration of therapy (3 days), whereas 71% had longer than guideline recommended duration. For showing effectiveness with a shorter duration of therapy prescription of any particular agent in the logistic regression model.

- **Figure OFID 3**
  - **A)** Duration of treatment for ciprofloxacin shows the distribution of the duration of therapy for all visits with uncomplicated cystitis. For ciprofloxacin, 29% of all visits led to a prescription according to guideline recommendations.
  - **B)** Duration of treatment for trimethoprim-sulfamethoxazole (TMP-SMX) shows the distribution of the duration of therapy for all visits with uncomplicated cystitis.
  - **C)** Duration of treatment for nitrofurantoin shows the distribution of the duration of therapy for all visits with uncomplicated cystitis.

Our study demonstrates discrepancies between the 2010 IDSA guidelines concerning the duration of treatment for uncomplicated cystitis. TMP/SMX was a recommended first-line agent. Despite being recommended as a first-line agent (FQs, TMP-SMX, and nitrofurantoin), the prescribing rate of nitrofurantoin was 1.33 times higher than the rate for other antibiotics, with most prescriptions being a sign of trend toward decreasing nitrofurantoin use in the 2010 IDSA guidelines and clinical practice, a situation commonly observed.

### DISCUSSION

- **Predictors of Antibiotic Treatment Duration**
  - **Value**
    - **β**
    - **Referent**
    - **-lactams, methenamine, clindamycin**
    - Includes amoxicillin-clavulanate, other antibiotics, and azithromycin.
    - The rate of concordance with the IDSA guidelines concerning the duration of treatment was also low for older age and presence of diabetes.
    - **Presence of diabetes**
      - **β** 0.45 (.08 to .05) <.001
      - **Referent** 1.68) <.001
    - **Other antibiotics**
      - **β** 0.81) .008
      - **Referent** -.37 to .30) 0.83

- **Pregnant women:** Our study demonstrated discrepancies between the 2010 IDSA guidelines and clinical practice, observed.

### Treatment of complicated UTI

- **Complicated**
  - Anyone other than a healthy woman without recurrent infections
  - Empiric therapy (7-14 days):
    - Non-pregnant: ciprofloxacin/levofloxacin
    - Pregnant women: Nitrofurantoin or cephalexin
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 may 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*

Drekonja DM. JAMA Intern Med. 2013

ESBL trends at UCSF

Oral antibiotics active against ESBL Gram negative pathogens

Prakash V. AAC 2009

n=46
Fosfomycin (Monorol)
- Activity against Gram pos and neg
- FDA approved for Rx of uncomplicated UTI
- Treatment for complicated infections:
  - 3 gm (mixed in 4 oz H$_2$O) Q2 days for 7-14 d

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

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

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: B-lactam
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

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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
Case

• 65 y/o female w/ DM presents to clinic for evaluation. **Complains of dysuria and frequency.** A UA and urine culture are sent.
• UA: **WBC->50,** 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
  – Midstream: $\geq 10^5$ CFU/ml
  – Cath: $\geq 10^2$ CFU/ml
• Pyuria is present $> 50\%$ of patients
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

Asymptomatic bacteriuria

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</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</td>
<td>9-27%</td>
</tr>
<tr>
<td>Elderly in LTC facilities (women; men)</td>
<td>15-50%</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>25-100%</td>
</tr>
</tbody>
</table>

Nicolle. CID. 2005
**Treatment of asymptomatic bacteriuria in diabetic women**

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

Harding GKM. NEJM 2003; Cai T. Clin Infect Dis. 2015

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**Asymptomatic bacteriuria in renal transplant recipients**

- > 2 mo post transplant + ASB, N=112
- 1ˢᵗ outcome: Pyelonephritis
  - 7.5% vs. 8.4% (OR 0.88, 95% CI 0.22-3.47)
- 2ⁿ outcomes: C diff, UTI, MDR infx, rejection
  - No significance difference

Origuen J. AJT. 2016

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**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. If other source identified, stop UTI treatment

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**Is asymptomatic bacteriuria protective?**

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Symptomatic UTI(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Antibiotics</td>
<td>Antibiotics</td>
</tr>
</tbody>
</table>

- 712 women with asymptomatic bacteriuria

- Symptomatic UTI:
  3 months: 11 (4%) vs. 32 (9%)
  6 months: 23 (8%) vs. 98 (30%)
  12 months: 41 (15%) vs. 169 (73%)

Stats
### Is asymptomatic bacteriuria protective?
- 712 women with asymptomatic bacteriuria

<table>
<thead>
<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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</table>

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


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
  - 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 w/ 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 Pre-Rx</th>
<th>Estriol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>67</td>
<td>67</td>
</tr>
</tbody>
</table>

Raz R. NEJM. 1993

Intra-vaginal estrogen

*Show me the data!*

Prevention of recurrent UTIs

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

Raz R. NEJM. 1993
Can increasing fluids reduce UTI risk?

- Premenopausal women w/ recurrent UTI
- Randomized: +1.5L/d vs. no change (n=140)
- Fluid group: more fluid, voids, reduce urine Osms
- 1° outcome: recurrent UTIs episodes in 12 m
  - 1.6 vs.3.1; OR .52, 95% CI (0.46-0.6), p<0.01

Hooton TM. ID Week. Oct 2017

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

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>P=.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: 
  - ½ TMP-SMX SS vs. placebo post-coital

Stapelton A. JAMA. 1990

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX</td>
<td>16</td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
</tr>
</tbody>
</table>

x 6 months

UTI

2 (13%) 9 (82%)

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

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</td>
<td>Intra-vaginal estrogen</td>
</tr>
<tr>
<td>Increase fluids (+1.5L/d)</td>
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</tr>
<tr>
<td>Methenamine hippurate</td>
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</tr>
<tr>
<td>Post-coital antibiotics</td>
<td>Post-coital antibiotics</td>
</tr>
<tr>
<td>Antibiotic suppression in select cases</td>
<td>*Obtain imaging and/or urology evaluation if hematuria w/o dysuria, elevated Cr, incontinence, stones, recurrent Proteus UTI</td>
</tr>
</tbody>
</table>

Post-coital antibiotics

Antibiotic suppression in select cases

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

Pre-menopausal

Post-menopausal

Cordero Ampuero J. Clin Ortho Relay Res. 2013
