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
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

IDSA updated 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 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

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?

- May be less efficacious
- Unlikely dangerous for Rx
- Danger increase for chronic suppression

You start TMP-SMX, culture reveals > 100K CFU/ml of enterococcus (Susceptible to amox, resistant to TMP-SMX)

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
  
Hooton TM. NEJM. 2013

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?

Hooton TM. NEJM. 2013
You start patient on TMP-SMX, culture reveals > 100K CFU/ml of enterococcus (Susceptible to amox, resistant to TMP-SMX)

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

How is guideline compliance?

Grigoryan. Open Forum Infect Dis. 2015
Nitrofurantoin

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 many be OK in men with UTI?

- 39,149 Veterans with UTI
- Antibiotic duration
  - $\leq 7$ 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

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

Oral antibiotics active against ESBL
Gram negative pathogens

% isolates susceptible

Fosfomycin
Nitrofurantoin
Doxycycline
Cipro
Amox-clav

n=46

Prakash V. AAC 2009
Fosfomycin (Monurol)

- Activity against Gram pos and neg
- FDA approved for Rx of uncomplicated UTI
- *Treatment for complicated infections:*
  - 3 gm (mixed in 4 oz H₂O) 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

Hooton TM. Clin Infect Dis. 2010
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
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

### Asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Population</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</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
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
- Patients > 3 months post renal transplant
- Diabetics

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
- 1° endpoint: Time to 1st symptomatic UTI
- 42% Rx vs. 40% placebo, p=0.42

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

Asymptomatic bacteriuria in renal transplant recipients

- > 2 mo post transplant + ASB, N=112
- 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. If other source identified, stop UTI treatment

Is asymptomatic bacteriuria protective?

- 712 women with asymptomatic bacteriuria

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<th>Follow-up</th>
<th>Symptomatic UTI (%)</th>
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Is asymptomatic bacteriuria protective?

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<tr>
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<th>No Antibiotics</th>
<th>Antibiotics</th>
<th>Stats</th>
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<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>
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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 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 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>
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Raz R. NEJM. 1993
Intra-vaginal estrogen
*Show me the data!*

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<th>% Colonized with organism</th>
<th>Pre-Rx</th>
<th>Post-Rx</th>
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</thead>
<tbody>
<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 w/ 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 w/ recurrent UTI
- Randomized: +1.5L/d vs. no change (n=140)
- Expert group: more water, 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

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Finally put to cranberry to rest…

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

<table>
<thead>
<tr>
<th>Outcome</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:
  - \( \frac{1}{2} \) TMP-SMX SS vs. placebo post-coital

Stapelton A. JAMA. 1990

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

\( x 6 \) months

Intermittent self-administration of antibiotics

- Healthy women with \( \geq 2 \) 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)


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**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>
<td>Increase fluids (+1.5L/d)</td>
</tr>
<tr>
<td>Methenamine hippurate</td>
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<tr>
<td>Post-coital antibiotics</td>
<td>Post-coital antibiotics</td>
</tr>
</tbody>
</table>

Antibiotic suppression in select cases

*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

Cordero-Ampuero J. Clin Ortho Rela Thy Res. 2013

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
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