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 year-old female with no significant past medical history 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

Efficacy of nitrofurantoin in elderly?

• Study of older women (mean age 79 years)
  – 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 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

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 (10²) 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
How is guideline compliance?

- Quinolones
- Nitrofurantoin
- TMP-SMX
- Other

Ciprofloxacin

- Duration according to guideline

TMP-SMX

- Duration according to guideline

Nitrofurantoin

- Duration according to guideline
Lecture outline

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- **Complicated UTI/pyelonephritis**
  - Asymptomatic bacteriuria
  - Recurrent UTIs
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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
  - ≤ 7 days: 35% (median 7 days)
  - > 7 days: 65% (median 10 days)
- Veterans who received > 7 days:
  - No reduction in recurrences
  - Increase *Clostridium difficile* infection

Drekonja DM. JAMA Intern Med. 2013
ESBL trends at UCSF

Oral antibiotics active against ESBL Gram negative pathogens

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, reduces duration of symptoms, relapse
  - 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 pyelonephritis
  - Use antipseudomonal agent other than fluoroquinolone

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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. Empiric 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 urinalysis is sent to look for proteinuria and when the leukocyte esterase is positive, the lab reflexively sends for culture
- 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: ≥10⁵ CFU/ml
  - Cath: ≥10² CFU/ml
- Pyuria is present > 50% of patients

Asymptomatic bacteriuria

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<table>
<thead>
<tr>
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<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>
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</tbody>
</table>

Nicolle. CID. 2005
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

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

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
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

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

<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;0.001</td>
</tr>
<tr>
<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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- Challenges in cystitis
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- Asymptomatic bacteriuria
- **Recurrent UTIs**
  - Pre-op urine screening

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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

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**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

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**Pathogenesis of UTI in women**

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

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
• Primary endpoint: Recurrent UTIs
  – 0.5 (estriol) vs. 5.9 (placebo) UTI/pt-yr; p < 0.001

<table>
<thead>
<tr>
<th>% Colonized with organism</th>
<th>Pre-Rx</th>
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</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>
</tbody>
</table>
Intra-vaginal estrogen

*Show me the data!

<table>
<thead>
<tr>
<th>% Colonized with organism</th>
<th>Pre-Rx</th>
<th>Post-Rx</th>
</tr>
</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
  - 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

* 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>
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<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>
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Postcoital antibiotics

- RCT in college women
- Intervention:
  - ½ TMP-SMX SS vs. placebo post-coital

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

Postcoital antibiotics

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
Prevention of recurrent UTIs

- Prevent vaginal colonization with 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. J Urol. 1983

Management of Recurrent UTIs*

Pre-menopausal
- Avoid spermicide
- Cranberry juice/tabs? Methenamine hippurate
- Post-coital antibiotics
  - Antibiotic suppression in select cases

Post-menopausal
- Intra-vaginal estrogen
- Cranberry juice/tabs? Methenamine hippurate
- Post-coital antibiotics

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

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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

- 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

Thank you

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