Antimicrobial Update: A focus on urinary tract infection
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Disclosure
• No real or potential conflict of interest to disclose.
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives
• Having completed the learning activities, the participant will be able to:
  – Identify the most likely causative pathogens in urinary tract infections.
  – Describe the clinical presentation of common urinary tract infections.
  – Design a plan of care for the person with urinary tract infection or asymptomatic bacteriuria.
Which commonly reported symptom is most sensitive for UTI in women of reproductive age?

- Frequency
- Burning
- Straining
- Urgency
- Pain with voiding

Diagnostics in UTI

- Urine dipstick, urinalysis
  - Pyuria present for UTI dx
    - Positive leukocyte esterase dipstick test
      - >10 white blood cells (WBCs)/mL=Pyuria threshold
      - Sensitive and specific finding
      - Testing for which WBC? Neutrophil

True or false?

- A positive nitrate test is highly specific for UTI, but lower sensitivity for bacterial UTI. True
- Microscopic hematuria is found in about half of cystitis cases. True
- In immunosuppression, leukocyte esterase testing in UTI could be negative despite bacterial UTI. True

Diagnostics in UTI (continued)

- Urine culture remains the criterion standard for the diagnosis of UTI.
  - Particularly important when
    - Immunosuppression
    - Recent urinary tract instrumentation
    - Recent exposure to antibiotics
    - Recurrent infection
    - Advanced age
Assessment Tip
Vaginitis vs. UTI

• While vaginal infection and irritation can cause dysuria, most women who have dysuria without vaginal discharge have a UTI, not vaginitis.

Evidence-based UTI Prevention
True or false?
In order to minimize risk of urinary tract infection, women should be advised about...

True or false?
Evidence-based Methods to Avoid Urinary Tract Infection in Women
• Postcoital voiding False
• Timed or frequent voiding False
• Wipe front to back False
• Avoid hot tub use False
• Do not wear pantyhose False

Acute Uncomplicated Cystitis
Risk Factors for Women

• Heterosexual intercourse
  – UTI more frequent in women ages 15–35 years.
  – Intercourse often precedes UTI onset.
• Frequency of intercourse often related to UTI incidence

Acute Uncomplicated Cystitis
Risk Factors for Women
(continued)

• Low lactobacilli colonization
  – Normal periurethral flora component
    • Produces hydrogen peroxide, lactic acid
  – Provides periurethral area, vagina w/pH that inhibits bacterial growth, blocks potential sites of attachment toxic to uropathogens

Acute Uncomplicated Cystitis
Risk Factors for Women
(continued)

• Low lactobacilli colonization (cont.)
  – Postmenopausal women
  – Recent antimicrobial use
  – Spermicides containing antibacterial detergent benzethonium chloride
  – Likely tampon use
Acute Uncomplicated Cystitis
Risk Factors for Women
(continued)

• History of UTI
  – Recurrent UTI occurs in 27% of women w/in 6 mo p 1st UTI
  – Increased bacterial receptor sites

• Constipation
  – Contributes to bladder instability in elder, child

Acute Uncomplicated Cystitis
Risk Factors in Either Gender

• Advancing age
  – Alterations in urinary tract structure (cystocele, uterine prolapse, BPH)
    • Encourages post void residual
  – Limited functional status
    • Impaired mobility, hygiene, toileting

Acute Uncomplicated Cystitis
Protective Factors in Either Gender

• Efficient bladder emptying
  – Lack of cystocele, rectocele, BPH, other anatomic, neurologic issues
Cranberry, Blueberry – Helpful or Not?

• Initial proposed MOA
  – High levels of benzoic acid that resulted in urinary acidification and bacteriostatic action
• Further study failed to support this hypothesis

(continued)

Cranberry, Blueberry – Helpful or Not?

• Cranberry “dose”
  – ≥300–400 mg BID in tablet form
  – 8–16 oz. (0.24–0.47 L) ≥30% cranberry juice blend
• Long-term adherence to cranberry products and expected benefit may be overestimated

UTI Therapies

Available at http://www.sanfordguide.com/
(T/F) The U.S. FDA advises that the adverse effects associated with fluoroquinolones (cipro-, levo-, moxifloxacin [-floxacin suffix]) generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options.

True or false?
True
The U.S. FDA advises that the adverse effects associated with fluoroquinolones (cipro-, levo- moxifloxacin [-floxacin suffix]) generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options.

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<tr>
<th>Type of infection</th>
<th>Usual pathogens</th>
<th>Regimens</th>
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| Acute, uncomplicated urinary tract infection (cystitis, urethritis) in nonpregnant women | *E. coli* (Gm neg, most common pathogen), *S. saprophyticus* (Gm pos), *Enterococci* (Gm pos) | **Primary**
If local *E. coli* resistance to TMP/SMX <20% and no allergy, then TMP/SMX-DS PO BID × 3 days
If local *E. coli* resistance to TMP/SMX >20% or sulfa allergy, nitrofurantoin 100 mg PO BID × 5 d or fosfomycin 3 G PO × 1 dose, all plus phenazopyridine (Pyridium®)
Acute, Uncomplicated Urinary Tract Infection (continued)

- **Alternative**
  - If local *E. coli* resistance to TMP/SMX >20% or sulfa allergy
    - All for 3 days, plus phenazopyridine (Pyridium®)
    - Ciprofloxacin 250 mg PO BID
    - Or
    - Ciprofloxacin ER 500 mg PO daily
    - Or
    - Levofloxacin 250 mg PO daily
    - Or
    - Moxifloxacin 400 mg PO

Acute, Uncomplicated Urinary Tract Infection (continued)

- **Alternative** (cont.)
  - Amoxicillin-clavulanate 875/125 mg PO BID × 5–7 days
  - Or
  - Cephalexin 500 mg PO BID × 5–7 days
  - Or
  - Cefdinir 300 mg PO BID × 3–7 days

True or false?
According to the recommendations in the Sanford Guide

- If failure on 3-day or other short course antimicrobial therapy, culture and treat for 2 weeks  True
Principles of Empiric Antimicrobial Therapy:
Never ask a drug to do something it cannot.

Using the antibiogram...
Which antibiotic should I chose?
Why refer to an antibiogram?
Extended-spectrum Beta-lactamase Producing Organisms

- AKA ESBL-producing organisms
  - Most often *K. pneumoniae*, *E. coli*, Acinetobacter
- Organism that produce enzymes that confer resistance to most beta-lactam antibiotics
  - Penicillins
  - Cephalosporins
  - Monobactam aztreonam

ESBL-producing *E. coli* Risk Factors for Acquisition per Sanford Guide

- History of repeated UTIs
- Recent inpatient health-care facility stay
  - For >3 d
- Obstructive uropathy
  - BPH, others
- Recent FQ or beta-lactam exposure
  - -floxacin, PCN-family, cephalosporin use, within p 3 months
- Travel to Asia, Middle East or Africa in past 3 months

Which of the following was the strongest risk factor for ESBL UTI, in rank order?

- History of repeated UTIs  2
- Presence of urinary catheter  3
- Prior antibiotic exposure  1

UTI Caused by ESBL-producing Organisms
Treatment Options

• Usually effective antimicrobials
  – Nitrofurantoin
  – Fosfomycin
  – Amoxicillin-clavulanate plus cefdinir

  Source: Sanfordguide.com

(continued)

• Usually effective oral antimicrobials
  – Nitrofurantoin
  – Fosfomycin
  – Amoxicillin-clavulanate plus cefdinir

  Source: Sanfordguide.com

Recurrent UTI Treatment
Per Sanford Guide
True or false?

- Use of spermicides, including spermicide-coated condoms, is a risk factor for recurrent UTIs in women of reproductive age. True

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<td>Recurrent UTI (≥3 culture-proven UTI per year in younger woman)</td>
<td>All of the aforementioned organisms</td>
<td>Treat any uncomplicated UTI, then trial of one of the following to prevent recurrences: TMP-SMX 80 mg/400 mg (single strength tab) PO q24h or 3 x /week; or TMP 100 mg PO once daily; or cephalexin 250 mg PO once daily; or fosfomycin 3 gm PO every 10 days administered for 6 months</td>
</tr>
</tbody>
</table>

- Also helpful with post menopausal women.
Repeated UTIs
Patient-initiated Therapy

- Patient has antimicrobial available
- Initiates therapy at 1st UTI sx
- Patient input
  - Clear understanding of length of UTI therapy
  - Signs and symptoms of treatment failure
  - When to seek provider assistance

Outcomes with Patient-initiated Therapy

- Study fails to demonstrate
  - Increase in rate of resistant pathogens
  - Poorer patient outcomes
  

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| Post-menopausal women: ≥3 culture + symptomatic UTIs in 1 year or 2 UTIs in 6 months | All of the aforementioned organisms | Treat as for uncomplicated UTI then consider one of the following:
  - Topical estrogen reduces risk by restoring normal vaginal flora
  - Nitrofurantoin more effective than vaginal estrogen but concern with pulmonary fibrosis with long-term use
  - Evaluate for potentially correctable urologic factors; cystocele, incontinence, increased residual urine volume (≥50 mL) |
Per Beers Criteria
True or false?
• There is evidence that vaginal estrogens for treatment of vaginal dryness and UTI prevention is safe and effective in women with breast cancer, especially at dosages of estradiol dose <25 mcg twice weekly.
  True

According to ACOG...
• Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms. True

Pyelonephritis
• Infectious inflammatory condition
  – Kidney parenchyma, renal pelvis
• Most episodes uncomplicated
  – No obstruction, urologic dysfunction
    • Women ages 18–40 years
    • Consider obstructive issue in male
  – No multidrug resistant uropathogen
Acute Pyelonephritis
Clinical Presentation

- Acutely ill appearance
  - Vomiting
  - Fever
- Irritative voiding symptoms
- Flank pain
- Costovertebral tenderness
- Pyuria

Clinical Presentation (continued)

- WBC left shift
- WBC casts

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| Acute uncomplicated pyelonephritis suitable for outpatient therapy (usually woman age 18–40 y, fever ≥102°F (38.9°C), CVA tenderness) | E. coli, Enterococci | Primary
  Ciprofloxacin 500 mg BID, ciprofloxacin ER 1000 mg daily, ofloxacin 400 mg BID, all for 7 days, levofloxacin 250 mg daily × 5 days. (One IV dose often given due to GI upset.)
  Alternative
  Amoxicillin w/clavulanate, cephalosporin, TMP/SMX-DS, all for 14 days
  Note: Obtain urine and blood cultures prior to initiating antimicrobial therapy. |
Ceftriaxone Use in Pyelonephritis

- 1–2 g/day IM or IV
  - Are there treatment alternatives?
  - If the gut works, oral FQ can reach similar therapeutic levels

According to the recommendations found in the Sanford Guide...

- In the presence of gram negative bacteremia associated with pyelonephritis, the length of effective antimicrobial therapy is:
  A. 3 days.
  B. 7 days.
  C. 10 days.
  D. 14 days.
Pyelonephritis Follow-up

- Urologic imaging not routine
  - Renal ultrasound, CT scan
- Consider imaging
  - Symptoms initially resolve but recur w/in 2 wks antimicrobial treatment ends
  - Urine culture yields original pathogen w/sensitivity profile
    - Retreat × 2 weeks while awaiting results

Reference
Source: Uncomplicated Cystitis and Pyelonephritis (UTI)
Available at http://www.idsociety.org/Organ_System/#Genitourinary

Mary
- 72-year-old woman
- HTN, T2DM, dyslipidemia
  - HgA1c=7.2% (0.072 proportion), BP=122/78 mm Hg
- Sustained non syncopal fall after tripping over grandchild's toy
- Evaluated in ED for hip pain
- No fracture revealed
Mary, UA in ED
- Protein=Negative
- Leukocyte esterase=Trace
- Nitrites=Negative
- RBC=1+
- U C and S=100K cfu *E. coli*
  - R=TMP/SMX, S=All others

Asymptomatic Bacteriuria
Epidemiology
- Healthy premenopausal women=1–5%
- Pregnant women=1.9–9.5%
- Postmenopausal women=2.8–8.6%
  - Age 50–70 years
- Women with diabetes=9–27%
- Men with diabetes=0.7–1%

Asymptomatic Bacteriuria
Epidemiology (continued)
- In older adult
  - >15% community-dwelling women age ≥65 y
  - ~3–19% of community-dwelling men age ≥65 y
Asymptomatic Bacteriuria
Defined per IDSA

• In absence of UTI sx
  – Clean-catch voided urine specimens with isolation of the same organism in quantitative counts of ≥10^5 cfu/mL
    • In men, × 1 specimen
    • In women, × 2 consecutive specimens

Asymptomatic Bacteriuria
Defined per IDSA
(continued)

• In catheterized men or women
  – Single catheterized specimen with isolation of a single organism in quantitative counts of ≥10^2 cfu/mL

Asymptomatic Bacteriuria
(continued)

• Epidemiology
  – Older long-term care residents
    • Women=25−50%
    • Men=14−40%
  – Patient with indwelling catheter
    • Short-term=9−23%
    • Long-term=100%
    – Source: http://www.aafp.org/afp/2006/0915/p985.html
Asymptomatic Bacteriuria Risk Factors (Except in Pregnant Woman)

- Altered elimination
  - Fecal impaction
  - Medications that encourage constipation, urinary retention such as anticholinergic drugs
- Anatomic variations
  - Cystocele, BPH

(continued)

- Hygienic issues
  - Fecal soiling, poor perineal hygiene
- Neurologic impairment
  - Impacting mobility, bladder emptying
- Postmenopausal hormonal changes

Population to Screen, Treat for Asymptomatic Bacteriuria

- Pregnant women
  - Bacteriuria associated with increased risk of preterm birth, low birth weight, perinatal mortality, pyleonephritis
  - Treat 3–7 days, dependent on antibiotic used
  - Antibiotic choice based on sensitivity of organism
Population to Screen, Treat for Asymptomatic Bacteriuria (continued)

- Treat?
  - If bladder instrumentation or surgery planned where risk of mucosal bleeding
    - Typically 1 week w/FQ
  - Unneeded treatment can facilitate resistant organisms development

Gina, 24-year-old Woman

- UTI history
  - Episodes at age 19, 22 years
  - Treated without sequelae

- 48 h history
  - Urinary frequency, urgency
  - Urine “just like blood” at times
  - No fever, constitutional sx, vaginal dx

Gina 24-year-old Woman

UA Results

- Positive
  - Leukocytes
  - RBC
  - Trace protein

- Negative
  - Nitrites
  - Hemoglobin
Hemorrhagic Cystitis
Visible Blood in Urine

Etiology
– Bacterial
– Adenovirus serotypes 11, 21

Secondary to another process
– Radiation, cancer chemotherapy, or select immunosuppressive medication


In all
– Irritative voiding symptoms

Presentation depends on origin
– Signs, sx infection if present
– Underlying disease if induced by chemo, meds


Treatment of Hemorrhagic Cystitis of Likely Infectious Origin

Treat
– Irritative voiding symptoms
– Empiric antimicrobial therapies pending culture results
– Consider urology consultation if symptoms persist beyond 5 days

Conclusion

Resources

- The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: To treat or not to treat? *Clin Infect Dis.* 2012;55(6):771
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