Disclosure and Conflict of Interest

• Dr. Alegro declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria.

Pharmacist Objectives

At the conclusion of this program, the pharmacist will be able to:
1. Describe the pathophysiology, common etiologies, and clinical presentation of urinary tract infections.
2. Summarize current practice guidelines for cystitis, pyelonephritis, and asymptomatic bacteriuria.
3. Discuss common adverse effects, drug interactions, and clinical pearls of antibiotics commonly used for treating UTI’s.
4. Apply treatment guidelines and antimicrobial stewardship strategies to a specific patient case in order to select the most appropriate agent for a UTI.
Technician Objectives

At the conclusion of this program, the technician will be able to:
1. Define the different types of urinary tract infections.
2. Recognize common signs and symptoms of urinary tract infections.
3. Classify antibiotics that are used for the treatment of urinary tract infections.

Pre-Test Question #1
Which of the following is a common etiologic cause of uncomplicated cystitis?
A. Escherichia coli
B. Pseudomonas aeruginosa
C. Staphylococcus aureus
D. Candida albicans

Pre-Test Question #2
Which of the following antibiotics would only be appropriate to use in patients presenting with lower urinary tract symptoms?
A. Ciprofloxacin
B. Trimethoprim-sulfamethoxazole
C. Nitrofurantoin
D. Ceftriaxone

Pre-Test Question #3
Which of the following patients would be an appropriate candidate for treating asymptomatic bacteriuria?
A. 29 y.o. pregnant female in her second trimester
B. 44 y.o. female scheduled to undergo 3 vessel coronary artery bypass graft (CABG) surgery
C. 52 y.o. male with WBC >200 in his urine and growing >100,000 CFU’s of Pseudomonas aeruginosa in his urine
D. 74 y.o. male with chronic indwelling foley catheter
Pre-Test Question #4

Which of the following has shown to be a potential adverse effect of fluoroquinolones?
A. Colitis secondary to *C. difficile*
B. Toxic psychosis
C. Peripheral neuropathy
D. All of the above

Still Feelin’ the Burn? You Might Have a Urinary Tract Infection...

Disease State Discussion

Definitions

- **Cystitis**
  - “Cyst” = bladder
  - Lower urinary tract infection
- **Pyelonephritis**
  - “Pyelo” = pelvis
  - “Nephro” = kidney
  - Upper urinary tract infection
- **Asymptomatic Bacteriuria**
  - Presence of bacteria in a urine sample in the absence of symptoms
Definitions

- Uncomplicated UTI (cystitis or pyelonephritis)
  - Women
  - Premenopausal
  - Non-pregnant
  - No known urological abnormalities
- Complicated UTI* 
  - Urinary obstruction, immunosuppression, pregnancy, poorly controlled diabetes, renal transplantation, indwelling catheters/devices, men, children, hospitalized patients.
  - Think structural or functional abnormalities

*Higher risk for persistent or recurrent infection as well as more highly resistant organisms

Epidemiology

- Commonly seen bacterial infection
  - Total healthcare costs in the U.S estimated to be $3.5 billion per year
- Significant cause of morbidity
  - Recurrent infections
  - Progression to urosepsis and bacteremia
  - Permanent renal damage
  - Adverse effects and bacterial resistance due to antibiotic overuse

The Microbiome and Urinary Tract Host Defenses

- The urethral mucosa is commonly colonized with bacteria (normal flora)
- The rest of the urinary tract under normal conditions remains relatively sterile
- Innate immunity
  - Proinflammatory – recruits polymorphonuclear leukocytes (PMN's) to urinary tract
  - Intensity of response can determine if progression to full infection and symptoms

Pathophysiology

- Women – Premenopausal – Non-pregnant – No known urological abnormalities

Definitions

Epidemiology

The Microbiome and Urinary Tract Host Defenses

Pathophysiology
**Pathophysiology**

- Infection can invade the urinary tract via three routes:
  - Ascending route (most common)
  - Hematogenous route
  - Lymphatic route
- High inoculum of virulent uropathogenic bacteria overcomes highly efficient host defenses

**Common Etiologies**

- Uncomplicated, community acquired
  - *E. coli*
  - *Proteus* spp.
  - *Staphylococcus saprophyticus*
  - *Klebsiella* spp.
  - Other enterobacteriaceae
- >50 years old
  - Increased *Proteus* prevalence
- Diabetes, spinal injury, chronic indwelling catheter
  - Concern for *Candida* spp. and *Enterococcus* spp.

**Risk Factors**

- Previous history of UTI
- Recent sexual intercourse (past 48 hours)
- Uncontrolled diabetes mellitus
- Female gender
  - Anatomical predisposition – shorter urethra in close proximity to the perianal area
- Age
  - Increased risk in men with increased age
  - Female gender if <35 or >65

**Diagnosis**

- Urinalysis:
  - **Significant bacteriuria**: (>100,000 colony forming units/mL): infection is probable
  - **Leukocyte esterase**: enzyme produced by neutrophils, helps define presence of pyuria
  - **Nitrites**: Positivity may indicate bacteria that reduces nitrate to nitrite (commonly *E. coli*)
  - **Squamous epithelial cells**: many present may indicate contaminated urine sample
**Clinical Presentation**

Cystitis
- Dysuria
- Urinary frequency
- Urinary urgency
- Suprapubic tenderness

Pyelonephritis
- Flank pain
- Fever
- Costovertebral angle tenderness
- PLUS signs/symptoms of cystitis

*In those who cannot mount a substantial immune/inflammatory response, these clinical presentations may be limited or manifest differently (i.e. elderly, spinal cord injury)*

**Antibiotic Stewardship in Treating Urinary Tract Infections**

- Goals (antibiotic stewardship in general):
  - Optimize clinical outcomes related to antibiotic use
  - Minimize toxicity
  - Reduce healthcare costs
  - Limit the selection for antimicrobial resistant strains
  - Right Drug, right Dose, right De-escalation, right Duration

- How do we achieve this?
  - Appropriate antibiotics that will be effective, safe, cost conscious, and as narrow spectrum as possible

**Patient Case**

SP is a 77 year old female with PMH of T2DM, osteoporosis, and HFpEF. She is brought to the ED from her nursing home s/p fall after she attempted to go to the bathroom on her own. A urinalysis was performed in the ED which showed positive leukocyte esterase, >100 WBC, positive nitrates, and moderate bacteria. Reflex urine culture is showing >100,000 E. coli. Which is the most appropriate treatment option for this patient?
Acute Uncomplicated Cystitis in Women (2010)

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Duration</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin 100mg PO BID</td>
<td>5 days</td>
<td>A-I</td>
<td>Cystitis ONLY; Cr/Ci cutoff &lt;30 ml/min</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole 160/800mg (1 DS) tablet PO BID</td>
<td>3 days</td>
<td>A-I</td>
<td>Avoid empirically if &gt;20% of local isolates of infecting strain are resistant (B-III)</td>
</tr>
<tr>
<td>Fosfomycin 3 grams x 1 dose</td>
<td>1 dose</td>
<td>A-I</td>
<td>Cystitis ONLY; Good option for resistant pathogens; may have inferior efficacy against susceptible pathogens compared to above choices</td>
</tr>
<tr>
<td>Levofloxacine 250mg PO daily</td>
<td>3 days</td>
<td>A-III</td>
<td>More recent recommendations discourage empiric use for acute uncomplicated cystitis</td>
</tr>
<tr>
<td>β-lactams (amoxicillin-clavulante, cefdinir, cefaclor, cefpodoxime, and cephalaxin)</td>
<td>3-7 days</td>
<td>B-I, B-III</td>
<td>May have inferior efficacy compared to other urinary agents, so current guidelines recommend if above options cannot be used</td>
</tr>
</tbody>
</table>

Acute Uncomplicated Pyelonephritis in Women (2010)

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Duration</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacine 500mg PO BID</td>
<td>7 days</td>
<td>A-III</td>
<td>Initial one-time intravenous dose of a fluoroquinolone, ceftriaxone, or aminoglycoside may be given</td>
</tr>
<tr>
<td>Levofloxacine 750mg PO daily</td>
<td>14 days</td>
<td>A-I</td>
<td>If used empirically, patient should receive a one-time dose of ceftriaxone or an aminoglycoside</td>
</tr>
<tr>
<td>β-lactams (amoxicillin-clavulante, cefdinir, cefaclor, cefpodoxime, and cephalaxin)</td>
<td>10-14 days</td>
<td>B-III</td>
<td>Oral beta-lactams have been shown to be less effective compared to other agents for pyelonephritis</td>
</tr>
</tbody>
</table>

If hospitalization is required (usually more on the complicated side):
Initial treatment with intravenous fluoroquinolone, aminoglycoside (+/- ampicillin), extended-spectrum cephalosporin or penicillin, or a carbapenem.
Decision is based on local resistance data and should be de-escalated pending susceptibilities.

Complicated Cystitis and Pyelonephritis

- No consensus definition
- More difficult to treat and higher risk for failure than uncomplicated
- Oral treatment with fluoroquinolones may be used, however concerns for resistance
- Empirc, broad spectrum intravenous antibiotics targeting multidrug-resistant organisms should be used for drug resistant, severe complicated urinary tract infections
Asymptomatic Bacteriuria

• Current guidelines (2005) being updated for 2018
• Main recommendations:
  – Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment. (A-II)
  – When do we treat people for asymptomatic bacteriuria?
    • Pregnant women (A-I): Treatment is 3-7 days (A-II)
    • Prior to transurethral resection of the prostate (TURP) (A-II)
      – Antimicrobial therapy should not be continued unless indwelling catheter remains in place
    • Prior to other urologic procedures for which mucosal bleeding is anticipated (A-III)
  – If treatment is appropriate, antibiotics should be targeted to cultures and susceptibilities

Review of Commonly Used Antibiotics for UTI’s

Drug Review: Fluoroquinolones

• Agents: ciprofloxacin, levofloxacin
• Mechanism of Action (MOA): Inhibits topoisomerase II and topoisomerase IV, essential enzymes in bacterial DNA replication
• Moxifloxacin does NOT reach adequate urinary concentrations and should not be used for treatment of UTI’s
• Food and Drug Administration (FDA) Indications:
  – Uncomplicated Cystitis (**2016 Update!)
  – Acute Pyelonephritis
  – Complicated Urinary Tract Infections
• Administration
  – May give with food to decrease GI upset
  – Ciprofloxacin must be given 2 hours before or 6 hours after and levofloxacin must be given 2 hours before or 2 hours after ingesting divalent cation containing substances
• Adverse Effects (ADEs):
  – Black Box Warnings: tendinitis and tendon rupture, peripheral neuropathy, CNS effects including toxic psychosis (hallucinations, delirium, etc). These can potentially be permanent.
  – Other ADEs: diarrhea, C. diff colitis, exacerbation of myasthenia gravis
FDA Warning – July 26, 2016

• “[T]he serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.”

Drug Review: Fluoroquinolones

• Clinical Pearls
  - Although fluoroquinolones are generally thought of as effective treatment options for UTIs, the safety risks outweigh the benefits in many cases
  - Efficacy is becoming questionable due to development of drug resistance
  - Fluoroquinolones should be avoided in treatment of uncomplicated cystitis when other alternatives are available
  - Moxifloxacin does not achieve adequate urinary concentrations to be effective against UTIs
  - Avoid use in pregnancy

Drug Review: Nitrofurantoin

• Mechanism of Action: reduction by bacteria creates reactive metabolites that inactivate or alter bacterial ribosomal proteins, causing inhibition of protein, DNA, RNA, and cell wall synthesis

• FDA Indications:
  - UTI Treatment (cystitis ONLY): 100mg PO twice daily or q6h
  - UTI prophylaxis: 50-100mg PO daily

• Spectrum of activity:
  - E. coli, Citrobacter spp., S. saprophyticus, E. faecalis
  - Acinetobacter and Pseudomonas are typically resistant

• Adverse Effects
  - Pregnancy: Category B, however caution if used at term if G6PD deficiency is present due to concern for hemolytic anemia and neonatal jaundice
  - GI intolerance
  - Pulmonary toxicity (chronic exposure, especially if >65 years old and renal dysfunction)

Drug Review: Nitrofurantoin

• Clinical Pearls:
  - Typically retains activity against E. coli because mechanisms of resistance must be multifactorial given the drug’s mechanism of action
  - Overall, short courses well-tolerated however concerns for prolonged use
  - Poor concentration outside of the bladder, so should be used ONLY for cystitis
  - Per manufacturer labeling, if CrCl is <60ml/min, use is contraindicated, however the 2015 Beers Criteria recommends avoiding use in elderly ≥65 if CrCl <30 ml/min
  - 2015 Canadian study showed that there was no compelling reason to avoid nitrofurantoin in chronic kidney disease (CrCl <60 ml/min)
  - Important UTI option in pregnancy and for prophylaxis
Drug Review: Trimethoprim-sulfamethoxazole

• Mechanism of Action: synergistically inhibits bacterial folic acid synthesis

• FDA Indications:
  – Uncomplicated (3-5 days) and Complicated (7-10 days) Cystitis
  – Pyelonephritis (14 days)

• Spectrum of Activity

Drug Review: Fosfomycin

• Mechanism of Action: phosphoric acid derivative that inhibits bacterial cell wall synthesis by inactivating pyruvual transferase enzyme

• FDA-approved indication:
  – Uncomplicated UTIs: one 3g dose

• Spectrum of Activity: Enterobacteriaceae, including extended-spectrum β-lactamase producers, enterococcus (including vancomycin-resistant strains), Pseudomonas aeruginosa

Drug Review: Trimethoprim-sulfamethoxazole

• Adverse Effects:
  – Rash, Stevens Johnsons Syndrome, Toxic Epidermal Necrolysis
  – GI upset, nausea, photosensitivity
  – Hyperkalemia (especially if concomitant meds, elderly)
  – Pregnancy Category D; Use should be avoided in the first and third trimesters of pregnancy due to concern for congenital malformations and kernicterus

• Clinical Pearls
  – Urinary pathogen resistance to trimethoprim-sulfamethoxazole is a major concern, so empiric treatment with TMP-SMX should be done cautiously and based on local antibiograms
  – Effective for both cystitis and pyelonephritis (need longer duration if upper tract infection)

Drug Review: Fosfomycin

• Adverse Effects:
  – GI upset
  – Headache and dizziness

• Clinical Pearls:
  – Limited systemic absorption (30-40%), so should NOT be used for severe pyelonephritis
  – Expensive and may be difficult to procure, but fosfomycin is a well-tolerated, oral option for uncomplicated and complicated cystitis caused by multidrug-resistant bacteria
  – Pregnancy Category B
**Drug Review: Beta-lactams**

- **Agents:**
  - Aminopenicillins: amoxicillin (+/- clavulanic acid), ampicillin
  - 1st generation cephalosporins: cefazolin (IV), cephalaxin (PO), cefadroxil (PO)
  - 2nd generation cephalosporins: cefuroxime (PO), cefaclor (PO)
  - 3rd generation cephalosporins: ceftriaxone (IV), cefpodoxime (PO), cefdinir (PO)

- **Mechanism of Action:**
  - Binds to penicillin-binding proteins which in turn inhibits bacterial cell wall synthesis

- **Adverse Reactions**
  - Rash, hypersensitivity
  - GI upset -> may lead to C. diff
  - Spectrum of Activity
    - Pertinent Gram Negatives: *E. coli*, *Proteus* spp., *Klebsiella* spp.

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**Post-Test Question #1**

Which of the following is a common etiologic cause of uncomplicated cystitis?

- A. *Escherichia coli*
- B. *Pseudomonas aeruginosa*
- C. *Staphylococcus aureus*
- D. *Candida albicans*
Post-Test Question #1

Which of the following is a common etiologic cause of uncomplicated cystitis?

A. *Escherichia coli*
B. *Pseudomonas aeruginosa*
C. *Staphylococcus aureus*
D. *Candida albicans*

Post-Test Question #2

Which of the following antibiotics would only be appropriate to use in patients presenting with lower urinary tract symptoms?

A. Ciprofloxacin
B. Trimethoprim-sulfamethoxazole
C. Nitrofurantoin
D. Ceftriaxone

Common Etiologies

• Uncomplicated, community acquired
  – *E. coli*
  – *Proteus* spp.
  – *Staphylococcus saprophyticus*
  – *Klebsiella* spp.
  – Other enterobacteriaceae

• >50 years old
  – Increased *Proteus* prevalence

• Diabetes, spinal injury, chronic indwelling catheter
  – Concern for *Candida* spp. and *Enterococcus* spp.

Post-Test Question #2

Which of the following antibiotics would only be appropriate to use in patients presenting with lower urinary tract symptoms?

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    - Pregnant women (A-I); Treatment is 3-7 days (A-II)
    - Prior to transurethral resection of the prostate (TURP) (A-II)
      - Antimicrobial therapy should not be continued unless indwelling catheter remains in place
    - Prior to other urologic procedures for which mucosal bleeding is anticipated (A-III)
  - Treatment should be targeted to cultures and susceptibilities

Post-Test Question #3

Which of the following patients would be an appropriate candidate for treating asymptomatic bacteriuria?

A. 29 y.o. pregnant female in her second trimester
B. 44 y.o. female scheduled to undergo 3 vessel coronary artery bypass graft (CABG) surgery
C. 52 y.o. male with WBC >200 in his urine and growing >100,000 CFU's of *Pseudomonas aeruginosa* in his urine
D. 74 y.o. male with chronic indwelling foley catheter

Post-Test Question #4

Which of the following has shown to be a potential adverse effect of fluoroquinolones?

A. Colitis secondary to *C. difficile*
B. Toxic psychosis
C. Peripheral neuropathy
D. All of the above
Post-Test Question #4

Which of the following has shown to be a potential adverse effect of fluoroquinolones?
A. Colitis secondary to *C. difficile*
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D. All of the above

Drug Review: Fluoroquinolones

- **Agents:** ciprofloxacin, levofloxacin
- **Mechanism of Action:** Inhibits topoisomerase II and topoisomerase IV, essential enzymes in bacterial DNA replication
- **Moxifloxacin** does not reach adequate urinary concentrations and should not be used for treatment of UTI's
- **FDA Indications:**
  - Uncomplicated Cystitis (**2016 Update!**)
  - Acute Pyelonephritis
  - Complicated Urinary Tract Infections
- **Black Box Warnings:**
  - Serious Adverse Reactions: tendinitis and tendon rupture, peripheral neuropathy, CNS effects including toxic psychosis (hallucinations, delirium, etc). These can potentially be permanent.
  - Exacerbation of muscle weakness in myasthenia gravis

Patient Case

SP is a 77 year old female with PMH of DM-II, osteoporosis, and HFpEF. She is brought to the ED from her nursing home s/p fall after she attempted to go to the bathroom on her own. A urinalysis was performed in the ED which showed positive leukocyte esterase, >100 WBC, positive nitrites, and moderate bacteria. Reflex urine culture is showing >100,000 *E. coli*. Which is the most appropriate treatment option for this patient?

What other important pieces of information do you need to know?

Patient Case

1. Is the patient symptomatic or asymptomatic?
2. Is the patient exhibiting signs and symptoms of lower or upper tract infection?
3. Is this patient’s UTI complicated or uncomplicated?
4. How “sick” is the patient?
5. Drug-related concerns – allergies, intolerances, adverse effects, drug-disease or drug-drug interactions
Patient Case

SP is a 77 year old female with PMH of DM-II, osteoporosis, and HFpEF. She is brought to the ED from her nursing home s/p fall after she attempted to go to the bathroom on her own. A urinalysis was performed in the ED which showed positive leukocyte esterase, >100 WBC, positive nitrites, and moderate bacteria. Reflex urine culture is showing >100,000 E. coli. Which is the most appropriate treatment option for this patient?

Take Home Points

1. Is the patient symptomatic or asymptomatic?
   - Presented with low grade fever and altered mental status
2. Is the patient exhibiting signs and symptoms of lower or upper tract infection?
   - Systemic signs so likely upper tract infection
3. Is this patient’s UTI complicated or uncomplicated?
   - Complicated given age, possibly with diabetes if uncontrolled
4. How “sick” is the patient?
   - No acute distress, not hypotensive or tachycardic
5. Drug-related concerns – allergies, intolerances, adverse effects, drug-disease or drug-drug interactions
   - Sulfa allergy – rash about ten years back; Current meds: calcium supplement once daily, alendronate 70mg PO once weekly, metformin 1000mg PO BID, canagliflozin 300mg PO daily, amlodipine 5mg PO daily, lisinopril 10mg PO daily. eGFR > 60 ml/min

Potential options:
- Fluoroquinolones
- Nitrofurantoin
- Fosfomycin
- Trimethoprim-sulfamethoxazole
- Beta-lactams

Drug-related concerns:
- Fluoroquinolones should be avoided in acute uncomplicated cystitis if other options are available
- Oral beta-lactams may be an effective, practical option for treating acute uncomplicated cystitis and pyelonephritis
- Drug resistance of E. coli to trimethoprim-sulfamethoxazole is a major concern in using this drug for empiric therapy
- Asymptomatic bacteriuria should not be treated except in the cases of pregnancy and urologic manipulation that may cause bleeding
**Additional Resources & References**

IDSA Practice Guidelines  
- http://www.idsociety.org/PracticeGuidelines

European Association of Urology Guidelines  
- http://www.uroweb.org/guidelines/online-guidelines

Johns Hopkins Antibiotic Guide  

**Speaker Contact Information**

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